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Proceedings of the 1st annual Acute Cardiac Unloading and REcover (A-CURE) symposium held on 25 August 2016 in Rome, Italy

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Acute Cardiac Unloading and Recovery

Proceedings of the first annual Acute Cardiac Unloading and REcovery (A-CURE) symposium held on 26th August 2016 in Rome, Italy

Session summaries by Katrina Mountfort, *Medical Writer, Radcliffe Cardiology*

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Acute Cardiac Unloading and Recovery

2nd Annual A-CURE Symposium

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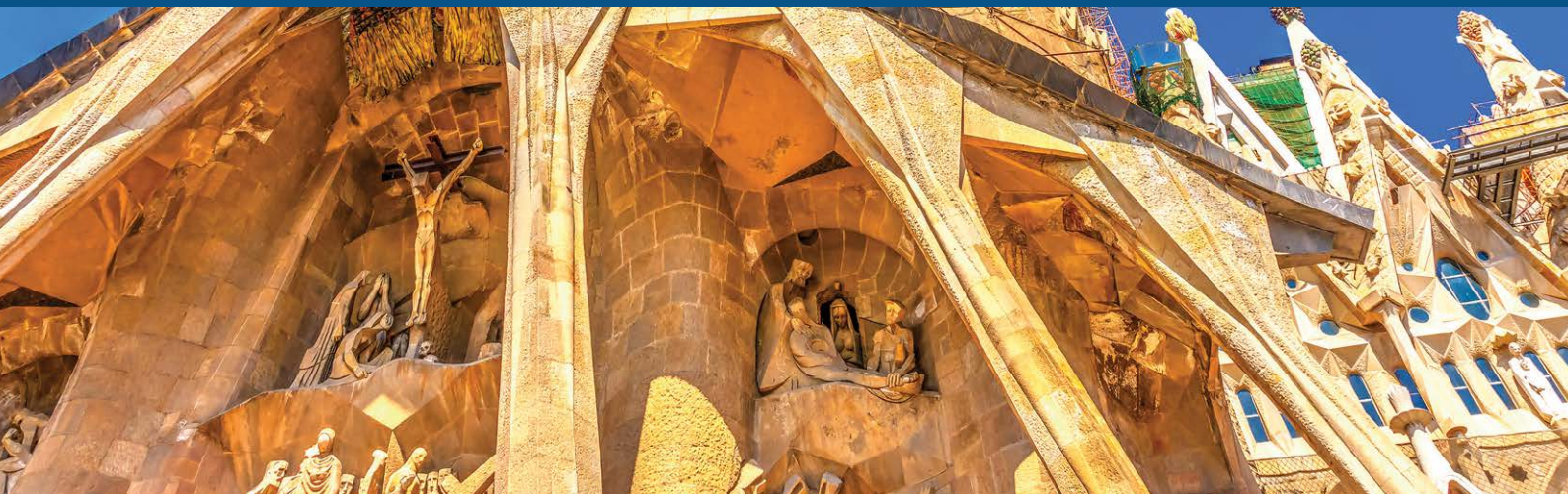

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Advancing the science and mechanistic understanding of acute cardiac unloading, supporting the translation of basic and clinical research into therapies aimed at heart muscle recovery.

ICR Interventional Cardiology Review

Foreword

Welcome to this special supplement of *Interventional Cardiology Review*. This supplement is devoted to the proceedings of the first annual Acute Cardiac Unloading and REcovery (A-CURE) symposium, which was held on 26 August 2016 in Rome, Italy. This 1-day meeting brought together experts from a number of disciplines – including interventional cardiologists, heart failure specialists, cardiac surgeons, molecular biologists and biomedical engineers – to discuss the science behind and clinical application of acute cardiac unloading. Over 100 physicians, clinical and preclinical researchers, basic researchers, medical students, post-doctoral scientists and graduate students from 21 different countries were in attendance.

The growing global heart failure patient population poses clinical, economic and social challenges and there is no clear line of sight to a sustainable solution. The goal of the A-CURE meeting was to share cutting-edge, cross-discipline basic and clinical research, looking at acute cardiac unloading as a therapeutic platform for the prevention of heart failure and the development of therapies aimed at heart muscle recovery. One of the focuses of this meeting was on advancing the paradigm shift currently underway in the management of myocardial ischaemia–reperfusion injuries. Although early coronary intervention has reduced the acute mortality in myocardial infarction (MI), the late development of heart failure is increasing at an alarming rate. For the first time, acute cardiac unloading within the clinic has been made technically feasible by the development of percutaneously-inserted ventricular assist devices (VADs) such as the Impella® (Abiomed) and the TandemHeart® (CardiacAssist Inc). These devices mechanically unload the heart and reduce myocardial oxygen consumption. Clinical and preclinical investigations from independent laboratories over the past decade have routinely demonstrated that acute unloading has beneficial impacts when treating acute MI and other aetiologies of acute heart failure. For the first time, the A-CURE symposium brought together leading researchers in the field of acute unloading to present their current work and generate open scientific discussions in a public forum.

This supplement features a number of presentations describing the basic science underlying acute unloading of the heart, its clinical applications, and the opportunities in and challenges of performing clinical trials. The morning's presentations were largely devoted to preclinical studies and the basic science underlying mechanical unloading. The meeting began with an overview from Eugene Braunwald, one of the most renowned figures in the field of cardiology. Daniel Burkhoff presented the basic science behind acute ventricular and myocardial unloading. Next, Kenji Sunagawa described vagal nerve stimulation, another approach to myocardial protection that has been combined successfully with mechanical unloading in animal models. Navin Kapur explored further the concept of mechanical unloading, discussing the mechanism of cardioprotection at the cellular level. In addition, Dr Kapur described a number of fascinating studies demonstrating that initially reducing left ventricular work and delaying coronary reperfusion may limit myocardial injury in acute MI. A member of Dr Kapur's research team, Michele Esposito, was the winner of the Young Investigator Scholarship presented by the A-CURE Working Group. Dr Esposito described her study demonstrating that primary unloading causes a change in gene expression within the infarct zone that initiates a number of cardioprotective processes during acute MI. To close the morning session, Patrick Hunziker shared insights from his considerable experience of implanting Impella VADs.

The afternoon's presentations had a stronger focus on clinical and practical studies. The keynote speaker, Joseph Hill, discussed the global health and economic burden of heart failure, as well as describing the factors affecting myocardial plasticity. Mark Anderson presented a surgeon's perspective on cardiac unloading and myocardial recovery. William O'Neill presented data from the catheter-based VAD Registry™, a global observational clinical registry designed to monitor patient safety and real-world outcomes of patients supported with the Impella device. James Udelson discussed the practical difficulties of designing clinical trials to test the efficacy and safety of left VADs in a patient population where event rates are low. Michael Cohen discussed the benefits of post-conditioning at the time of reperfusion in acute MI. Ryan Tedford described the use of mechanical support for right-sided and biventricular failure. Finally, Derek Hausenloy identified other opportunities, in addition to unloading, for reducing infarct size following MI. Dr Kapur closed the meeting by acknowledging that the day had been ground-breaking in involving such a diversity of expertise from multiple disciplines.

Interventional Cardiology Review would like to thank all expert reviewers who contributed towards this edition. A special thanks goes to our editorial board for their continuing support and guidance. We hope that you find this supplement informative and interesting. ■

Acute MI to Heart Failure: the Past, the Present and the Future

Presented by Dr Eugene Braunwald

Brigham and Women's Hospital, Harvard Medical School and Partners Healthcare System, Boston, USA

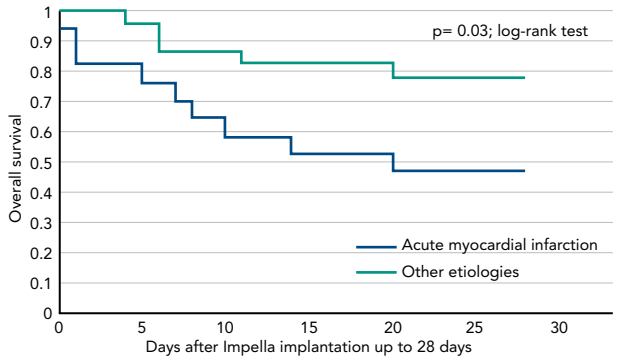
Dr Eugene Braunwald is one of the most eminent figures in modern cardiology and has authored more than 1,000 peer-reviewed publications. His work has increased current understanding of congestive heart failure, coronary artery disease and valvular heart disease. Among his notable works are the Thrombolysis in Myocardial Infarction studies, which elucidated the pathophysiology of acute myocardial infarction. He is also responsible for *Braunwald's Heart Disease*, the most widely read textbook of cardiology in the world.

Dr Braunwald began by discussing his early work on the determinants of myocardial oxygen consumption.[1,2] The idea that early reduction of myocardial oxygen demands and improvement of coronary perfusion might reduce infarct size dates back to the early 1970s.[2] This concept was advanced further in 1976 with the first publication of coronary reperfusion after coronary thrombolysis,[3] and in 1981 when it was proven that thrombolytic reperfusion salvaged myocardial tissue.[4] These findings led to the establishment of the Thrombolysis in Myocardial Infarction (TIMI) study group by the National Institutes of Health in 1985. Among this group's most important developments was the TIMI Risk Score, which assesses the risk of death and ischaemic events in patients experiencing unstable angina. The next major advance in the relationship between acute myocardial infarction (AMI) and heart failure (HF) was in 1987, when Pfeffer et al. found that the haemodynamic profile of chronic HF secondary to myocardial infarction (MI) could be pharmacologically altered in rats, but the improvements were significantly diminished in hearts with large infarcts.[5] This finding led to the first report of post-AMI cardiac remodelling in 1990.[6] These findings established the pathophysiological basis for the progression to HF in patients with AMI and were a key milestone toward the development of reperfusion strategies, including primary percutaneous coronary intervention (PCI). A 2013 study found that in Medicare beneficiaries, hospitalisation for HF following AMI decreased only slightly from 1998 to 2010 and that 1-year mortality remained essentially unchanged.[7] Until recently, it was not known whether the extent of coronary artery disease (CAD) was associated with the occurrence of HF after AMI. In a recent paper, however, atherosclerotic burden was found to be an indicator of post-MI HF regardless of HF type and independent of recurrent MI.[8] While it has been long established that the use of PCI to treat infarct arteries improves prognosis, in 2013 Wald et al. demonstrated the value of preventive PCI of non-infarct arteries with major stenosis in patients with ST-elevation myocardial infarction and multivessel CAD undergoing infarct artery PCI. Preventive PCI significantly reduced the risk of major adverse cardiac events in these patients.[11]

Dr Braunwald then turned his focus to the challenges faced in the management of AMI complicated by cardiogenic shock (CS). An acute ST-elevation myocardial infarction complicated by CS is associated with high mortality and CS is the leading cause of death in patients with AMI. A recent study used the Cath-PCI Registry® to evaluate trends in demographics, clinical characteristics, management strategies and in-hospital outcomes in patients with CS-AMI who underwent PCI from 2005 to 2013. The study found that, despite the evolution of medical technology and contemporary therapeutic measures, in-hospital mortality of AMI-CS patients continues to rise.[9] There is a need to improve outcomes in these patients. Another recent study found that survivors of AMI-CS had a higher risk of death and/or hospitalisation during the first year after discharge compared to those without CS, and that the risk was highest in the early post-discharge period (first 60 days). After this time, the prognosis was similar in patients with or without CS.[10]

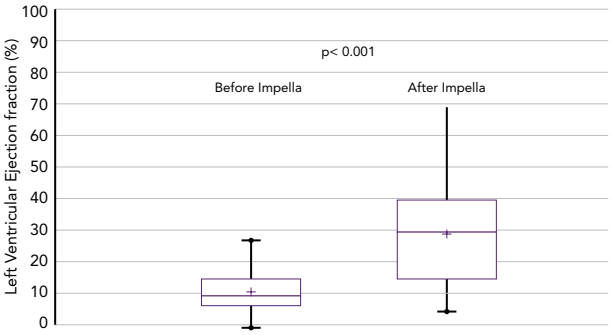
The failure of pharmacological treatments to maintain adequate perfusion and to prevent irreversible end-organ failure in many patients with CS has led to attempts to improve outcomes by mechanical circulatory support (MCS) devices. Until recently, initiation of MCS with an intra-aortic balloon had a class I recommendation for the treatment for CS-AMI and had become widely used. However, a 2012 study found that use of the intra-aortic balloon did not

Figure 1: Use of the Impella 5.0 for refractory cardiogenic shock: 28 day survival



Source: Gaudard et al, 2015[15]

Figure 2: the Impella 5.0 for refractory cardiogenic shock: effect on left ventricular ejection fraction



reduce 30-day mortality in patients with MI and CS.[12] In recent years, the use of percutaneously-inserted left ventricular assist devices prior to PCI has become increasingly important. The TandemHeart™ (CardiacAssist Inc) has proven beneficial in patients in severe CS refractory to intra-aortic balloon pump and vasopressor therapy, but CS patients still had worse outcomes in terms of mortality than those without CS.[13] A 2014 study showed that early use of the Impella® 2.5 prior to PCI was associated with more complete revascularisation and improved survival in the setting of refractory CS-AMI.[14] The Impella 5.0 has also been studied for CS resulting from AMI, dilated cardiomyopathy and postcardiotomy cardiac failure: this has demonstrated impressive outcomes in terms of mortality (see *Figure 1*). Furthermore, following removal of the Impella, patients' left ventricular ejection fraction improved significantly ($p<0.001$) when compared to baseline (see *Figure 2*).[15]

As a result of these findings, the 2015 clinical expert consensus statement on the use of percutaneous MCS devices in cardiovascular care stated that percutaneous MCS provides superior haemodynamic support compared to pharmacological therapy. The guidelines also stated that in profound CS, MCS using intra-aortic balloon is less likely to provide benefit than continuous flow pumps. Dr Braunwald discussed the importance of early placement of an appropriate MCS as being key in patients in CS who fail to stabilise or quickly show improvement after initial intervention. Furthermore, MCS may be considered for patients undergoing high-risk PCI.[16]

Dr Braunwald emphasised the need to develop strategies to reduce reperfusion injury, which is a major contributor to the final myocardial infarct size. There is also a need to reduce myocardial oxygen demands and to initiate early pharmacological treatment to reduce ventricular size and diminish wall stress. Secondary prevention of recurrent AMI is also important. This should involve intensive reduction of low-density lipoprotein through the use of proprotein convertase subtilisin/kexin type 9 inhibitors to reduce recurrent AMI.

Dr Braunwald concluded by emphasising that early application of these new MCS devices is needed in AMI-CS and acute, decompensated HF. Brief, temporary MCS should be applied for a longer period and may become a bridge to surgically-implanted durable left ventricular assist devices, biventricular assist devices, cardiac transplantation and recovery. ■

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The Science Behind Acute Ventricular and Myocardial Unloading

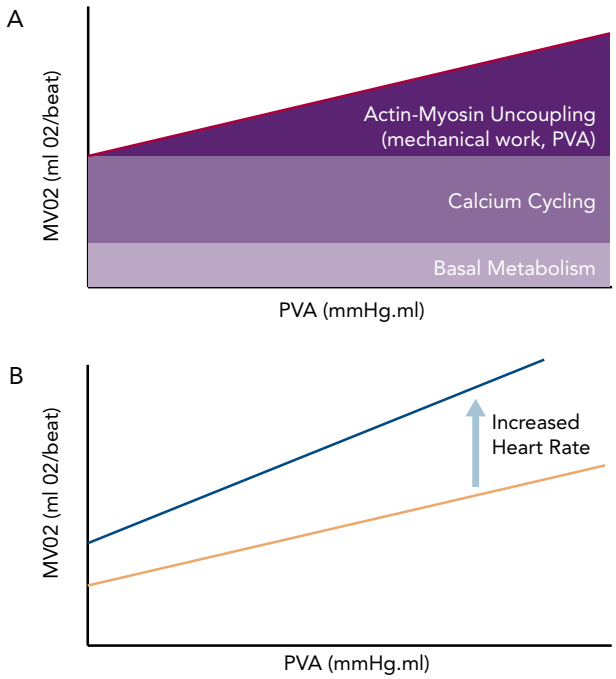
Presented by Daniel Burkhoff

Cardiovascular Research Foundation and Columbia University, New York, USA

Dr Burkhoff is an Associate Professor of Medicine at Columbia University, Division of Cardiology. He has authored more than 200 peer-reviewed publications. He is a world expert in pressure–volume relationships in the heart.

Dr Burkhoff began his presentation by outlining clinical goals in the setting of acute myocardial insult, including myocardial infarction, cardiogenic shock and chronic heart disease. These goals include myocardial salvage to minimise the amount of myocyte loss and to prevent, or at least limit, myocardial and ventricular remodelling with the aim of maintaining normal left ventricular (LV) size and function. Another important goal is to improve both short- and long-term survival: this is poor in patients presenting with cardiogenic shock in the first 30 days, and the risk of death persists over several years. The major physiological goals are to achieve a normal haemodynamic profile in terms of cardiac output, mean arterial pressure, central venous pressure and pulmonary capillary wedge pressure. However, these approaches do not specifically target myocardial injury in acute myocardial infarction (AMI). It is also

Figure 1a): Relationship between oxygen consumption and PVA; b) Impact of heart rate



important to reduce LV preload pressure to prevent acute stretch of the ventricular wall and subsequent remodelling, and to minimise myocardial oxygen consumption. Dr Burkhoff emphasised how myocardial oxygen consumption – the major contributors to which are heart rate, LV contractility and myocardial mechanical work (pressure–volume work) – may be influenced by cardiac unloading.

An important concept underlying the lack of success of pharmacological interventions such as inotropes in the treatment of AMI is that these approaches increase the power expenditure of the heart, thereby increasing the stress placed on the organ. This contrasts with what occurs in acute LV unloading. Acute cardiac unloading is defined as the reduction of total mechanical power expenditure (as opposed to work) of the ventricle, which correlates with reduction in myocardial oxygen consumption and the haemodynamic forces that lead to ventricular remodelling.

The use of LV support has been an area of active clinical research since the mid-1990s. In 2003, Meyns et al. first reported that the use of an early version of the Impella® (Abiomed) device reduced infarct size in animal models. This study also found that the area of infarct is related to oxygen consumption during ischaemia and reperfusion.[1] The index of myocardial work that correlates most closely with myocardial oxygen consumption is known as the pressure–volume area (PVA). This is the sum of the stroke work and the potential energy, i.e. the energy that is stored in the myocardial filaments after contraction rather than being released as external work. Heart rate and contractility are also important determinants of myocardial oxygen consumption. There is a linear relationship between PVA and myocardial oxygen consumption, and this relationship increases with increased contractility.[2] It is worth noting that there is still a substantial amount of oxygen consumption in the absence of mechanical work, which is needed for the basal metabolism of cells as well as the processes of calcium cycling responsible for contractile activation. Increasing contractility

Figure 2: Effect of the Impella on LV loading and energetics

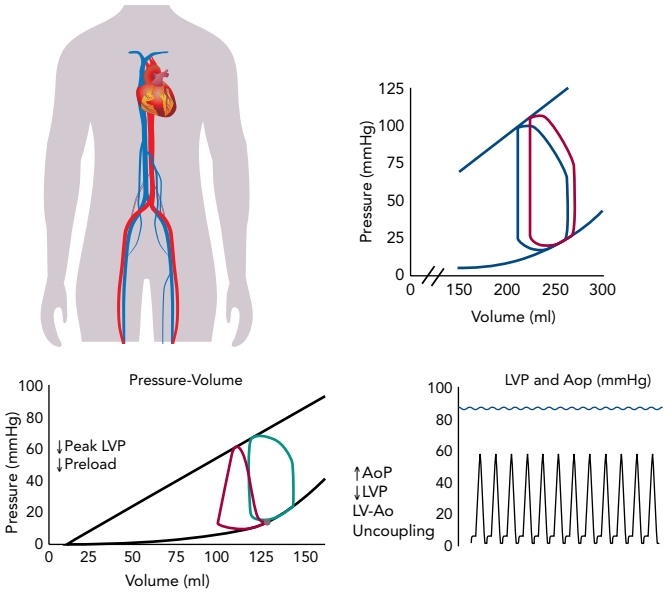
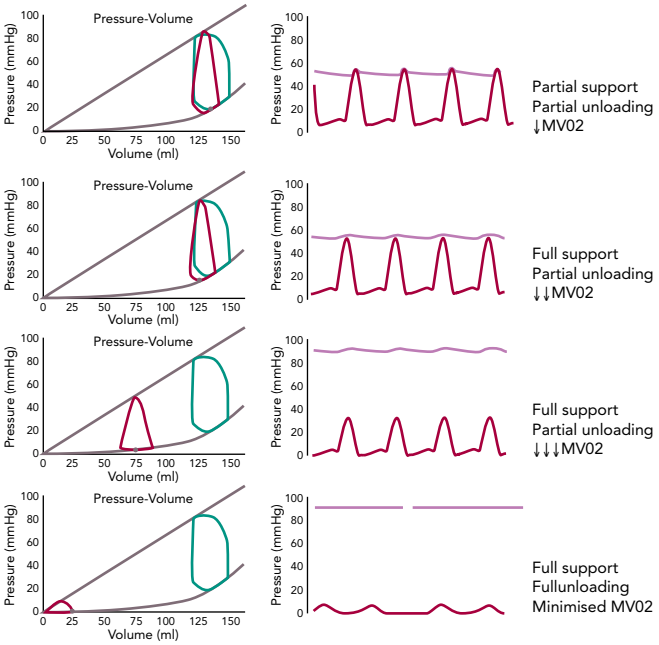


Figure 3: 'Dose dependence' of unloading



increases both calcium cycling and oxygen consumption. Heart rate has a significant impact on the relationship between oxygen consumption and PVA because each contraction involves the release of calcium and oxygen consumption, increasing the intercept and slope (see *Figure 1*).

The physiological goals of myocardial unloading may be achieved by various means. These include pharmacological interactions involving ionotropic agents or vasopressors and the use of mechanical circulatory support (MCS) devices. The use of ionotropes increases heart rate, contractility and PVA, while the use of vasopressors increases total peripheral resistance. Since the resulting increase in heart rate has a detrimental effect on oxygen consumption, if cardiac recovery is a therapeutic goal the use of these agents should be minimised.

Dr Burkhoff next compared the available MCS devices, including the intra-aortic balloon pump, the shortcomings of which were discussed in Dr Braunwald's presentation. Another device, the TandemHeart™ (CardiacAssist Inc), is a left ventricular assist device that pumps blood from the left atrium to the aorta. Implantation requires trans-septal puncture, which may be a challenging procedure in an acute setting. A third MCS, peripheral extracorporeal membrane oxygenation (ECMO), is an intervention that draws blood from the vena cava and pumps it into the descending aorta, but this increases the LV afterload. The Impella ventricular support device aspirates blood from the left ventricle into the aorta. Since these four devices take blood from different regions of the heart, they have different effects on LV energetics.[3] Each device has a characteristic impact on the pressure–volume loop.

While the patient is on peripheral ECMO support, the left ventricle must eject blood through the aorta. The ventricular end diastolic pressure will therefore rise to accommodate the increase in arterial pressure resulting from ECMO support. This results in an increase in the preload on the ventricle, and as a consequence the PVA and oxygen consumption increase. This is energetically unfavourable to the heart. Furthermore, the increased diastolic ventricular pressures can actually promote detrimental myocardial remodelling.

The Impella device has the opposite effect on myocardial energetics. It functions by aspirating blood directly from the ventricle into the aorta. As a result, the pressure–volume loop shifts left towards a lower volume, end diastolic pressure is reduced and PVA decreases. Since the reduction in the PVA means a reduction in myocardium oxygen demand, this effect is favourable (see *Figure 2*). Also important is the concept of LV–aortic uncoupling. If sufficient unloading is provided, the maximum pressure generation of the ventricle is reduced. If this pressure falls below the mean arterial pressure, the aortic valve will not open and blood is no longer ejected from the ventricle, thereby minimising the mechanical work of the heart. In this way, LV–aortic pumping alone maintains sufficient cardiac output and aortic pressure is uncoupled from LV function. Thus, acute unloading can greatly decrease myocardial energy consumption and the haemodynamic forces that drive ventricular remodelling processes. This is contrary to pharmacological interventions such as inotropes, that increase myocardial energy consumption and exacerbate unfavourable haemodynamic forces. The use of the Impella can thus potentially replace inotropes and avoid these detrimental effects, all while achieving physiological goals.

Dr Burkhoff discussed the important concept of the dose dependence of unloading, i.e. the relationship between the degree of support and degree of unloading. It is important to distinguish between partial support/partial unloading and full support/full unloading, and to understand that unloading and support are not necessarily equivalent (see *Figure 3*). Partial support and partial unloading occurs when the heart continues to provide some of the cardiac output while the device provides the rest. In this scenario, the aortic valve still opens and closes and the heart ejects blood. In full support/partial unloading the entire cardiac output is provided by the MCS. In this scenario, the entire cardiac output is provided by the device, the heart is not ejecting blood and the aortic pressure is uncoupled from ventricular function. Oxygen consumption is reduced. During full support/partial unloading, however, the volume unloading of the ventricle is not maximised. Maximum reduction in ventricular volume and oxygen consumption is achieved during full support/full unloading. In this scenario, mechanical support is increased such that the ventricular preload (volume) is minimised. This shifts the pressure–volume relationship further leftward, minimising the PVA.

In summary, with acute haemodynamic compromise in the setting of myocardial insult, the aims are to restore normal haemodynamics, minimise LV filling pressure, minimise oxygen consumption, prevent remodelling and enhance myocardial salvage. Unlike MCS, pharmacological approaches increase oxygen consumption and increase the load on the left ventricle. Different methods of MCS have different effects on haemodynamics and myocardial energetics. Venous-to-aortic devices do not unload the heart or reduce oxygen consumption, whereas left ventricle-to-aorta devices do. The latter also uncouple the left ventricle and aorta, allowing for unloading of the left ventricle while restoring arterial blood pressure and flow. ■

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Neuromechanical Unloading for Acute Myocardial Infarction

Presented by Kenjo Sunagawa

Center for Cardivascular Medicine, Kyushu University, Fukuoka, Japan

Kenji Sunagawa is the founder and Professor of the Center for Disruptive Cardiovascular Medicine at Kyushu University, Fukuoka, Japan. He joined the cardiovascular group at the Department of Biomedical Engineering, Johns Hopkins University, in 1978 and helped establish the concept of the pressure–volume relationship of the heart.

Dr Sunagawa began by highlighting the concept of ischaemia as an imbalance between oxygen supply and demand. Previous interventions have focused on increasing oxygen supply, but this approach may be insufficient to improve outcomes. Mechanical

unloading has the effect of decreasing oxygen demand and can be considered 'functional reperfusion'. However, while it is possible to dramatically reduce myocardial oxygen consumption by the use of left ventricular assist devices (LVADs), Dr Sunagawa is exploring additional complementary approaches to further reduce myocardial oxygen demand to provide cardiac protection.

Another approach to myocardial protection is vagal nerve stimulation (VNS). It is well established that VNS has anti-ischaemic effects. These are mediated by complex mechanisms, including heart rate reduction, anti-adrenergic effects and anti-inflammatory effects (see *Figure 1*).[1] Various preclinical studies have demonstrated that VNS results in marked reductions in infarct size following acute myocardial infarction.[1–6] Since VNS removes acute myocardial infarction-induced neuromechanical and inflammatory stress, it has been termed neural unloading.

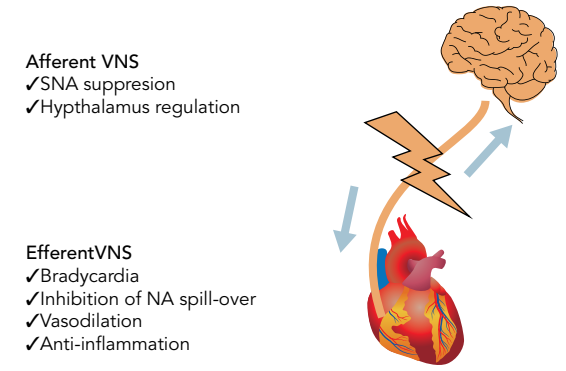
This technique of neural unloading has recently been investigated in conjunction with mechanical unloading. In order to stimulate the vagal nerve in a minimally invasive manner, a catheter with electrodes was inserted into the superior vena cava of a dog. This rapidly decreased the heart rate and, as a consequence, reduced myocardial oxygen consumption by >50%.[7]

In order to investigate the impact of this investigation on infarct size, an ischaemia reperfusion model was created in 24 dogs by occluding the left anterior descending coronary artery for 180 minutes and then reperfusing. Left ventricular unloading was performed with the Impella CP® (Abiomed) device. Transvascular VNS was performed with a pacing catheter in the superior vena cava. The neuromechanical unloading started 90 minutes after the onset of ischaemia and ended 60 minutes after reperfusion. Dogs were then assigned to one of four groups: ischaemia reperfusion (n=7), LVAD (n=6), VNS (n=4) and LVAD plus VNS (n=5). One month after the intervention, the infarct size and cardiac function were compared. The use of LVAD plus VNS reduced the infarct size by >70% ($p<0.05$; see *Figure 2*).[8]

This combined strategy of mechanical and neural unloading is clearly a powerful intervention and provides almost complete ventricular support. A key factor underlying the success of this approach is the heart rate reduction provided by the combined technique. It has therefore been hypothesised that the combination of mechanical circulatory support and pharmacological heart rate reduction may be beneficial in acute myocardial infarction. The I_f inhibitor ivabradine is a bradycardic agent; ongoing studies are investigating the combination of ivabradine and LVADs on oxygen consumption in acute myocardial infarction.[9]

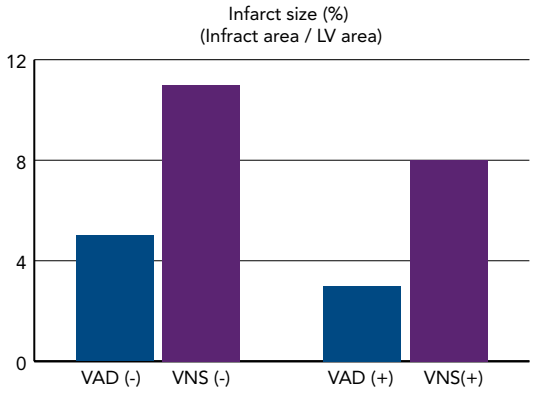
Dr Sunagwa concluded that the combination of LVAD and VNS synergistically reduces infarct size beyond that observed by LVAD unloading alone, preserves left ventricular function, and prevents heart failure in the long term. In order to establish total unloading as a treatment for acute myocardial infarction in humans, the development of higher flow percutaneous pumps is essential. In addition to this, in order to maximise the beneficial impacts, the simultaneous regulation of LVAD and VNS needs to be optimised in further studies. ■

Figure 1: Cardioprotective effects of VNS



VNS = vagal verve stimulation; SNA = sympathetic nerve activity; NA = nerve activity.

Figure 2: Reduction of infarct size with combined mechanical and neural unloading



VAD = ventricular assiste device; VNS = vagal nerve stimulation

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Primary Left Ventricular Unloading and the Mechanical Conditioning Hypothesis

Presented by Navin K Kapur

Cardiac Biology Research Center, Tufts Medical Center, Boston, USA

Dr Kapur is an Associate Professor in the Department of Medicine at Tufts Medical Center. His research focuses on acute and chronic heart failure, circulatory support device development and cardioprotective mechanisms in the setting of acute myocardial infarction.

Dr Kapur began by considering the reasons for the paradigm shift in interventional therapy targeting ischaemia-reperfusion injuries. The past decade has seen a transition in outcomes for patients presenting with acute myocardial infarction (AMI). A cohort study (n=7,733) of older patients with first myocardial infarction (MI) showed that although the in-hospital mortality decreased by 28 % over 5 years, the 5-year incidence of heart failure increased by 25 %.[1] The burden of ischaemic heart failure has become the new challenge in the treatment of MI. The current treatment paradigm focuses on rapid reperfusion to limit myocardial damage. However, the significant improvement in door-to-balloon times (DBTs) in the past 10 years (to <90 minutes) has had no impact on mortality rates, which remain at around 7 % for patients with anterior MI and 27 % for those with cardiogenic shock.[2]

Dr Kapur maintained that reperfusion has become a double-edged sword: while prolonged ischaemia can cause substantial injury, restoration of perfusion to the ischaemic heart can exacerbate tissue damage. DBTs have decreased because of the adage that 'time is muscle'. When a coronary vessel becomes occluded, the acute ischaemic insult activates a process within cardiac myocytes involving a decrease in oxidative phosphorylation and adenosine triphosphate synthesis, which leads to a decrease in intracellular pH due to calcium influx and lactate elevations within these myocytes. This can lead to downstream effects on coronary function whereby the mitochondria become dysfunctional, generate reactive oxygen species and may even burst, resulting in cell death and necrosis. The current treatment of reperfusion creates a feed-forward mechanism, inducing further mitochondrial and oxidative damage. However, the body has an inherent counter-regulatory mechanism. First, at the endothelial level, endogenous tissue plasminogen activator attempts to autolyse thrombotic occlusions. At the cardiac myocyte level, there is a significant increase in salvage kinase activation, largely of extracellular-regulated kinase and protein kinase B. These kinases initiate an antiapoptotic signalling pathway designed to counteract the effect of reperfusion injury.

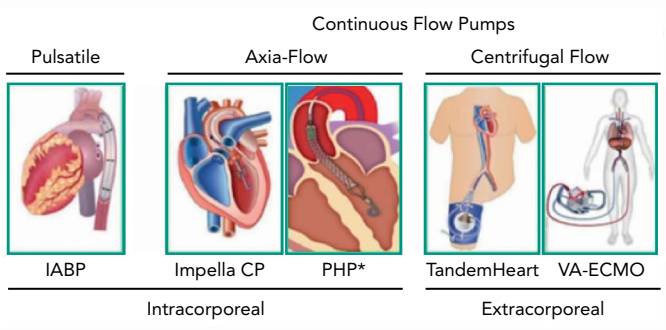
It is clear that many barriers exist to cardioprotective approaches and numerous drug trials attempting cardioprotection in the setting of AMI have failed. The critical barriers to success have been the mandate for rapid coronary reperfusion (i.e. DBT), the inability to target multiple cascades affecting reperfusion injury and the challenges of managing haemodynamic instability. A recent editorial critically appraised current approaches and asked the question: is it time to give up on cardioprotection?[3] Pre-ischaemic conditioning is not feasible, post-ischaemic conditioning has limited feasibility, and studies have been inconclusive. Remote ischaemic conditioning has been associated with limited efficacy and findings have not been conclusive. There is therefore a need for new approaches to cardioprotection in AMI.

A key theme of the A-CURE meeting is the novel paradigm of limiting myocardial ischaemia by minimising oxygen demand then restoring oxygen supply, a procedure that has been termed functional reperfusion. Insights from the surgical management of ST-elevation MI have taught us that a procedure beginning with unloading (cardiopulmonary bypass) followed by reperfusing ischaemic myocardium results the in restoration of coronary function.[4] However, this surgical mindset contrasts with the interventional approach and has not been adopted due to our limited ability to unload the myocardium without major cardiac surgery.

Over the past decade, a number of percutaneous mechanical circulatory support devices have become available (see *Figure 1*) and these have been described in previous presentations. The earliest work with intra-aortic balloon pumps showed that initiating mechanical support during infusion and reperfusion can reduce infarct size.[5] This model is limited, however, in that the device is activated at the onset of ischaemia and remains on throughout reperfusion, so it is hard to translate to clinical use. Further studies have used axial-flow pumps (Impella®, Abiomed) as a direct left ventricular (LV) loading mechanism and focussed not only on activation timing but also investigated the concept of total and partial unloading. An early study in sheep found that if Impella is activated during reperfusion alone, the degree of unloading correlates with a reduction in infarct size.[6]

Dr Kapur's team has been investigating the novel hypothesis that initially reducing LV work and delaying coronary reperfusion may limit myocardial injury in AMI. The choice of delayed reperfusion was driven by necessity in order to replicate events in the catheterisation laboratory. The study employed the TandemHeart® (CardiacAssist Inc) device, which requires transseptal implantation and the use of two large cannulas that take time to implant. Fortuitously, the delayed reperfusion proved to be one of the critical components in translating acute unloading to the setting of AMI. The study used a closed chest swine model, again replicating typical events in the catheterisation laboratory. In the MI group (n=4), MI was induced by occlusion of the left anterior descending (LAD) artery for 120 minutes, followed by 120 minutes of reperfusion without mechanical support. In the mechanically-supported group (MI plus unload; n=4), percutaneous left atrial-to-femoral artery bypass was initiated after 120 minutes of ischaemia, and LAD artery occlusion was prolonged for an additional 30 minutes, followed by 120 minutes of reperfusion with device

Figure 1: Mechanical Circulatory Support Devices



IABP = intra-aortic balloon pump; PHP = percutaneous heart pump; VA-ECMO = veno-arterial extracorporeal membrane oxygenation

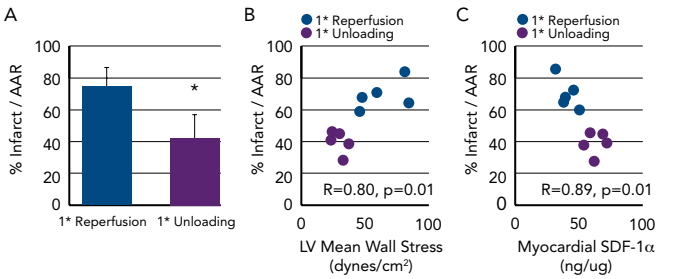
support. A significant reduction in infarct size was seen, which correlated with the reduction of LV stroke work.[7]

An editorial, published alongside this article, posed a number of questions. First, is it clinically feasible to use devices requiring transseptal implantation in the setting of AMI? What is the optimal timing of delayed reperfusion? What was the mechanism responsible for the beneficial effects?[8] These questions formed the basis of Dr Kapur's next studies. At the time he had been studying the feasibility of left atrial unloading compared with LV unloading and concluded that the Impella provided the most effective unloading signature, giving a reduction in LV pressure and volume. In addition, the Impella device eliminated the need for transseptal puncture arterial access. A study was designed to test the hypothesis that initially reducing LV work and extending the delay to coronary reperfusion may limit myocardial injury in AMI. In the primary reperfusion group, the LAD artery was reperfused for 120 minutes. In the primary unloading group, after 90 minutes of ischaemia the axial flow pump was activated and the LAD artery left-occluded for an additional 60 minutes, followed by 120 minutes of reperfusion. There was a significant 43 % reduction in infarct size in the primary unloading group compared to primary reperfusion (73 ± 13 % versus 42 ± 8 %; p=0.005). There was a correlation between infarct size reduction and LV wall stress.

Another interesting finding was that unloading activates biological cardioprotective processes, increasing myocardial levels of the chemokine stromal cell-derived factor (SDF)-1 alpha, and that the regression plot of infarct size against SDF-1 alpha levels in the myocardium was almost linear (R=0.89; p<0.01; see *Figure 2*).[9] This study led to the mechanical conditioning hypothesis: first unloading the LV, then delaying reperfusion activates a cardioprotective programme that limits myocardial damage in AMI (see *Figure 3*).[9]

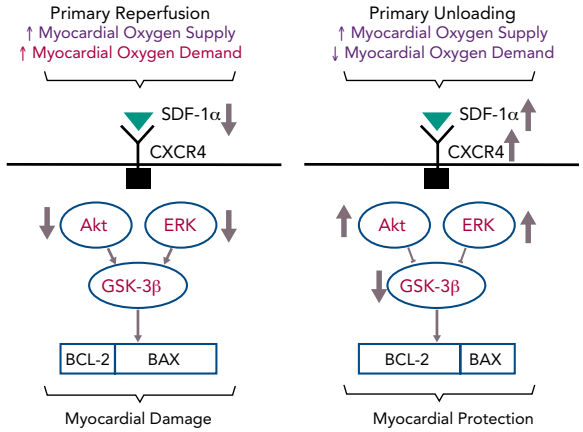
This hypothesis prompted further questions: how important is the delayed reperfusion? How important is the role of the kinases (i.e. is the mechanism primarily haemodynamic or biological)? What is the long-term effect of this intervention on LV recovery? Dr Kapur's team is addressing these questions in a number of ongoing studies. In one currently unpublished study, a series of animals were divided into groups with ischaemia reperfusion alone or a delay in reperfusion after activating the Impella device of 15, 30 and 60 minutes. In the final group, the Impella device was activated after balloon reperfusion. Results showed that 15–30 minutes of primary unloading was required to achieve infarct size reduction. A further study

Figure 2: Effect of Mechanical Circulatory Support Before Reperfusion in Acute Myocardial Infarction



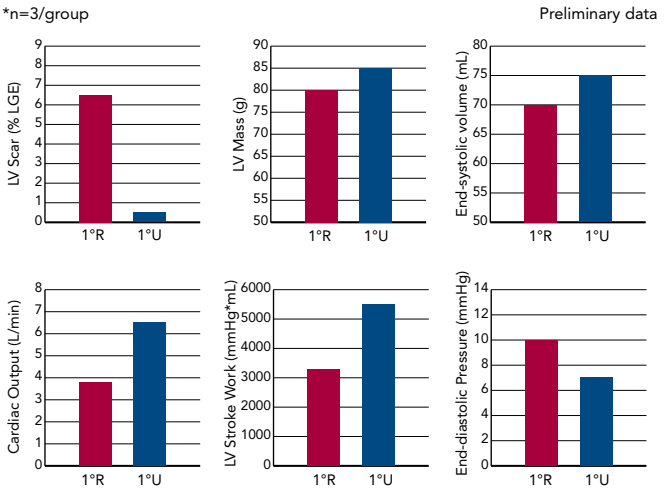
Source: Kapur et al, 2015.[9] AAR = assessment of the area at risk; LV = left ventricular; SDF-1 = stromal cell-derived factor 1

Figure 3: The Mechanical Conditioning Hypothesis



AKT = protein kinase B; BAX = BCL-2-associated protein; BCL-2 = B-cell lymphoma 2; CXCR4 = C-X-C chemokine receptor type 4; ERK = extracellular signal-regulated protein kinase; GSK-3β = glycogen synthase kinase 3 beta; SDF-1 = stromal cell-derived factor 1

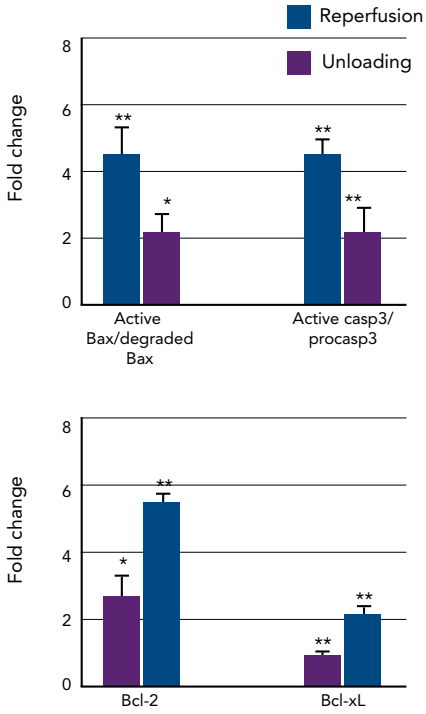
Figure 4: Primary Unloading Promotes Left Ventricular Remodelling: Preliminary Data



LGE = late gadolinium enhanced; LV = left ventricular; 1°R = primary reperfusion; 1°U = Primary unloading

investigated the biological mechanisms for this finding and found that delayed reperfusion is required to activate cardioprotective signalling involving SDF-1 alpha. In another set of studies, following occlusion of the LAD artery, C-X-C chemokine receptor type 4 inhibitors (which inhibit SDF-1 alpha influx) or kinase inhibitors were administered. Both interventions increased the infarct size, demonstrating that

Figure 5: The Effect of Primary Unloading on Apoptosis



Bcl-2 = B-cell lymphoma 2; Bcl-xL = B-cell lymphoma–extra large

loss of kinase function attenuates the cardioprotective effect of primary unloading. In the final study, SDF-1 alpha was administered via intracoronary delivery to try to augment its cardioprotective effect. However, it was not possible to further reduce the infarct size by this method.

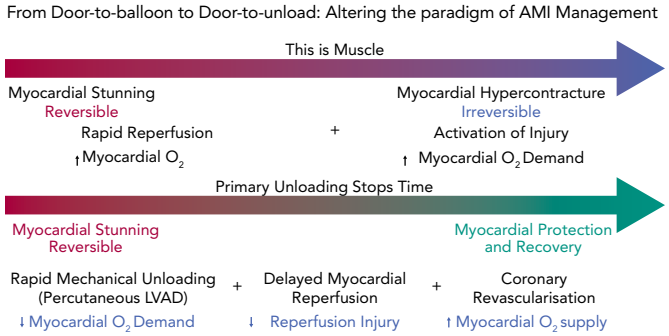
The final question – does acute unloading impact LV recovery? – was answered in a study with a 28-day follow-up period. In the primary reperfusion group, the infarct scar at 28 days was significantly larger than that in the primary unloading group. In terms of function, the primary reperfusion group showed a characteristic LAD artery infarct pattern whereas the primary unloading group showed primarily intact myocardium. Preliminary data (n=3) showed significant reductions in LV scar (see *Figure 4*).

In summary, there is a point at which the injury clock can be stopped and a protective process initiated that will limit the damage once reperfusion begins. This is the focus of Dr Kapur's future work.

Young Investigator Scholarship Presentation

Michele Esposito, a member of Dr Kapur's research team, presented the abstract that won the Young Investigator Scholarship awarded by the A-CURE Working Group. This study tested the hypothesis that primary unloading promotes myocardial salvage in AMI through regulation of gene expression within the infarct zone. The LAD artery of male pigs (n=4/group) was occluded for 90 minutes. In the primary reperfusion group, the LAD artery was reperfused for 120 minutes. In the primary unloading group, after 90 minutes of ischaemia a mechanical circulatory support device was activated and the LAD artery left-occluded for an additional 30 minutes, followed by 120 minutes of reperfusion. Myocardial infarct size was quantified by triphenyl tetrazolium chloride staining. Whole-transcript expression analysis was performed using a porcine microarray platform.

Figure 6: Changing the Paradigm in the Management of Acute Myocardial Infarction



AMI = acute myocardial infarction

Quantitative polymerase chain reaction confirmed the expression of select genes from regulated pathways. Scanning electron microscopy evaluated mitochondrial integrity within infarct zones. Sham operated LV samples were used as controls.

Consistent with previous studies, primary unloading reduced infarct size compared to reperfusion alone, from 65 % to 34 %. Gene expression analysis yielded a heat map representing the 2,200 genes significantly regulated by primary reperfusion or primary unloading ($p<0.01$). A significant shift in gene expression was seen: the primary unloading group showed a heat map similar to the sham controls. The investigators then identified a number of key regulatory pathways altered by primary unloading, including inflammatory and fibrotic pathways. Specifically, matrix metallopeptidases MMP2 and MMP9 were upregulated in the reperfusion group and downregulated in the unloading group. MMP2 and MMP9 are involved in the breakdown of extracellular matrix, leading to adverse remodelling, and are markers of inflammatory response.

In the reperfusion group, there was increased expression in SMAD3, an intracellular signal transducer and transcriptional modulator that, following mechanical stretch, is phosphorylated by transforming growth factor-beta, and then converts fibroblasts to myofibroblasts, increasing adverse remodelling. Expression of genes in the electron transfer chain, which is responsible for adenosine triphosphate synthesis and other important pathways involved in cellular metabolism, was decreased in the reperfusion group compared with the unloading and sham groups, suggesting that unloading preserves the integrity of the electron transfer chain during AMI.

Finally, examination of mitochondrial integrity revealed a significantly increased number of intact mitochondria per cardiac myocyte in the unloading versus reperfusion group. Since mitochondrial function is linked to apoptosis, key components of the apoptotic pathway were examined. A higher density of the pro-apoptotic active BAX protein and procaspase-3 were seen in the reperfusion group, whereas higher densities of degraded, inactive, BAX and caspase-3 were seen in the sham and unloading groups. Higher levels of antiapoptotic agents B-cell lymphoma 2 and B-cell lymphoma–extra large were identified in the unloading group (see *Figure 5*).

In summary, this study identified for the first time that primary unloading triggers a global shift in gene expression within the infarct

zone that is associated with preserved mitochondrial integrity and cellular respiration, reduced apoptosis, inflammation and fibrosis during the acute phase of MI. These data suggest that unloading the left ventricle and delaying reperfusion promotes cardioprotective signalling and may be a novel approach to limiting myocardial damage during AMI and preventing the subsequent development of ischaemic heart failure.

Dr Kapur concluded by stating that the burden of ischaemic heart failure will grow and that new approaches to cardioprotection in AMI are needed. Primary unloading reduces infarct size through a two-pronged approach: first by reducing the wavefront of MI and second by activating a cardioprotective process (see *Figure 6*). However, prospective randomised controlled studies are required to test the clinical validity of these preclinical findings. ■

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Cardiac Unloading and Recovery in Cardiogenic Shock: From Disease Modelling to Real Patients

Presented by Patrick Hunziker

Medical Intensive Care Unit and Cardiology, University Hospital Basel, Switzerland

Professor Patrick Hunziker is the Deputy Chief of the Intensive Care Unit of the University Hospital Basel. He obtained his MD from the University of Zurich with post-graduate training at Massachusetts General Hospital and Harvard Medical School. Professor Hunziker has authored more than 140 peer-reviewed articles.

Professor Hunziker began by discussing the need for and limitations of evidence-based medicine. While it is established that the strongest evidence for a therapeutic intervention is obtained from a systematic review of randomised controlled trials involving a homogeneous patient population, each human is unique. There are more potential human phenotypes than atoms in the universe. Similarly, the risk factors for cardiovascular disease are so numerous that it is impossible to produce an algorithm for assessing risk in clinical practice. In addition, acute myocardial infarction (AMI) is a disease that changes over time and is a different disease even after 3 hours. Considering these factors, the conventional requirements of a clinical trial (i.e. a homogeneous patient population) do not exist.

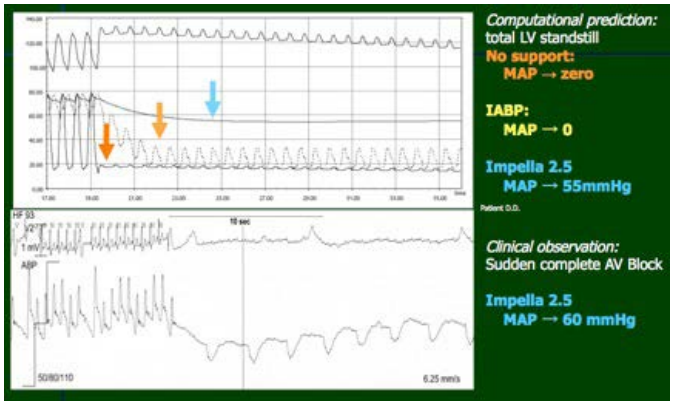
There is a need for knowledge-based, individualised medicine with an emphasis on an interdisciplinary approach. We must focus on and learn from individual patients, employing personalised treatment modalities, and adapt treatment regimens on a case-by-case basis. In AMI, our priority should be the avoidance of death and minimising myocardial necrosis through improved hospital management, the use of percutaneous coronary intervention (PCI) in unstable patients and the management of cardiogenic shock (CS).

Prof Hunziker has implanted around 300 Impella® (Abiomed) devices and provided practical insights from his experience of using bedside simulations. The first case was of a patient in severe arrhythmia. The mean arterial pressure (MAP) was zero. The use of an intra-aortic balloon pump had no effect on MAP; however, the use of the Impella raised the MAP to 55 mmHg (see *Figure 1*). The same patient subsequently experienced sudden complete atrioventricular block. By using the Impella 2.5 in this patient, MAP was maintained at 60 mmHg. In the second case, a patient presented with profound left ventricular (LV) failure. Combining mechanical support and vasodilators proved effective in this patient, and had a beneficial effect on oxygen consumption. In both cases, mechanical support by the Impella gave the physician the advantage of restoring MAP (and perfusion pressure), even in the absence of cardiac function.

There is a need to optimise the use of mechanical circulatory support (MCS) devices in routine clinical practice. One paradigm currently under investigation is the combined use of MCS and vasodilators in order to optimise organ perfusion in CS, as well as minimising LV wall stress and LV work. A LV assist device (Impella) is employed first, followed by the administration of vasodilator drugs (nitrates or angiotensin-converting-enzyme inhibitors) with a target MAP of 65 mmHg (see *Figure 2*).

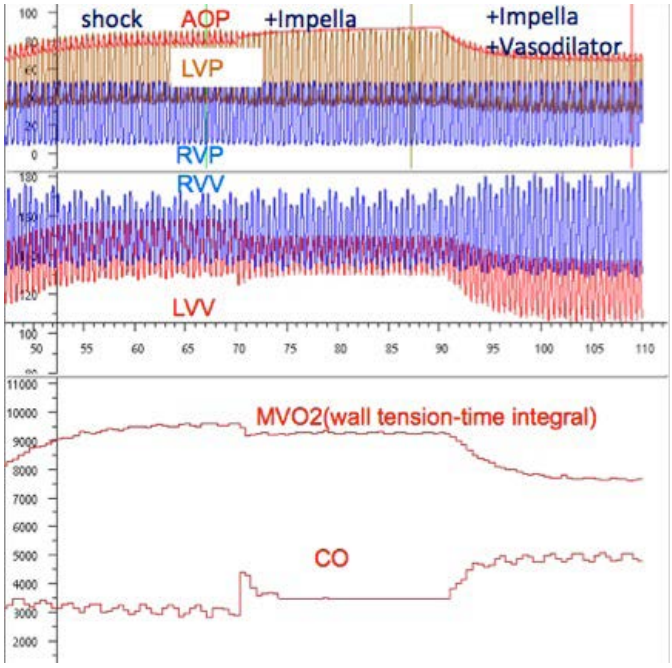
In order to further develop the use of the Impella in CS, there is a need for improved monitoring and a willingness to change approaches based on haemodynamic data. The most important factor in the treatment of CS is time; early haemodynamic support is essential to avoid a systemic inflammatory response. Operator speed is crucial and increases with experience. It is feasible that implantation time

Figure 1: The Use of Mechanical Circulatory Support in Severe Arrhythmia



AV = atrioventricular; IABP = intra-aortic balloon pump; LV = left ventricular; MAP = mean arterial pressure

Figure 2: The Combined Use of Vasodilators and Mechanical Circulatory Support in Acute Myocardial Infarction

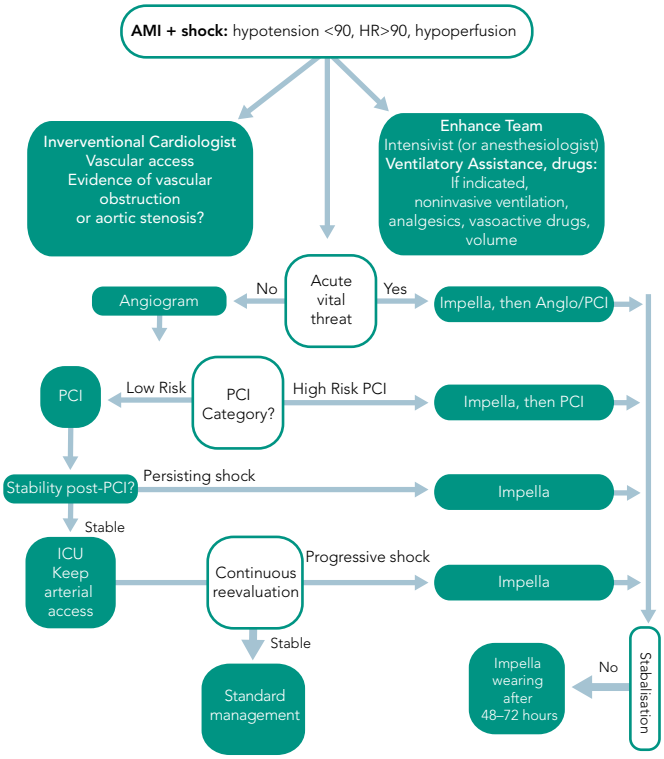


AOP = arterial blood pressure; LVP = left ventricular pressure; LVV = left ventricular volume; MVO2 = myocardial oxygen consumption; RVP = right ventricular pressure; RVV = right ventricular volume;

may be reduced to 1–2 minutes in the future. However, it is also vital to optimise treatment decisions by correctly incorporating the use of the Impella device within current treatment algorithms.

While it may be easy to identify CS, deciding in which patients we should delay reperfusion is less straightforward. *Figure 3* shows an algorithm proposed by Prof Hunziker for the treatment of patients presenting with AMI and CS. This algorithm highlights the heterogeneity within both the patient population and the treatment of AMI itself. In selecting patients to undergo Impella implantation, it

Figure 3: Proposed Algorithm for the Treatment of Acute Myocardial Infarction and Cardiogenic Shock



AMI = acute myocardial infarction; ICU = intensive care unit. PCI = percutaneous coronary intervention

is useful to consider the potential for brain stem recovery if patients are supported early and given adequate therapies.

This presentation sparked a debate about whether current evidence was sufficient to provide haemodynamic support at small centres. Around 60 % of cases of CS are treated at small centres in the US, with a potential delay caused by patient transportation to a larger centre. In many cases, some form of advanced haemodynamic support might allow these sites to either reperfuse more safely on site and/or facilitate the safer transfer of these patients to expert facilities. The question was raised as to whether all primary PCI centres should be mandated to Impella. The consensus opinion was not at this time but perhaps this will develop over the coming years. Prof Hunziker strongly encouraged centres with primary PCI capability to start MCS on site but to be in close communication with a central hub. There was a recognised lack of sufficient evidence to indicate that MCS be initiated in these centres followed by patient transfer. Problems relating to geography may become an important factor, as journey times to a central hub may be long in some regions.

Prof Hunziker concluded by observing that the A-CURE symposium provides an excellent platform for future progress towards new paradigms in AMI and cardiopulmonary resuscitation. The use of modelling and monitoring will enable the optimal use of new technologies for personalised disease management. ■

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Keynote Speech

Heart Failure: The Path Ahead

Presented by Joseph A Hill

UT Southwestern Medical Centre, Dallas, TX, USA

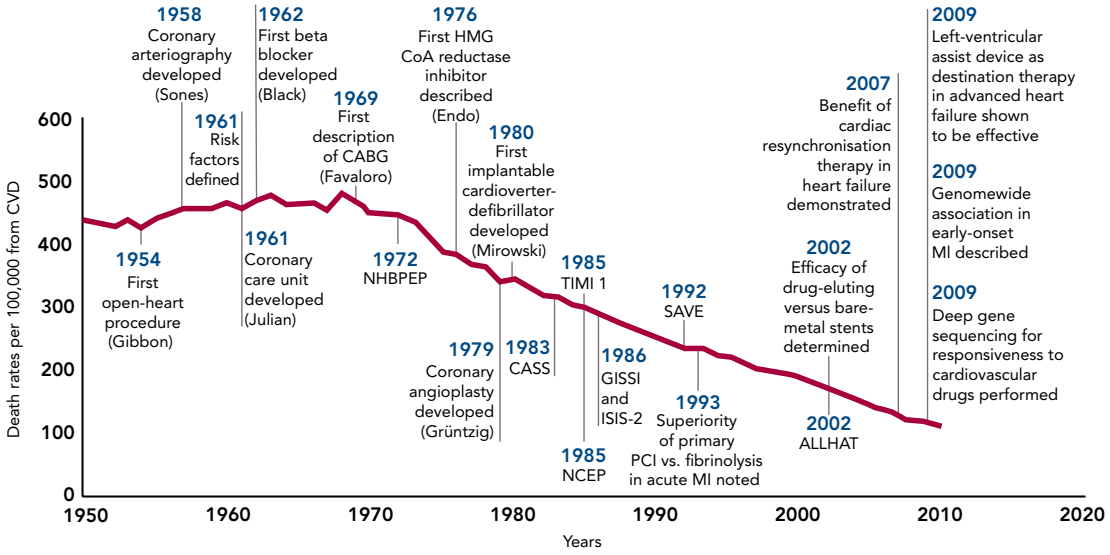
Joseph Hill is a Professor in the Department of Internal Medicine's Division of Cardiology and the Department of Molecular Biology at UT Southwestern Medical Center and is the Chief of Cardiology and Director of UT Southwestern's Harry S Moss Heart Center. He is the current Editor-in-Chief of *Circulation*.

Professor Hill's presentation placed the concept of myocardial unloading into the broader topic of heart failure (HF), a growing clinical, economic and social problem due to its increasing incidence and poor prognosis. At present we cure very few diseases but instead turn acute disease into chronic disease, which we manage progressively. Thanks to numerous clinical advances in the management of acute myocardial infarction (MI), in-hospital mortality has fallen substantially, from 30 % in the 1960s to around 2–3 % today, and we are moving into an era of lifelong disease management.[1] The decreased mortality from cardiovascular disease is impressive when compared to other diseases. The decline in age-adjusted mortality in relation to scientific advances is 75 % (see *Figure 1*); by comparison, the reduction for cancer is 10 %.[1] However, this reduction in MI mortality has been accompanied by an increased incidence of HF[2,3] and thus, despite these successes, cardiovascular disease remains the leading cause of death worldwide. There is a need to halt the rise in HF incidence. This has led to an upsurge in interest in mechanical circulatory support devices, which form the focus of the symposium.

A major cause of HF is cardiac remodelling due to hypertrophic growth, the primary mechanism by which the heart reduces stress on the ventricular wall. The heart is a remarkably plastic organ and can grow by up to 50 % under different circumstances including exercise and pregnancy, but also in pathological conditions such as hypertension and infarction.[4] These changes can occur rapidly. The heart can also atrophy by up to 70 % in situations such as the use of implantable ventricular assist devices, cancer and bed rest.[4] Factors contributing to remodelling include elevated preload, ischaemia, metabolic and neurohumoral factors. One signalling pathway known to be responsible for disease-related plasticity involves class I and II histone deacetylases (HDACs). If a heart is exposed to thoracic aortic constriction to increase afterload, it will grow by about 40 %. If the heart is then exposed to a broad-spectrum inhibitor of HDACs, the growth response is halved, suggesting that some of the growth is HDAC-dependent.[5] HDAC inhibitors can also reverse pathological cardiac hypertrophy and restore cardiac function by suppressing autophagy.[6]

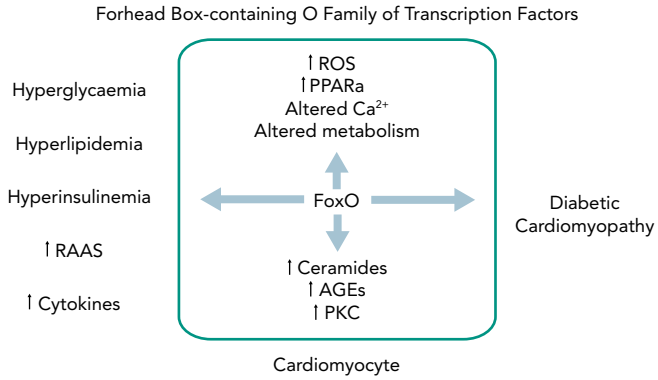
Another example of myocardial plasticity focuses on metabolic stress due to the deterioration of healthy lifestyles.[7] Obesity trends in the US over the past 25 years show astounding changes in prevalence. In 1995, all US states had obesity rates >10 %. By 2000, only one state had obesity rates <15 % and rates of 20–24 % emerged. By 2005 we saw the emergence of obesity rates >30 %. By 2010, all states had obesity rates of at least 20–24 %.[8] These trends in obesity are now being seen worldwide[9] and are accompanied by the rising prevalence of diabetes. It is

Figure 1: Decline in Deaths from Cardiovascular Disease in Relation to Scientific Advances



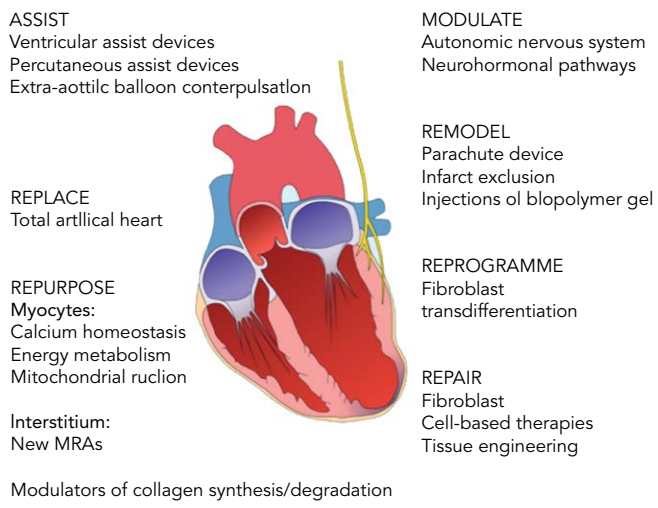
ALLHAT = Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial; CABG = coronary artery bypass graft; CASS = coronary artery surgery study; GISSI = Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico; HMG CoA = 5-hydroxy-3-methylglutaryl-coenzyme A; ISIS–2 = second international study of infarct survival; NCEP = national cholesterol education program; SAVE = Survival and Ventricular Enlargement ; TIMI = thrombolysis in myocardial infarction; Source: Nabel and Braunwald, 2012.[1]

Figure 2: The Role of *Foxo1* in Diabetes-related Cardiovascular Disease



AGEs = advanced glycation end products; Ca = calcium; PPAR = peroxisome proliferator-activated receptors; PPK = protein kinase C; RAAS = renin–angiotensin–aldosterone system

Figure 3: Promising New Interventions in Cardiovascular Disease



MRA = magnetic resonance angiogram. Source: Udelson and Stevenson, 2016[15]

estimated that 50 % of the Chinese population is prediabetic; consequently diabetes-associated heart disease is set to become a global pandemic. Expert cardiologist Eugene Braunwald has stated that: "The thrombcardiologist of the 20th century will be replaced by the diabetocardiologist of the 21st century."

Recent advances in understanding of the pathophysiology of diabetes have identified potential new therapeutic targets. The forkhead box-containing O family of transcription factors (FoxOs) regulate essential cellular functions and are emerging as key mediators in cardiac insulin signalling and myocardial plasticity.[10] Patients with diabetes have atherosclerotic disease, hypertension and a toxic intra-myocyte milieu. FoxOs are capable of rendering a cell insulin-resistant *in vitro*[11] and have been found to be activated in the cardiac tissue of mice with diabetes. FoxO activity is linked with many aspects of myocardial plasticity, which may be reversed by the deletion of *Foxo1*. Activity includes cardiac dysfunction and cardiac remodelling, glucose dysregulation, a shift in substrate utilisation and lipid accumulation, as well as metabolic stress-induced ventricular dysfunction, structural remodelling and cardiac fibrosis.[10] Administration of tamoxifen to animals exposed to a high-fat diet silences *Foxo1* and allows the heart to undergo robust recovery (unpublished data). The ability to metabolise glucose can also be attenuated with tamoxifen.

Another growing public health problem is HF with preserved ejection fraction (HFpEF). HFpEF occurs in 40–60 % of newly-diagnosed HF cases, has an annual mortality of 3–30 % and accounts for a healthcare expenditure of more than $20 billion in 2010.[10] In contrast to HF with a reduced ejection fraction, patients with HFpEF still do not benefit from evidence-based treatment options. It remains one of the most challenging clinical syndromes because there are no reliable preclinical models and so it is impossible to develop new therapies. None of the currently-available therapies have shown improved clinical outcomes in trials of HFpEF and these patients' prognosis has remained unchanged over the past 15 years.[11] This is partly due to the numerous proposed pathophysiological mechanisms underlying the condition, which involve multiple organs.[12] If current trends persist, HFpEF will spread into the developing world and be responsible for 7.8 million premature cardiovascular disease (CVD) deaths in 2025.[13] In addition to this, the costs of CVD, both direct and indirect, are projected to increase substantially.[14]

Despite the challenge ahead, Professor Hill ended on a note of optimism. A number of new interventions for CVD appear promising (see *Figure 3*).[15] Projections have shown that National Institutes of Health funding translates into improvements in CVD mortality.[16] Furthermore, opportunities lie in the field of genetics. It has been hypothesised that cardiomyocyte-specific *Foxo* deletion will sustain cardiac function in the setting of insulin resistance.[17] By focusing on the molecular basis of diabetes, we have the potential to mitigate the projected healthcare cost of this growing epidemic. Finally, as highlighted by other presentations at the A-CURE symposium, mechanical unloading can minimise the infarct size and thus has the potential to reduce the incidence of HF. ■

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Cardiac Unloading and Myocardial Recovery: Clinical Utility from a Surgeon's Perspective

Presented by Mark Anderson

Hackensack University Medical Center, Philadelphia, PA

Mark Anderson was previously the Chair of the Cardiothoracic Surgery at Einstein Medical Center in Philadelphia. Dr Anderson specialises in the surgical management of heart failure and myocardial recovery.

Dr Anderson gave a surgeon's perspective on cardiac unloading. He commenced by reminding the congress that cardiopulmonary bypass is the foundation of cardiac unloading. By placing the patient on bypass, the heart is completely unloaded, allowing the surgeon to conduct the necessary procedure. However, while more patients are surviving following acute myocardial infarction (AMI), evidence indicates that heart function is not being necessarily recovered. This increased survival rate with insufficient heart recovery is leading to more hospital admissions and an increased rate of heart failure.

Mechanical circulatory support (MCS) is increasingly being recognised as a valuable intervention in AMI. The US Food and Drug Administration states that: "The Impella 2.5, Impella CP, Impella 5.0 and Impella LD catheters, in conjunction with the Automated Impella Controller console, are intended for short-term use (≤4 days for the Impella 2.5 and Impella CP and ≤6 days for the Impella 5.0 and Impella LD) and indicated for the treatment of ongoing cardiogenic shock (CS) that occurs immediately (<48 hours) following AMI or open heart surgery as a result of isolated left ventricular failure that is not responsive to optimal medical management and conventional treatment measures with or without an intra-aortic balloon pump. The intent of the Impella system therapy is to reduced ventricular work and to provide support necessary to allow heart recovery and early assessment of residual myocardial function." This statement emphasised the potential for the Impella® (Abiomed) pump in heart recovery and established a role for surgery in MCS.

Following the availability of these powerful new interventions, clinicians need guidance on how to optimise their use. *Table 1* shows the factors that should be considered when choosing the level of support in haemodynamic deficit and when surgery is needed. Another tool that can help in clinical decision-making is cardiac power output, a potent indicator of mortality.[1] Interventions can be targeted on the basis of early cardiac power output and subsequently assessed. Full unloading can optimise recovery, but there is a need to meet the demands for increased unloading and support. The early decision to both initiate and escalate MCS is particularly important in optimising outcomes. The Impella 5.0 is the most commonly used device for escalation in current surgical clinical practice.

There is also a need for more clinical evidence to guide the use of these devices. Since large randomised clinical trials involving cardiogenic shock patients are difficult to conduct, the global catheter-based Ventricular Assist Device Registry™ has been created.[2] Its purpose is to capture data reflecting real-world use of Impella devices in current clinical practice and provide insights into patient characteristics, co-morbid conditions, outcomes, patterns of care and the performance metrics of participating institutions to guide improvement in ventricular assist device use. Data from the registry show that surgical devices are still needed in advanced cases. Percutaneous technology is still associated with disadvantages, including instability of femoral artery placement and the restriction of the patient being confined to bed to recover. Axillary artery implantations allow for patient mobility and a more rapid patient recovery.

Table 1: Haemodynamic Deficit: Considerations for the Treatment of Cardiogenic Shock

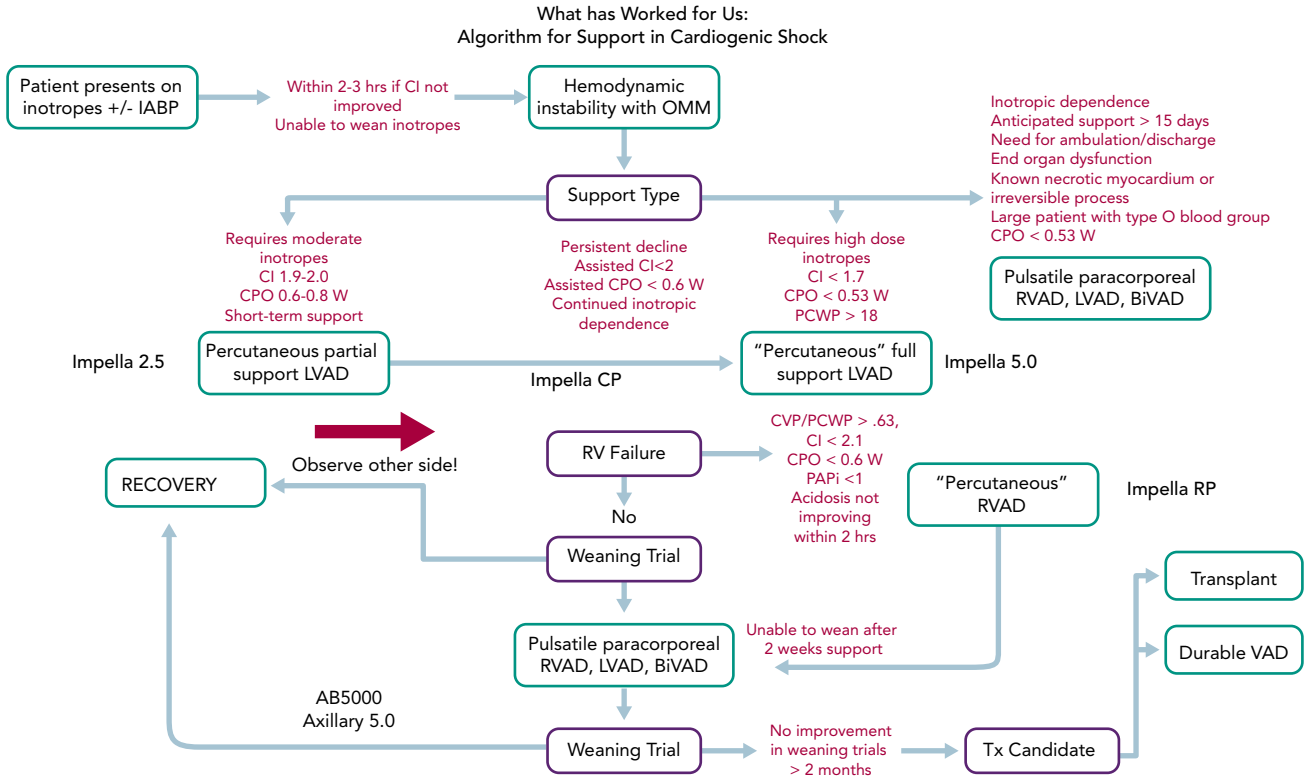
			Haemodynamic Burden										
	EF %	SBP mmHg	40	50	60	74	85	95	110	120	130	140	Mass (kg)
			1.4	1.5	1.7	1.8	2.0	2.2	2.3	2.5	2.6	2.7	BSA (m^2)
Haemodynamic Burden	40	90–100	0.5	0.6	0.8	0.8	0.9	1.1	1.1	1.0	1.2	1.4	
	35	80–90	0.8	0.9	1.2	1.3	1.5	1.6	1.6	1.8	1.8	2.1	
	30	70–80	1.1	1.3	1.5	1.8	2.1	2.1	2.4	2.4	2.4	2.9	
	25	50–70	1.4	1.7	2.1	2.3	2.6	2.7	3.0	3.1	3.2	3.3	
	20	45–55	1.8	2.1	2.6	2.7	3.1	3.3	3.4	3.5	4.1	4.3	
	15	30–45	2.1	2.4	3.0	3.3	3.5	3.8	4.1	4.3	4.8	4.9	
													Deficit

Green: <2.0 L/min Impella 2.5; orange: 2–4 L/min Impella CP/5.0; red >4.0 L/min Impella 5.0/LD. Orange and red: consider surgical options.
BSA = body surface area; EF = ejection fraction; SBP = systolic blood pressure.

The use of ventricular assist devices in AMI complicated by cardiogenic shock has a number of advantages: it completely rests the heart, reduces the need for inotrope/pressor support and provides stability during acute events. It is an effective bridging strategy and an optimal recovery platform. In order to optimise its use in routine clinical practice, there is a need for collaboration between interventional cardiologists and surgeons.

Dr Anderson finished by highlighting the need for a standard treatment algorithm and presented an algorithm that has proven effective in his centre (see *Figure 1*). He concluded that this meeting has demonstrated some important paradigm shifts in the management of cardiogenic shock, from partial unloading to optimal unloading; from later referral to early escalation; univentricular MCS to biventricular MCS; and the concept of a bridge to recovery rather than to a transplant. ■

Figure 1: Algorithm for Support in Cardiogenic Shock



BiVAD = biventricular assist device; CI = cardiac index; CVP = central venous pressure; CPO = cardiac power output; IABP = intra-aortic balloon pump; LVAD = left ventricular assist device; OMM = optimal medical management; PCWP = pulmonary capillary wedge pressure; RV = right ventricular; RVAD = right ventricular assist device; Tx = transplant; VAD = ventricular assist device

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Acute Unloading in the Setting of Acute Myocardial Infarction Complicated by Cardiogenic Shock

Presented by William W. O'Neill

Henry Ford Health System Center for Structural Heart Disease, Detroit, MI

Dr William O'Neill is the Medical Director of the Henry Ford Health System and pioneered the use of angioplasty in heart attack treatment. In the field of structural heart disease, he performed the first transcatheter aortic valve replacement procedure in the US in 2005. He has received numerous awards and has authored more than 300 peer-reviewed articles and abstracts.

Dr O'Neill began his presentation by highlighting the need for improved outcomes in cardiogenic shock (CS). Mortality in CS used to be as high as 90 % in the 1960s. Thirty years ago, the first studies reporting the outcomes of angioplasty for CS were published. Results showed a survival rate of 50 %. Survival has not improved since then. A recent cohort study found that long-term outcomes in CS remain poor.[1] This represents a clear, unmet need.

While the advent of mechanical circulatory support (MCS) devices offers promise in terms of improving outcomes in CS patients, there is a need for more evidence in support of their use. The catheter-based Ventricular Assist Device Registry™ (cVAD Registry™) is a global observational clinical registry designed to monitor patient safety and real-world outcomes of patients supported with the Impella® (Abiomed) device. Dr O'Neill presented registry data from his patients who were in severe haemodynamic compromise. These data showed that the use of increasing numbers of inotropes prior to MCS implantation is associated with worse survival and may increase the size of an infarct.

The time between onset of CS and initiation of MCS is also an important determinant of survival. *Figure 1* shows in-hospital survival rates as a

Figure 1: In-hospital Survival Rates as a Function of Shock Onset to Mechanical Circulatory Support Implantation

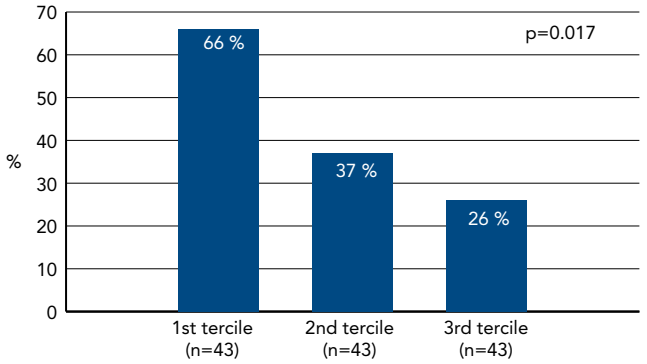
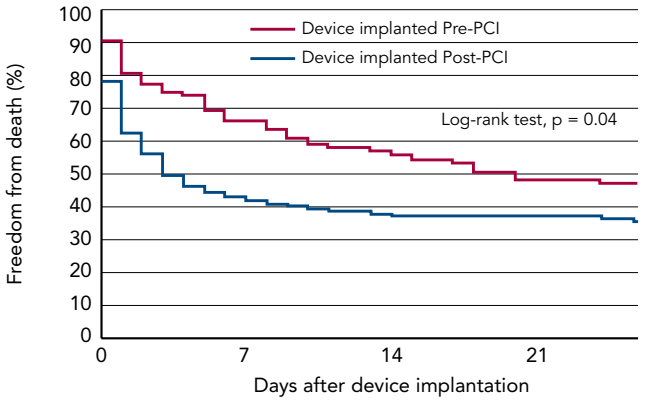


Figure 2: Kaplan–Meier Curve for Freedom from Death (to 30 days) by Device Implanted Before or After Percutaneous Coronary Intervention (PCI)



function of shock onset to MCS initiation in a cohort of 129 patients. In the first tercile (n=43), the time from onset of shock to support was 1.5 hours. In the second tercile (n=43), the time was between 1.5 and 4.0 hours and in the third tercile (n=43) it was >4 hours. A very steep gradient of survival versus time to onset of support was seen. If CS occurred >4 hours before MCS was initiated, survival was only 26 %; while survival was 66 % if CS patients received MCS within 1.5 hours from the onset of CS. In Dr O'Neill's experience, patients are delayed for too long before being transferred to specialist centres. The resulting prolongation of CS may lead to irreversible end-organ damage.

Dr O'Neill shared his research into clinical outcomes based on whether patients had the Impella device implanted before or after coronary reperfusion in the setting of acute myocardial infarction (AMI) complicated by CS.[2] This work showed there was a clear advantage to initiating Impella support prior to percutaneous coronary intervention. The separation of the curves occurs very early after percutaneous coronary intervention, reinforcing the belief that early MCS initiation is a key determinant of clinical outcomes.

These data highlight the need for a paradigm shift in the management of CS. Dr O'Neill asserted that interventionalists need to shift their thinking from door-to-balloon time to door-to-support time. The initiation of Impella prior to reperfusion may prolong the overall door-to-balloon time, but this delay is probably justified in the settings of AMI-CS as it provides end-organ perfusion and cardiac unloading.

Dr O'Neill was asked which he would consider a priority for a randomised controlled trial. In reply, he pointed out that 55 % of CS patients in the cVAD Registry would be ineligible for a clinical trial because of exclusion criteria such as out-of-hospital cardiac arrest. In a high-risk situation that needs immediate action, there is no time to speak to family members and obtain consent for inclusion in a randomised trial. While the latter may be possible for haemodynamically-stable AMI patients, registries are a better option to assess outcomes in CS. As the cVAD Registry continues to accrue data, Dr O'Neill expects to see an increased proportion of patients receiving MCS prior to coronary reperfusion, with corresponding improvements in survival. ■

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Incorporating Infarct Size into Trial Composite Endpoints: Implications for Unloading Trials

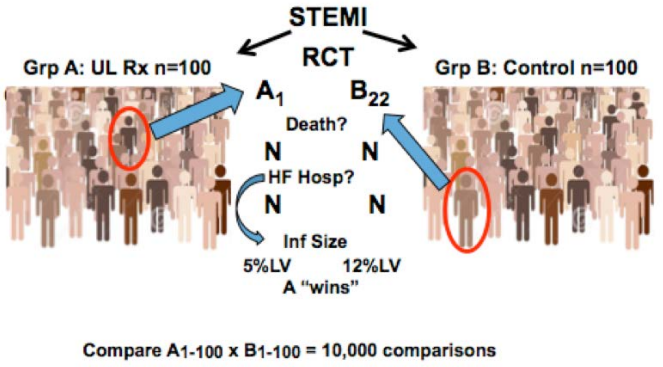
Presented by James E Udelson

Division of Cardiology, CardioVascular Center, Tufts Medical Center, Boston, USA

Dr James Udelson is the Chief of the Division of Cardiology as well as the Director of Nuclear Cardiology at Tufts Medical Center. Dr Udelson's research interests involve new therapeutic modalities in the setting of heart failure as well as chronic coronary artery disease.

Dr Udelson began his presentation by highlighting the problems of clinical trials enrolling heart failure (HF) patients. Clinical trials are extremely expensive and the majority of patients do not contribute to the primary endpoint. This is demonstrated in contemporary clinical trials in HF, where event rates are usually low. In the recent Prospective Comparison of Angiotensin Receptor–Neprilysin Inhibitor with Angiotensin-Converting–Enzyme Inhibitor to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) trial, the 1-year rate of cardiovascular death/hospitalisation was 10–12 %; therefore, in order to demonstrate statistical significance,

Figure 1: Illustration of the Finkelstein–Shoenfeld Method



HF = heart failure; Inf = infarct; LV = left ventricle; RCT = randomised controlled trial; STEMI = ST-segment myocardial infarction; UL = unloading.

the trial needed to enrol >8,000 patients.[1] In the 2012 Abciximab Intracoronary versus intravenous Drug Application in ST-elevation myocardial infarction (AIDA STEMI) trials, a three-point composite endpoint was used, but despite recruiting >2,000 patients, the trial had an event rate of only 7 % at 90 days and statistical significance was not achieved.[2]

As the use of cardiac unloading moves into less severely ill patients, such low event rates will become an issue in trial design. There is therefore much interest in biomarkers as surrogates in trials. A marker is considered a surrogate when it is in the causal path between the remedy and the outcome.[3,4] Markers may be serum biomarkers, such as troponins or natriuretic peptides, or imaging biomarkers, such infarct size, left ventricle volume and ejection fraction. All intervention effects pass through the marker in the causal path or are captured by the marker.

Dr Udelson focused on the use of infarct size measured by cardiac magnetic resonance (CMR) imaging as a plausible marker for myocardial infarction (MI). A large body of data shows that infarct size influences established clinical outcomes such cardiovascular death and HF hospitalisation. However, therapeutic intervention-induced changes in the surrogate marker need to be reflected in changes in the clinical outcome. At present, no marker is able to achieve this standard. Biomarkers that are 'prognostic' are not necessarily good surrogate markers in terms of assessing the effects of therapy. As an example, premature ventricular complexes following MI are strongly associated with an unfavourable prognosis. However, in the Cardiac Arrhythmia Suppression Trial (CAST), suppression of premature ventricular complexes led to an increased mortality.[5] Likewise, low high-density lipoprotein is prognostic of an increased risk of incident coronary artery disease, but the use of the cholesteryl ester transfer protein inhibitor torcetrapib to raise high-density lipoprotein levels increased mortality due to its effects on glucose, insulin and HbA_{1c} in subjects in the Investigation of Lipid Level Management to Understand its Impact in Atherosclerotic Events (ILLUMINATE) trial.[6]

The question of whether infarct size is an appropriate surrogate endpoint was addressed in a recent study by Dr Udelson's research team: a pooled patient-level meta-analysis from 10 randomised primary percutaneous coronary intervention in ST-elevation MI trials (n=2,632 patients) in which infarct size was assessed within 1 month after randomisation by either CMR imaging or technetium-99m single-photon emission CT, with clinical follow-up for ≥6 months. A strong correlation was seen between infarct size (per 5 % increase) and subsequent mortality (1.19; 95 % CI [1.18 to 1.20]; p<0.0001) and hospitalisation for HF (adjusted hazard ratio: 1.20; 95 % CI [1.19–1.21]; p<0.0001), independent of age, sex, diabetes, hypertension, hyperlipidaemia, current smoking, left anterior descending versus non-left anterior descending infarct vessel, symptom-to-first device time and baseline thrombolysis in MI flow 0/1 versus 2/3. Infarct size was not significantly related to subsequent reinfarction. For every 1 % reduction in infarct size, there was a 16 % reduction in HF hospitalisation but no effect on all cause mortality.[7] The investigators plan to meet with the US Food and Drug Administration (FDA) to discuss whether these data support the incorporation of infarct size into trial outcomes.

If the FDA approves the use of infarct size as a surrogate endpoint in clinical trials, the next challenge will be how to incorporate it. Two methods may be useful: the Finkelstein–Schoenfeld method[8] and the 'win ratio',[9] which involve a hierarchical comparison of events/timing in pairs of patients from the groups in the trials. The analyses account for clinical priority (e.g. death is more important than HF hospitalisation) and allow the potential incorporation of longitudinal measures such as the change in 6-minute walk distance or biomarkers. Most importantly, these methods enable all patients in a trial to contribute to the endpoint.

Dr Udelson illustrated this concept by considering a hypothetical randomised controlled ST-elevation MI trial that investigates cardiac unloading. Group A comprises 100 patients who receive unloading, while group 2 comprises 100 controls (see *Figure 1*). The investigator takes a patient (e.g. patient 1) from group A and another (e.g. patient 22) from group B and compares them. At the first level of hierarchy, the investigator compares whether either patient died. If B22 died but A1 was alive at study completion, then A 'wins' that comparison. If both patients died but A1 died at 12 months while B22 died at 8 months, then group A 'wins'. However, in HF or acute MI trials, most patients do not die. The following step is to consider the next level, i.e. HF hospitalisations. If B22 was hospitalised but A1 was not, then group A 'wins'. In ST-elevation MI, neither of these events may occur so it may be necessary to move to a marker with a plausible relationship with outcomes. If A1 has an infarct size of 5 % but B22 has an infarct size of 12 %, then group A 'wins' that comparison. If each person in group A is compared in this way with each person in group B, we obtain 10,000 comparisons.

This approach is familiar to the FDA. It was used in cohort B of the transcatheter aortic valve replacement group in the Placement of AoRtic TraNscathetER Valves (PARTNER) trial, which had co-primary endpoints of all-cause mortality (p<0.0001 favouring the device) and a hierarchical composite of death/recurrent hospitalisation, analysed by the Finkelstein–Schoenfeld method. Results showed superiority of the device (p<0.0001).[10]

Dr Udelson concluded that incorporating validated markers into hierarchical composites may allow reasonable sample sizes for trials of approaches to ST-elevated MI such as mechanical circulatory support. ■

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10. FDA. FDA Executive Sumamry: Edwards SAPIEN™ Transcatheter Heart Valve, model 9000TFX, sizes 23mm and 26mm and accessories (RetroFlex 3™ Delivery System, models 9120FS23 and 9120FS26; RetroFlex™ Balloon Catheter, models 9120BC20 and 9120BC23; and Crimper, models 9100CR23 and 9100CR26).

Summary of Presentations Exploring Other Aims of the A-CURE Group

The A-CURE Working Group also aims to explore the potential limitations of applying acute unloading in the clinical setting. One of these limitations may be found in data from Professor Michael Cohen of the University of South Alabama, which suggest that many patients being treated for acute myocardial infarction (MI) come into the clinic with the preconditioning signalling cascades already activated due to the wide use of P2Y12 inhibitors.[1,2] Many experimental therapies look to exploit these same signalling cascades for therapeutic purposes. If these signals have already been activated in the patients, then experimental therapy will have a limited effect. Professor Cohen concluded that in all preclinical models of ischaemia/reperfusion, any intervention being investigated for its cardioprotective qualities must be evaluated in the presence of P2Y12 blockade to determine whether the second intervention's protection is additive to that of currently indicated anti-platelet agents.

Dr Ryan Tedford, Assistant Professor of Medicine at Johns Hopkins School of Medicine, gave a presentation on the use of mechanical support for right-sided and biventricular failure. Even patients with chronic right ventricular (RV) failure respond to reductions in afterload. Clinical data suggest that, despite reducing RV load, left ventricular assist device (LVAD) implantation initially worsens the RV adaptation to load. However, continued LVAD support results both in improved RV afterload and RV adaptation as the load decreases, and the relationship between these two remains constant over time.[3] RV mechanical circulatory support can be initiated early or later in the treatment of RV failure. Data comparing the benefits of primary versus delayed support have been mixed. A 2009 study found that early implantation of biventricular devices was associated with better outcomes compared to delayed implantation,[4] suggesting that the timely implantation of a primary RV assist device is potentially beneficial. A separate study found that temporary RV mechanical circulatory support is an acceptable way to manage postoperative RV failure[5] and that this is preferable to biventricular support.[6] In most cases, and in the setting of contemporary LVADs, temporary RV support and optimisation of RV load may be sufficient.

Professor Derek Hausenloy of Duke-National University of Singapore discussed the challenges of reducing infarct size following acute MI. The most promising future interventions to limit MI scar size each require application prior to percutaneous coronary intervention (PCI) in order to maximise their effects. This observation aligns with data surrounding the ability of acute unloading to limit MI scar size. It has been shown that applying the glucagon-like peptide-1 agonist exenatide prior to PCI, metoprolol prior to PCI, or remote ischaemic conditioning prior to or at the time of PCI may each limit MI scar formation.[7] Professor Hausenloy concluded that new techniques such as unloading and newer therapeutic targets and strategies should further improve outcomes. ■

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Summary and Concluding Remarks

Following the presentations, the panel summarised some of the key points raised at the meeting. It is evident that clinical trials for mechanical circulatory support pose challenges that are in part mechanistic but also related to trial design. If we can reduce the cost of how we screen and enrol patients, we may allow for better evaluations of new devices and interventions, with definitive answers at the conclusion of the trial. Clinical studies in the setting of cardiogenic shock are challenging to execute, but there is a need for data.

One of the key messages of the session was the there is no one size fits all approach and we should be thinking of individualised rather than broad treatment plans. Moving forward, we now have an amazing tool that can provide haemodynamic support and avoid the use of vasopressors. However, some patients may still need vasopressors or inotropes. In these cases, the use of additional haemodynamic support will dramatically decrease morbidity.

The management of acute myocardial infarction and chronic heart failure (HF) present different challenges In the future, A-CURE may split into two groups: one focused on acute myocardial infarction and the other on chronic HF, since acute unloading will have very different effects on the two states. We need to establish the precise nature of these differences before contemplating a split. In the chronic HF setting, there is a need for a balance between left and right ventricular support. The right ventricle is dependent on the left ventricle for function, so any support for the right ventricle must not indirectly impact left ventricular function. More studies are needed in the chronic HF setting.

In terms of acute unloading, compelling evidence has been presented in favour of delaying reperfusion in order to provide mechanical circulatory support, but before moving this approach into the clinic, caution was advised; the priority should be to ensure robust protection for the patient, and delaying reperfusion for up to half an hour may not be feasible in all cases. More clinical evidence is needed to support this intervention. We need to strive for definitive answers to whether cardiac unloading is beneficial and not rely on subanalyses of clinical trials. Finally, the fields of chronic and acute unloading are merging and the focus on oxygen supply rather than demand is a fascinating approach.

Dr Kapur closed by stating that this had been a ground-breaking meeting and acknowledged support in the form of sponsorship from Abiomed. ■

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Proceedings of the 2nd annual Acute Cardiac Unloading and REcover (A-CURE) symposium held on 25 August 2017 in Barcelona, Spain

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Acute Cardiac Unloading and Recovery

Proceedings of the annual Acute Cardiac Unloading and REcovery (A-CURE) symposium held on 25 August 2017 in Barcelona, Spain

Session summaries by Katrina Mountfort, *Medical Writer, Radcliffe Cardiology*

The development of this supplement was funded by Abiomed.

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ICR Interventional Cardiology Review

Foreword

Welcome to this special supplement of *Interventional Cardiology Review*. This supplement is devoted to the proceedings of the second annual Acute Cardiac Unloading and REcovery (A-CURE) Working Group meeting, which was held on 25 August 2017 in Barcelona, Spain. The A-CURE Working Group is comprised of leading academic experts in clinical and basic cardiac research and is dedicated to advancing the science and clinical application of acute cardiac unloading. This meeting also brought together experts from multiple disciplines, including interventional cardiologists, heart failure specialists, cardiac surgeons, molecular biologists and biomedical engineers.

Cardiac traumas such as myocardial infarction (MI), myocarditis, cardiomyopathy and cardiogenic shock impair the ability of the heart to pump blood, resulting in end organ failure and, ultimately, death. Most therapeutic approaches to these traumas aim to maintain cardiac output but, in the process, impose further stress on the heart. This meeting focused on the use of new technologies in the treatment of these traumas. Acute cardiac unloading decreases myocardial oxygen consumption and maximises the ability of the heart to rest and recover after damage. Mechanical unloading employs percutaneously inserted ventricular assist devices such as the FDA-approved and CE-marked Impella family of devices, the Tandem Heart and the Investigational HeartMate PHP.

This supplement features a number of presentations covering a broad range of subjects related to cardiac unloading. The first sessions were devoted to the basic science underlying the concept of mechanical unloading. The meeting began with a presentation by Daniel Burkhoff describing the basic science behind acute ventricular and myocardial unloading. This was followed by Navin Kapur, who provided some insights into the molecular basis of mechanical unloading, describing the mechanism of cardioprotection at the cellular level. Gene therapy is receiving considerable current interest as a therapeutic strategy in heart failure (HF). Roger Hajjar presented data in support of his hypothesis that acute mechanical unloading using the Impella may improving gene delivery by enhancing viral uptake. Jacob Møller closed the first session by comparing the differential haemodynamic responses of Impella and extracorporeal membrane oxygenation (ECMO) support in a new large animal model of cardiogenic shock.

In the second session, which discussed progress towards a clinical mandate for cardiac unloading, Carsten Tschöpe examined the role of acute mechanical unloading as a bridge to recovery in patients with fulminant myocarditis. Babar Basir described the Detroit Cardiogenic Shock Initiative, which has produced a protocol for the treatment of cardiogenic shock. Finally, Perwaiz Meraj presented details of the first prospective feasibility study to evaluate the use of the Impella CP pump for unloading of the left ventricle prior to primary percutaneous coronary intervention in patients presenting with acute ST-segment elevation MI. The morning ended with three talks from featured abstracts: Carlos Del Rio presented data from his investigation into how mechanical support may affect the mechano-energetic relationship in the heart, Silvia Burchielli described a study that showed that cardiorespiratory support in a swine model of acute MI was able to drastically reduce mortality and provide an effective bridge to reperfusion, and Kiyotake Ishikawa discussed his innovative research demonstrating that left ventricle support using Impella reduces left atrial stretch and inhibits atrial arrhythmias through reduced oxidative stress.

The afternoon's presentations had a stronger focus on the clinical applications of ventricular unloading. The keynote speaker, Valentin Fuster, discussed the evolution of cardiovascular disease therapy, including identifying risk at early stages of life, treating subclinical disease and the challenges of treating older patients. Elazar Edelman discussed the use of hysteresis loops generated by support devices to track cardiac function. Mark Anderson described the clinical applications of the Impella RP, which is designed for right heart support. Ralf Westenfeld discussed the role of Impella support in facilitating pulmonary decongestion in cardiogenic shock. This session ended with Dirk Westermann discussing the use of the combination of ECMO and Impella support in cardiogenic shock.

The meeting concluded with two talks from selected abstracts. Kapil Lotun presented a study investigating mechanical circulatory support during cardiac arrest. In addition, Daniel Scheiber, the Young Investigator Scholarship awardee, described his research demonstrating that mitochondrial reactive oxygen species production is reduced in the left ventricle of mechanically unloaded hearts.

The presentations highlighted some exciting new developments and represent the substantial advances in the field of acute myocardial unloading and recovery in the last year. The A-CURE Working Group meeting is unique in involving a diverse group of experts from multiple disciplines within a unique setting.

Interventional Cardiology Review would like to thank all expert reviewers who contributed towards this edition. A special thanks goes to our Editorial Board for their continued support and guidance. We hope that you find this supplement informative and interesting. ■

Perspectives on Acute Unloading

Presented by Daniel Burkhoff, MD, PhD

Cardiovascular Research Foundation and Columbia University, New York City, NY, USA

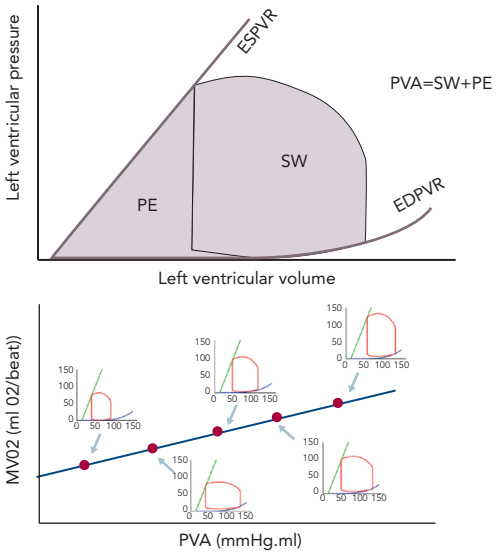
Dr Burkhoff is an Associate Professor of Medicine at Columbia University, Division of Cardiology. He has authored more than 300 peer-reviewed publications and is a world expert in heart failure, haemodynamics, and heart muscle mechanics. Dr Burkhoff is a founding member of the A-CURE Working Group and Co-Chair of the 2017 A-CURE Symposium.

Dr Burkhoff introduced the meeting by emphasising the need for consistent terminology in the field of acute cardiac unloading. The proposed definition of unloading is the reduction of total mechanical power expenditure of the ventricle, which correlates with reductions in myocardial oxygen consumption and haemodynamic forces that lead to ventricular remodelling.

The aim of myocardial unloading is twofold: first to achieve myocardial salvage and second to prevent heart failure (HF) and cardiac remodelling. It is important to recognise these as two distinct and important goals of acute cardiac unloading.

The benefits of left venticle (LV) unloading are well documented in both basic and clinical literature. Pharmacological unloading using captopril, an angiotensin-converting enzyme inhibitor, in an animal model of myocardial infarctino (MI) was first reported in 1985, and showed a shift in the end diastolic pressure.[1] Following this initial study, the shift from basic to clinical research occurred rapidly. Clinical trials showed that, after anterior MI, ventricular dilation is progressive and that captropril may curtail the process, as well as reducing filling pressures and improving exercise tolerance.[2]

Figure 1: Determinants of myocardial oxygen consumption



PE = potential energy; MVO2 = myocardial oxygen consumption; PVA = pressure volume area; SW = stroke work.

However, there are inherent limitations to pharmacological approaches to myocardial unloading. Unloading the LV and decreasing heart rate by these methods leads to a corresponding compromise in aortic pressure and cardiac output. Appropriate device-based therapies can overcome these limitations, as well as facilitating optimal use of other pharmacological or device-based therapies. These can have synergistic effects.

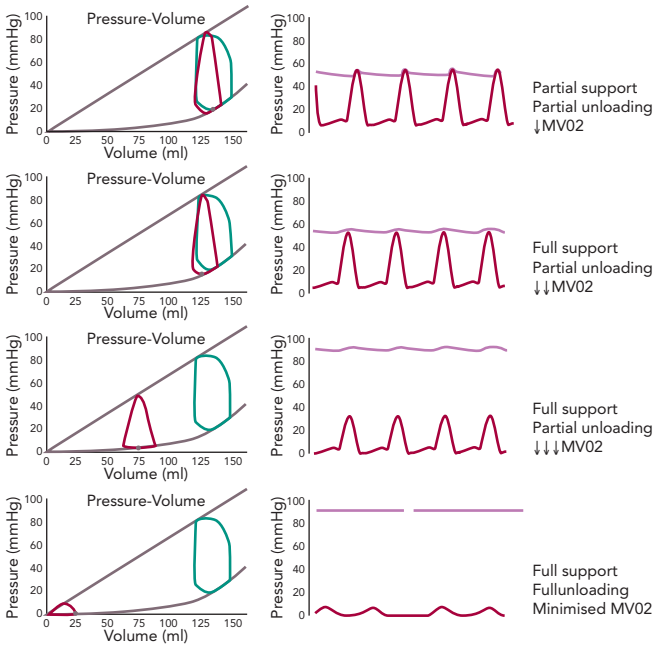
A 2003 study by Meyns et al. showed that by providing LV support using a catheter-mounted axial flow pump during the ischaemic period and during reperfusion the infarct size was reduced in animal models. Furthermore, oxygen demand during unloading is not an 'all-or-nothing' phenomenon, but there is a dose-dependence; the more unloading is achieved, the more oxygen demand can be reduced during the ischaemic period and during reperfusion, and the more myocardial salvage can be achieved.[3] Since the publication of this study, a growing body of literature has established the benefits of mechanical myocardial unloading,[4–8] and has led to the increased clinical application of the technique.

The difference between myocardial unloading using drugs and devices can be demonstrated by examining the impact of LV-aorta (LV-Ao) assist devices on haemodynamics and energetics. An LV-Ao device takes blood directly from the LV to the aorta and maintains systemic and coronary perfusion pressures while simultaneously unloading the ventricle – a phenomenon known as LV-aortic pressure uncoupling.

Uncoupling the LV from the systemic circulation minimises the mechanical work of the heart. This concept is the essence of the differences between drugs and devices and explains why devices are more effective than drugs alone in unloading the LV.

Dr Burkhoff emphasised that the determinants of myocardial oxygen consumption are not solely determined by the stroke work of the heart. This is important to remember when comparing different modes of mechanical circulatory support such as the left ventricular assist device (LVAD), which takes blood from the LV to the aorta and ECMO, which takes blood from the right atrium to the aorta. The oxygen consumption of the heart is linearly related to a parameter known as the pressure volume area (PVA) (see *Figure 1*). This is the sum of the stroke work and the potential energy, i.e. the energy that is stored in the myocardial filaments after contraction rather than being released as external work. It is also important to note that even when the heart is producing no external work, it still consumes energy, largely due to calcium cycling, but also due to basal metabolism. As drugs increase contractility, they increase oxygen consumption independent of the

Figure 2: The 'dose-dependence' of myocardial support and unloading



MVO2 = myocardial oxygen consumption.

increased workload of the heart because of the increased energy requirement for calcium cycling.

It is also important to understand that the effects of unloading are not restricted to the acute phase, and ventricular support has known consequences on ventricular remodelling associated with HF. Long-term mechanical unloading of the failing ventricle can, under certain conditions, lead to reverse remodelling, a restoration of a normal pressure-volume relationship in failing heart. Sustained unloading offers the potential for significant and sustained myocardial recovery through this reverse remodelling process; this was first reported in human hearts in 1996.[9]

Studies of LV unloading are still in their infancy but basic research is accelerating, and clinical studies are in their early stages. Therefore, Dr Burkhoff stressed the need to introduce consistency in the literature and into clinical studies, not only in terminology, but also in methodologies. We need to think critically of the methodologies that are being used, particularly in terms of measuring pressure-volume loops. It is difficult to compare studies that enrol different patient populations. It is also important to be consistent in the definition of clinical trial endpoints.

With respect to terminology, it is essential to understand the difference between support and unloading, and their dose-dependence (see *Figure 2*). Partial support and partial unloading occurs when the heart continues to provide some of the cardiac output while the device provides the remainder. This results in decreased myocardial oxygen demand and a small reduction in the PVA. In full support/partial unloading, the entire cardiac output is provided by the device, and there is still a volume cycle in the ventricle to generate some LV pressures throughout the cardiac cycle. In this scenario, the aortic pressure is uncoupled from ventricular function, and the pressure-volume loop shifts further leftwards and myocardial oxygen consumption is further decreased. Only when the ventricle is fully unloaded and the heart is performing zero work, i.e. during full support/full unloading, is myocardial oxygen consumption minimised. This shifts the pressure-volume relationship further leftward, almost obliterating the PVA. This emphasises the fact that unloading is dose-dependent and, in clinical practice, the flow rate of a device may have a different impact on different patients depending on their loading conditions that result from the use of the device.

In his closing remarks, Dr Burkhoff also highlighted the Training and Education in Advanced Cardiovascular Haemodynamics (TEACH) training initiative that aims to enhance the understanding of basic haemodynamic principles. This will involve two courses that will be held at Transcatheter Cardiovascular Therapeutics (TCT) Annual Meeting 2017 (www.tctmd.com, www.crfteach.com and www.pvloops.com). ■

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Insights into the Molecular Basis of Acute Cardiac Unloading and Cardioprotection

Presented by Navin K Kapur, MD, FACC, FSCAI

Cardiac Biology Research Center, Tufts Medical Center, Boston, MA, USA

Dr Kapur is an Associate Professor and Executive Director of Cardiovascular Center for Research and Innovation Tufts Medical Center in Boston. His research focuses on acute and chronic heart failure, circulatory support device development, and cardioprotective mechanisms in the setting of acute myocardial infarction. Dr Kapur is founding member of the A-CURE Working Group, and Co-Chair of the A-CURE Symposium.

Dr Kapur began by presenting an overview of the history of left ventricle (LV) unloading over the past decade. He noted that mechanical devices developed in recent years have provided hope for heart failure (HF) patients who previously had no options. The mechanical devices that have been employed for unloading have developed from biventricular devices (BVADs) and HeartWare® HVAD® pumps, where the aim was cardiac replacement as bridge to transplant or destination therapy, to an increasing use of percutaneous technologies such as the Impella pumps, where the goal is cardiac recovery and not replacement. He highlighted that percutaneous heart pumps have given clinicians the chance to promote the recovery of a patient's native heart.

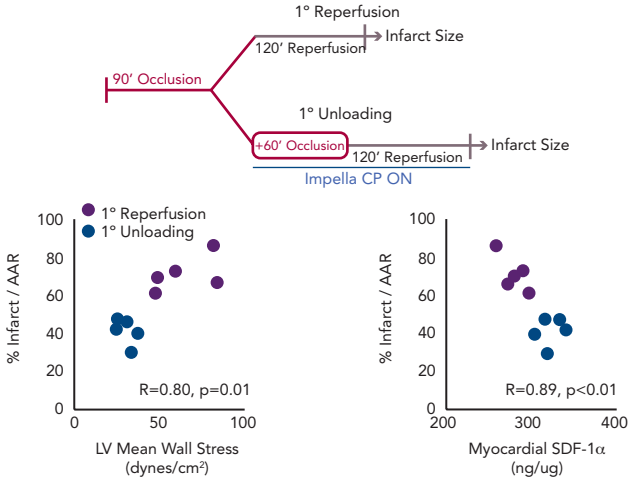
He then presented a brief history of the A-CURE movement, which began in Boston in 2015 and has since hosted meetings in Paris and Rome prior to this meeting in Barcelona. In those 2 years, research has progressed rapidly from preclinical testing to clinical trial launch. However, despite considerable progress in the field of LV unloading, questions remain, notably whether we can reduce the burden of ischaemic HF after a myocardial infarction (MI), and what are the cardioprotective mechanisms underlying LV recovery.

Myocardial infarct size remains an important target of therapy.[1] However, even if infarct size is reduced following an MI, if the haemodynamics are consistent with HF, this will remain a major cause of mortality for patients.[2] Two years ago, Dr Kapur's team published the concept of the primary unloading hypothesis, which suggested that first unloading the LV, then delaying reperfusion, activates a cardioprotective programme that limits myocardial damage in acute MI (*Figure 1*).[3] This study also identified an early molecular signal, release of the cytokine stromal-derived factor 1 alpha (SDF-1-alpha), which is known to be cardioprotective. This correlated with infarct size and led to the hypothesis that mechanical unloading leads to an increase in the SDF-1 CXCR4 signalling pathway, which is linked to a number of other cardioprotective mediators, including protein kinase B, extracellular signal-regulated kinase and glycogen synthase kinase 3 beta. This results in a shift to a cardioprotective phenotype.

Another important question concerns the kinetics of primary unloading: how important is the delay to reperfusion? Dr Kapur's team tested the idea of delaying reperfusion after activating the Impella device by 15, 30 or 60 minutes. Delaying reperfusion appeared to be necessary for reducing infarct size (see *Figure 2*).[4] One possible reason for this is that functional reperfusion may reduce the area of risk. With the left anterior descending artery (LAD) still occluded, enhanced collateral flow through non-occluded vessels may lead to a reduction in the area at risk. This may, in part, drive the benefits in terms of reducing infarct size.

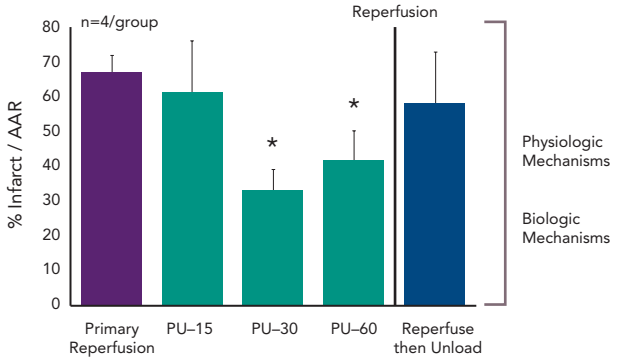
The release of SDF-1-alpha in ventricular tissue is highest after a 30-minute delay in reperfusion. In order to fully understand the biological

Figure 1: The primary unloading hypothesis



AAR = area at risk; LV = left ventricle; SDF-1a = stromal-derived factor 1 alpha

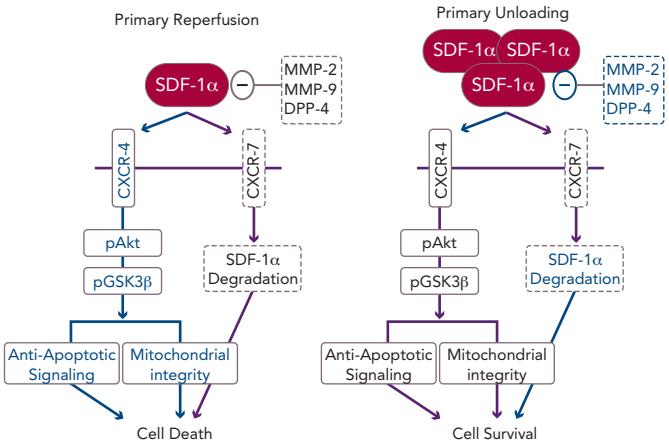
Figure 2: Effect of delaying reperfusion



* p<0.05 versus Primary Reperfusion

AAR = area at risk; PU = primary unloading. Source: Kapur et al, 2016

Figure 3: Effect of primary unloading in the myocyte at the molecular level



CXCR = C-X-C chemokine receptor; DPP dipeptidyl peptidase; GSK = glycogen synthase kinase 3 beta; MMP = matrix metalloproteases; pAKT = protein kinase B; SDF-1a = stromal-derived factor 1 alpha. Source: Kapur et al, 2017

mechanisms underlying unloading, it was important to explore the cause of this release. SDF-1-alpha is ubiquitously expressed, but is rapidly degraded by a number of metalloproteases as well as dipeptidyl peptidase-4 (DPP4) and the CXCR7 pathway.[5] Further study revealed that primary unloading reduces the activity of these proteases that promote SDF-1-alpha degradation. Dr Kapur's team is currently investigating the hypothesis that, by reducing the activity of these degradation pathways, primary unloading can increase the concentration of SDF-1-alpha in the myocardium, particularly during acute injury, leading to a protective phenotype that increases cell survival (*Figure 3*).[6] It is known that ischaemic injury leads to an uncoupling of SDF-1-alpha and CXCR signalling.[7] Dr Kapur suggested that primary unloading re-aligns the SDF-1-alpha:CXCR signalling axis, which is vital for myocardial repair.

An important question to address was whether the acute cardioprotective effect of primary unloading provides a durable reduction in HF. The cardiac response to increased work includes a reactivation of foetal genes, and remodelling following acute MI is largely driven by the foetal gene programme.[8] An animal study found that, compared to primary reperfusion, primary unloading reduces LV scar and preserves cardiac output at 30 days after acute MI.[6] No early signs of change in cardiac volume were seen but this may be due to the short timescale of the study. The study also showed that, at 30 days, primary unloading limits the activation of a gene programme associated with maladaptive cardiac remodelling. It also reduces tissue expression and circulating levels of brain natriuretic peptide, an important marker of HF, and increases the circulating levels of SDF-1-alpha in the first week, which correlates directly with reduction of scar size. Primary unloading appears to mechanically reprogramme myocardial responses to injury in acute MI, which involves the foetal gene programme.[9]

In summary, research to date has provided a platform for further investigation. Administration of primary unloading and stabilising haemodynamics following acute MI offer the potential for interventions that have until now been considered impossible. These include the administration of adjunct pharmacotherapy during an anterior STEMI including intravenous beta blockade, intracoronary vasodilators, glucose, insulin, potassium, SDF-1-alpha, protease inhibitors, and neuromodulation. Current research is investigating the administration of intravenous esmolol during primary unloading to increase the oxygen supply:demand ratio.

Dr Kapur concluded by reminding the audience that, in 2015, it was predicted that mechanical preconditioning would not translate into a successful clinical strategy that reduces myocardial infarct size.[10] In 2017, the US Food and Drug Administration approved a Phase I clinical trial examining the safety and feasibility of primary unloading. ■

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Impella Support and Cardiac Gene Therapy for Heart Failure

Presented by Roger J Hajjar, MD

Icahn School of Medicine at Mount Sinai, New York, NY, USA

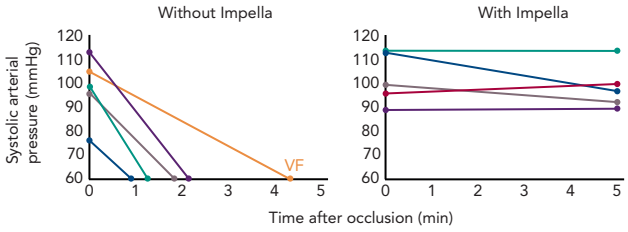
Dr Hajjar is the Director of the Cardiovascular Research Center and the Arthur and Janet C Ross Professor of Medicine at the Mount Sinai School of Medicine. His research focuses on molecular mechanisms of heart failure (HF) and his team has validated the cardiac sarcoplasmic reticulum calcium ATPase pump (SERCA2a) as a target in HF, developed methodologies for cardiac-directed gene therapy, examined the functional consequences of *SERCA2a* gene transfer in the failing heart, and conducted first-in-man clinical trials testing the efficacy of gene transfer in patients with HF. Dr Hajjar is a founding member of the A-CURE Working Group.

Dr Hajjar began by examining the role of gene therapy in HF. He drew a distinction between cellular therapy, which allows the introduction of new cells that can help the remodelling of damaged or diseased myocardium or extracellular matrix, and gene therapy, which focuses on altering the function of diseased cardiac cells at the level of the single gene. In the last decade there has been invigorated interest in cardiac gene therapy as a result of increasingly efficient gene transfer technologies and safer vectors that allow the homogeneous transduction of cardiomyocytes. Critical advances that have supported the increased use of gene therapy include the ability to induce long-term expression of the target gene, viral vectors with higher cardiac specificity and minimally invasive vector delivery techniques.[1,2] Dr Hajjar's team is investigating gene replacement therapy using adeno-associated virus (AAV) vectors delivering the *SERCA2a* gene. These vectors have been demonstrated to be safe and non-pathogenic; the majority of the population has been exposed to the wild-type virus in childhood without any evidence of disease.

The efficiency of gene transfer is has been a major obstacle to the successful translation of gene therapy into the clinic. The rate of *in vivo* viral transduction reported in clinical trials is too low to induce any physiological impact. The efficiency of gene transfer to the heart can be improved by increasing perfusion pressure, coronary flow, vector dose, and dwell time. The preferred method of administering the vector is through percutaneous intracoronary artery infusion, since this approach more readily ensures gene delivery to the viable myocardium. The Calcium Up-Regulation by Percutaneous Administration of Gene Therapy In Cardiac Disease (CUPID) clinical trials investigated this method of intracoronary administration of AAV type 1 (AAV1)/SERCA2a in patients with Class III/IV HF. CUPID 1 was a randomised, double-blind, placebo-controlled, Phase IIa study in patients with advanced HF. Following the administration of intracoronary AAV1/SERCA2a or placebo, significant increases in time to clinical events and decreased frequency of cardiovascular events were observed at 12 months in the treatment group (hazard ratio=0.12; P=0.003), and mean duration of cardiovascular hospitalisations over 12 months was substantially decreased (0.4 versus 4.5 days; P=0.05) on high-dose treatment versus placebo.[3]

The follow-up and larger Phase IIb study (CUPID 2) is the largest gene transfer study carried out in humans to date (n=250). However, AAV1/SERCA2a at the dose tested did not show an improvement in the primary endpoint.[4] Possible reasons for this disappointing result include insufficient myocardial uptake, because the AAV concentration was too low (the US Food and Drug Administration did not allow the use of higher doses), and the method of gene transfer was inadequate. While previous data in animals had showed a high percentage of infected cardiomyocytes (30–75 %), data from CUPID 2 showed that the uptake in humans was much lower (<0.5–1 %). The method of gene transfer in CUPID 2 trial was clearly inadequate.

Figure 1: Coronary occlusion with and without left ventricular support



Source: Hajjar et al, 2017

Dr Hajjar presented his current hypothesis that involves improving gene delivery by using the Impella device to enhance viral uptake. He proposed that Impella support could affect uptake in two ways. First, viral uptake is adversely affected by increased left ventricle (LV) diameter, end diastolic pressure and sympathetic activation, leading to increased wall stress. Further, the inflammation, cell death, ischaemia and myocyte destruction at the time of a myocardial infarction (MI) also provides a hostile environment for vectors. Acute unloading with the Impella mitigates these adverse conditions. Second, the Impella could be used to haemodynamically support the patient while the vector is delivered into the coronary system during temporary coronary balloon occlusion. This would allow for a longer dwell time and minimise the risk of haemodynamic collapse.

Dr Hajjar presented data from his current studies. In a porcine model of subacute ischaemic HF, MI is induced, and the heart is allowed to remodel for 2 weeks. Gene delivery under Impella support then commences at this time point. Early data shows that this approach reduces LV wall stress, decreases end diastolic pressure, increases epicardial coronary flow, and increases myocardial perfusion, specifically in the infarct region (see *Figure 1*).[5] Thus far, all pigs receiving Impella support during vector delivery while occluding the coronary artery have been successfully bridged through the procedure without incident, while all pigs that did not receive mechanical support suffered haemodynamic collapse and required cardioversion or other intervention.

In conclusion, these ongoing studies hope to demonstrate that by enhancing coronary flow, perfusion pressure can be increased while at the same time the unloading will allow a better environment for more aggressive gene delivery. ■

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Comparative Haemodynamic Response to Impella Versus Extracorporeal Membrane Oxygenation Support in a Porcine Cardiogenic Shock Model

Presented by Jacob E Møller

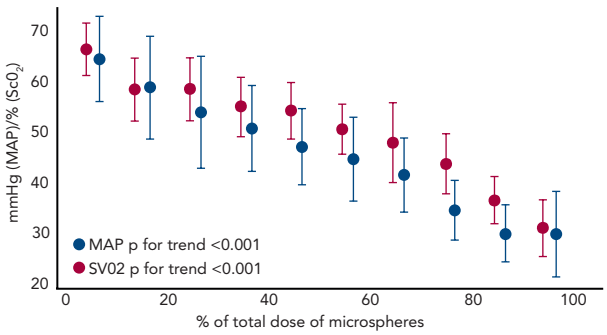
Odense University Hospital, Denmark

Professor Møller is a Professor and Head of Cardiac Research at Odense University Hospital Denmark. Professor Møller has published more than 160 peer-reviewed articles. His research focuses on cardiogenic shock, myocardial infarction, heart failure, valvular disease, and controlled clinical trials. Professor Møller is founding member of the A-CURE Working group.

Prof Møller opened his talk by emphasising the importance of understanding the whole concept of unloading the heart in a clinical setting, particularly in patients with cardiogenic shock (CS). Despite the urgent need for experimental research in the field of CS, there are limited options in large animal models enabling research using devices applied to human subjects. Since it is impossible to conduct controlled haemodynamic studies at the bedside in patients with CS undergoing mechanical circulatory support, Prof Møller's team is developing an animal model that mimics severe CS after myocardial infarction. This aim of this model is to allow for detailed haemodynamic assessment of the CS state. However, inducing CS in large animal is associated with unacceptably high rates of premature mortality and the inability to acquire a complete data recoding. An ideal model would avoid this, would anatomically mimic humans, and would allow for the placement of a device percutaneously in the same manner as in the catherterisation laboratory.

Prof Møller's work has focused on porcine models for the various size advantages they have compared to other animals. In particular, large porcine models allow for the placement of multiple catheters, enabling monitoring of the heart and peripheral perfusion. The induction of CS was based on an earlier model that involved the repeated injection of plastic microspheres into the left main coronary artery. In this model, this causes microembolisation in the coronary circulation and stepwise elevations of left ventricle end-diastolic pressure (LVEDP).[1] The new model uses Contour embolisation particles, which are small and irregular flakes of polyvinyl alcohol 45–150 microns in diameter. Serial injections of these particles into the coronary circulation allows precise control of the degree of CS, ultimately producing increased lactate and severe LV failure (see *Figure 1*). Of note, induction of CS using this model was achieved in a study of 16 animals without the loss of a single animal. The pressure-volume loops from the LV confirmed the low pressure-volume area (PVA), demonstrating the severity of the CS. This model also allowed percutaneous placement of an extracorporeal membrane oxygenation (ECMO) cannula and an Impella CP® assist device, aiming to mimic conditions that would be used in the catheterisation laboratory.

Figure 1: Controlled cardiogenic shock in a porcine model



MAP = mean arterial pressure; SVO2 = mixed venous oxygen saturation. Source: Moller et al, 2017

This model was employed in a study that aimed to compare active unloading with the Impella CP to VA-ECMO in large pigs with profound acute CS. The clinical endpoints were PVA, LVEDP and organ perfusion. Following the induction of profound CS, six pigs were treated with VA-ECMO, and six pigs treated with the Impella CP.[2] As expected, the afterload was increased with ECMO, and the pressure-volume loop initially shifted rightward (reflecting increased myocardial work), but eventually resulted in a small leftward shift, likely reflecting the recovery of contractility while on support. In contrast, the Impella was found to provide almost full support immediately, giving partial unloading with low pulsatility, then the LV recovered. The PVA and LVEDP were significantly higher in CS pigs treated with the ECMO compared with Impella. Lactate was normalised in both groups. However, the ECMO-treated animals immediately restored renal perfusion, and this aspect was more efficient than the Impella.

In conclusion, this study confirms the ability of the Impella CP to unload the heart efficiently and effectively while providing increased tissue perfusion. However, ECMO is superior in restoring systemic perfusion in the acute stages of support. Chronic studies would be necessary to assess the effect of both platforms on restoring systemic perfusion relevant to the clinical setting. ■

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Institutional Algorithms, Mechanical Circulatory Support & Patient Outcomes: The Detroit Cardiogenic Shock Initiative

Presented by Babar Basir

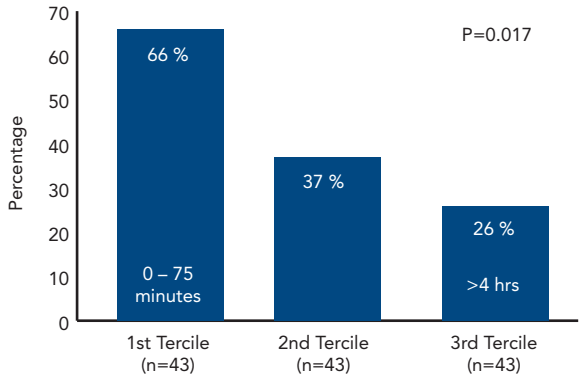
Henry Ford Hospital, Detroit, MI, USA

Dr. Basir is an Interventional Fellow at the Henry Ford Hospital in Detroit, Michigan.

Dr Basir commenced his presentation by reminding the audience that, despite the fact that the number of cases of cardiac shock (CS) during acute myocardial infarction (AMI) has steadily risen,[1] the rates of in-hospital mortality have remained unchanged for more than 20 years.[2] A group of physicians, including Dr Basir, examined the Abiomed Impella Quality (IQ) database on Impella use, with the aim of identifying factors that may be associated with survival. They used this information to derive an institutional protocol that could be systemically implemented across several hospitals in the region of the Henry Ford Hospital. This prospective approach was focused on improving survival in this patient population. Of note, there is a wide variation in outcomes with Impella use across different sites: IQ data (791 sites supporting >4 patients with AMI CS, 15,529 patients total) show that the bottom 20 % performing sites have a mean survival of only 30 %, whereas the top 20 % of sites have a higher volume of Impella utilisation and a mean survival of 76 %. In 2016, the mean survival rate was 58 %, a relative improvement of 14 % since the US Food and Drug Administration (FDA) approval on the Impella.[3]

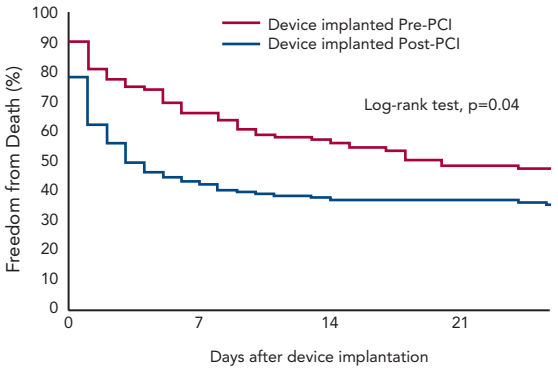
One factor observed to be associated with early mortality in AMI/CS is increased inotrope exposure.[4] This does not determine causality as the severity of a patient's condition correlates with the number of inotropes and vasopressors. Nevertheless, it is likely that the load of inotropes and vasopressors directly influences outcomes.[5] Similarly, a delay in support is clearly associated with mortality in AMI/CS. Data indicate that if a patient receives mechanical circulatory support (MCS) in the first 75 minutes following AMI, outcomes are substantially improved compared with those who have a longer delay in support (see *Figure 1*).[5] In addition, the use of haemodynamic support prior to percutaneous coronary intervention (PCI) has been shown to improve survival, due to effects on the reperfusion injury and ischaemia (see Dr Navin Kapur's talk). The separation of the Kaplan–Meier curves occurs very early following PCI, reinforcing the idea that early MCS is a key determinant in clinical outcomes (see *Figure 2*).[5]

Figure 1 In-hospital survival rates as a function of shock onset to mechanical circulatory support implantation



Source: Basir et al, 2017a

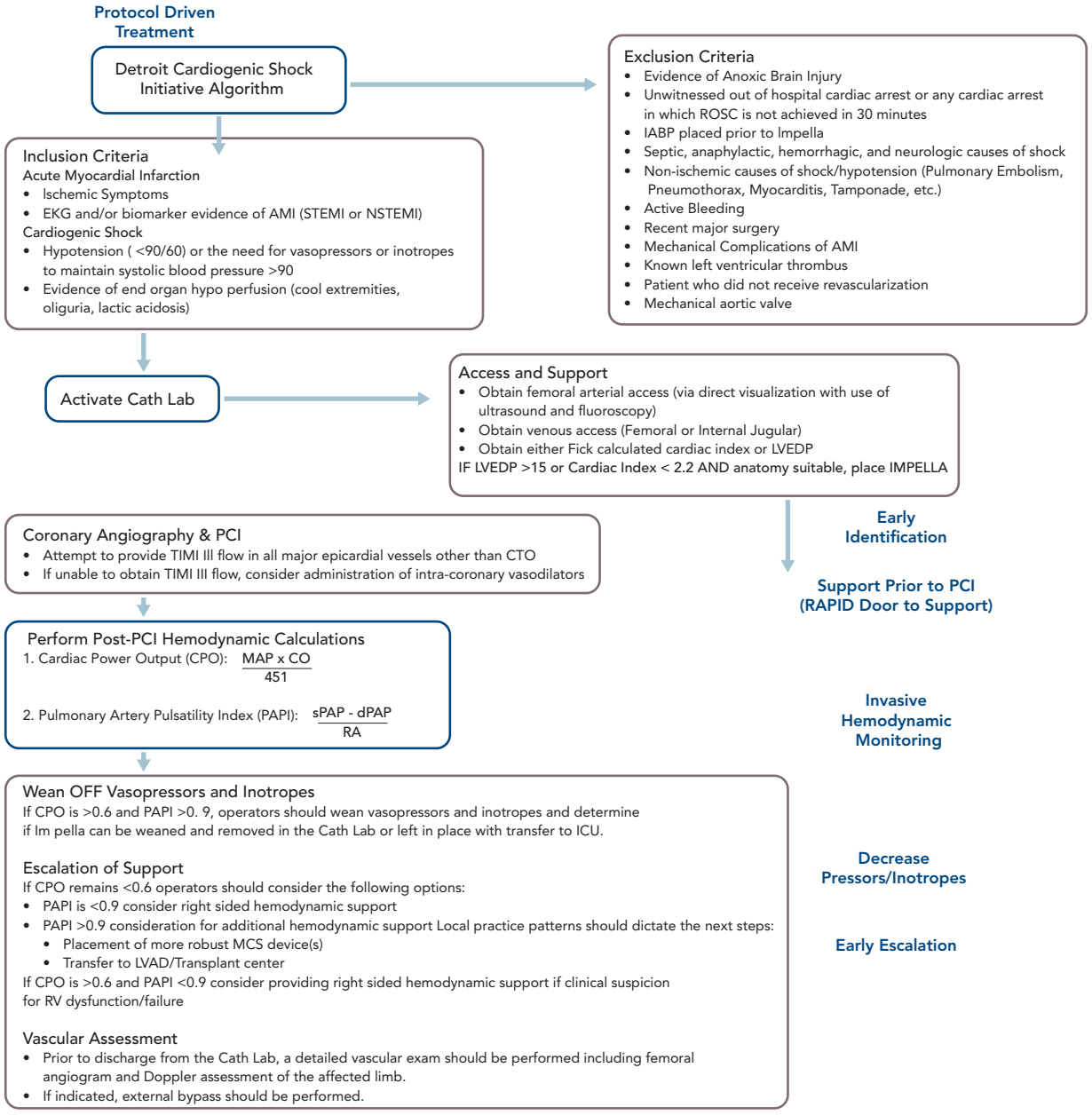
Figure 2: Kaplan–Meier curves for freedom from death (to 30 days) by device implanted pre/post PCI



Source: Basir et al, 2017a

These factors have been used to develop a protocol for use by the Detroit Cardiogenic Shock Initiative (CSI), a collaboration between four hospitals

Figure 3: Detroit Cardiogenic shock initiative: treatment protocol



AMI = acute myocardial infarction; CO = cardiac output; CPO = cardiac power output; CTO = chronic total occlusion; dPAP = diastolic pulmonary artery pressure; ECG = electrocardiogram; IABP = intra-aotic balloon pump; ICU = intensive care unit; LVEDP = left ventricular end diastolic pressure; MAP = mean arterial pressure; NSTEMI = non ST-elevation myocardial infarction; PAPI = pulmonary artery pulsatility index; PCI = percutaneous coronary intervention; RA = right atrial pressure; ROSC = return of spontaneous circulation; RV = right ventricular; sPAP = systolic pulmonary artery pressure; STEMI = ST-elevation myocardial infarction; TIMI = thrombosis in myocardial infarction. Source: Basir et al, 2017b

in Detroit, under the leadership of Dr William O'Neill, with the aim of increasing survival in MI/CS (see *Figure 3*).[6] This protocol is specific to a defined group of patients, and has proscribed exclusion and inclusion criteria. Although this was a protocol-led treatment, individual decisions were based on operator preference. Nevertheless, this approach allows for better assessment of real-world outcomes. The protocol was comprised of early detection of CS, immediate catheterisation laboratory activation, mechanical support prior to PCI, invasive haemodynamic monitoring, decreased vasopressor/inotrope use and early escalation to a larger support device if needed (cardiac power output < 0.6 W and a pulmonary artery pulsatility index <0.9). Quality measures include door-to-support time of less than 90 minutes, establishment of Thrombolysis In Myocardial Infarction (TIMI) III flow, weaning of vasopressors and inotropes, maintaining a cardiac power output in excess of 0.6 W and improving survival to discharge.

Using this protocol, the Detroit CSI pilot study has been initiated and has treated 41 patients at the time of the A-CURE Symposium. The average age of participants was 65 years, and 70 % were male. A total of 95 % were taking vasopressors and 41 % were in cardiac arrest.[6] This patient populations is similar to that of the SHOCK trial (n=302).[7] The population differed from that in the Impella versus Intra-Aortic Balloon Pump in Cardiogenic Shock (IMPRESS) trial (n=48), a prospective trial in which the patients were much sicker, all were mechanically ventilated and 92 % had a cardiac arrest.[8] In the Detroit CSI study, the median lactate levels were 4.7 g/dl compared with 8.2 g/dl in the IMPRESS trial.

Of 55 screened patients, 14 were excluded based on the inclusion/exclusion criteria. The pilot study showed favourable outcomes. Out-of-hospital cardiac arrest occurred in 6 participants and there were 11 in-hospital cardiac arrests. Overall survival rate was 76 %, compared

with 53 % in the SHOCK trial and 53 % in IMPRESS.[7,8] Implantation of Impella prior to PCI occurred in 66 % of participants and there was a 66 % improvement in cardiac power output (0.57 W to 0.95 %; P<0.001) after the initiation of MCS and PCI. Of note, as the study progressed, protocol adherence increased, with a corresponding improvement in outcomes.[6]

In conclusion, rapid early delivery of MCS guided by invasive haemodynamic monitoring is associated with significantly improved survival in an AMI/CS patient population. This multi-institutional effort demonstrates the effectiveness of an institutionalised protocol to address CS and significantly improve patient outcomes in this difficult patient cohort. Dr Basir described this as a "war on shock", which involves a systematic team effort using regional shock protocols that can be summarised as follows:

A – Access
B – Basic Haemodynamics (blood pressure, left ventricular end diastolic pressure and cardiac power output)
C – Circulatory Support
D – Decrease vasopressors and inotropes
E – (Early) Escalation. ■

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Paradoxical Mechano-energetic Costs of Acute Mechanical Intra-ventricular Unloading

Presented by Carlos Del Rio

QTest Labs, Columbus, Ohio, MyoKardia, CA, USA

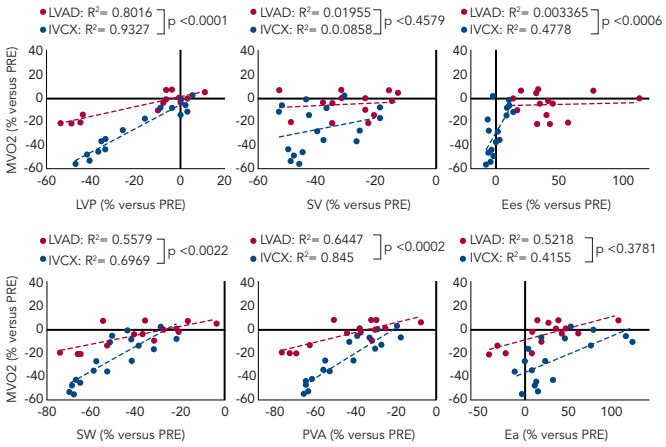
Dr. del Rio is a Research Scientist at MyoKardia in San Francisco, California. He was the recipient of the Best in Research Scholarship for the 2017 A-CURE Symposium.

Dr Del Rio presented data from his investigation into how mechanical support may fundamentally alter the mechano-energetic relationship in the heart. He began by providing the background to his study. By design, durable intra-cardiac left ventricular assist devices (LVAD) support the systemic circulation and cardiac output by removing blood from the left ventricle (LV), resulting in preserved systemic pressures and decreased stroke work (SW), stroke volume, filling pressures and preload. Unfortunately, these beneficial effects have not translated to recovery of heart function in these patients. In questioning this, Dr Del Rio examined the determinants of oxygen consumption in the left heart, particularly contractility and haemodynamic load. Historically, researchers have assumed that the heart does not respond to its altered physiological state resulting from implantation of an LVAD. Dr Del Rio's team proposed the hypothesis that LVAD support can lead to paradoxical increases in the effective arterial elastance (Ea) and intrinsic cardiac contractility during ventriculo-arterial coupling, therefore hindering mechano-energetic unloading.[1] This imposes an intrinsic barrier to achieving LVAD-mediated recovery/reverse remodelling.

Dr Del Rio described an experiment in which an LVAD was inserted into a healthy animal and provided chronic partial support (>70 % of cardiac output). Over the course of 7 weeks, rather than maintain a steady state of lower device-dependent LV end diastolic volumes, the preload increased despite LVAD support. The Ea also showed an acute increase that normalised over time as the LV end diastolic pressure increased. There was a concomitant increase in early contractility, increased ventricle fibrosis and early release of atrial natriuretic peptide (ANP). There was an acute increase in contractility and an increase in fibrosis of the ventricle. This suggested that chronic partial support in healthy animals may trigger LV remodelling.

A subsequent study assessed the acute effects of LVAD support on systemic haemodynamics, LV mechano-energetics, and myocardial oxygen consumption (MVO_2) *in vivo*.[2] The study involved 12 mixed-breed sheep (34 to 54 kg), which were given acute LVAD support. The study assessed MVO_2, using coronary sinus/arterial sampling catheters and left circumflex artery [LCX] coronary flow probe), systemic/LV haemodynamics, cardiac output (pulmonary artery flow) and load-independent LV inotropy/lusitropy via pressure-volume relationships. A continuous-flow LVAD (RotaFlow) device was used. Energetic components were determined before and during LVAD unloading, at both partial (50 % support, aortic valve opening) and complete (100 % uncoupling) support). These were compared with data obtained during partial inferior vena cava occlusion (IVCX, n=8) at matched level of volume unloading. Data were also collected when

Figure 1: Effect of LVAD support on the MVO_2 versus PVA relationship in the ventricles



Ea =left ventricle chamber elastance; Ees = effective arterial elastance; IVCX = preload; VAD = left ventricular assist device; PVA = pressure-volume area; SW = stroke work.
Source: Del Rio et al, 2017

phenylephrine was administered to restore systemic haemodynamics (IVCX+PE) in order to mimic partial support.

Results showed that partial LVAD support (57±4 % total cardiac output) preserved systemic/peak LV pressures (–3 ± 2 %) and cardiac output (–1±1 %), while decreasing LV preload (–13 ± 2 %), filling pressures (–29±7 %) and stroke volume (–28±5 %). Both the estimated LV chamber elastance (Ea; +40±11 %) and effective arterial elastance (Ees; +33±7 %) increased with support. The release of ANP was also reported during partial support. Despite marked reductions in SW (–29±5 %) and PVA (–31±4 %), there was a negligible change in MVO_2 (+1±2 %). By contrast, complete support (109±9 %) decreased LV pressures (–33±10 %), normalised ANP release, and normalised Ea (–1±14 %) but not Ees (+54±12 %). There were further reductions in SW and PVA, with moderate MVO_2 reductions (–13±4 %). Unsupported reductions in the preload (IVCX) decreased pressures. There was a decrease in MVO_2 (–39±4 %), and PVA (–58±4 %). The Ea and Ees remained unchanged. Pressure support (CTRL+PE) increased Ea and blunted the MVO_2 reductions (–7±2 %). Of interest, the LVAD support altered the MVO_2 versus PVA relationship in the ventricles (see *Figure 1*).[2]

In conclusion, acute intra-cardiac LVAD support, particularly under partial unloading, can trigger mechano-energetic alterations, paradoxically hindering the ability of an LVAD to energetically unload the ventricle. There may be a limit to MVO_2 reductions under LVAD support. Use of the LVAD engages intrinsic coupling mechanisms of the ventricles. Finally, an LVAD is, perhaps, perceived as a 'stress' signal, reflected in the release of ANP. On the basis of this research, Dr Del Rio said that there was a need for an increased understanding of the coupling and the mechanism that allows the heart to perceive the LVAD signal. This may allow us to pharmacologically inhibit this mechanism and increase the effectiveness of LVAD-mediated unloading on heart recovery. This should give us the beneficial effects of circulatory support as well as the potential for PVA reduction without a shift in the PVA/MVO_2 relationship. ■

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Door to Unload in ST-segment elevation MI: Safety and Feasibility Study

Presented by Perwaiz M Meraj MD FACC FSCAI

Director of Research, Associate Program Director, Fellowship, CHIP, Advanced Hemodynamic Support and Complex Structural Heart, Northwell Health, Hofstra Northwell Health School of Medicine, New York, USA

Dr Meraj is an Interventional Cardiology Specialist at the Hofstra Northwell Health School of Medicine in New York.

Dr Meraj began his presentation with an overview on the current treatment paradigm in acute myocardial infarction (MI) with or without cardiogenic shock (CS), which focuses on primary perfusion in the first 2 hours. In acute coronary occlusion, time is of the essence, and the relationship between shorter door-to-balloon (DTB) times and improved outcomes is well established. Maximal benefit of reperfusion therapy is observed when the therapy is applied within 2 hours of the patient presenting at the hospital.[1] This has led to the adoption of a target 90 minutes DTB time. However, the maximal effect of DTB time may have been reached. Recent data have indicated that while the average DTB has fallen well below 90 minutes, a corresponding drop in mortality rates of MI patients has not been observed.[2] Additional strategies are therefore needed to reduce in-hospital mortality rates in this population.

Understanding the balance between myocardial oxygen supply and demand in MI has enabled us to develop effective left ventricle (LV) unloading protocols.[3,4] Numerous preclinical investigations have supported the hypothesis that primary LV unloading and delaying coronary reperfusion provides both cardioprotective signalling and myocardial salvage. These scientific investigations have in part led to a recent paradigm shift in acute MI management that proposes door-to-support time as an emerging target of therapy to reduce reperfusion injury and improve outcomes associated with MI/CS.[5]

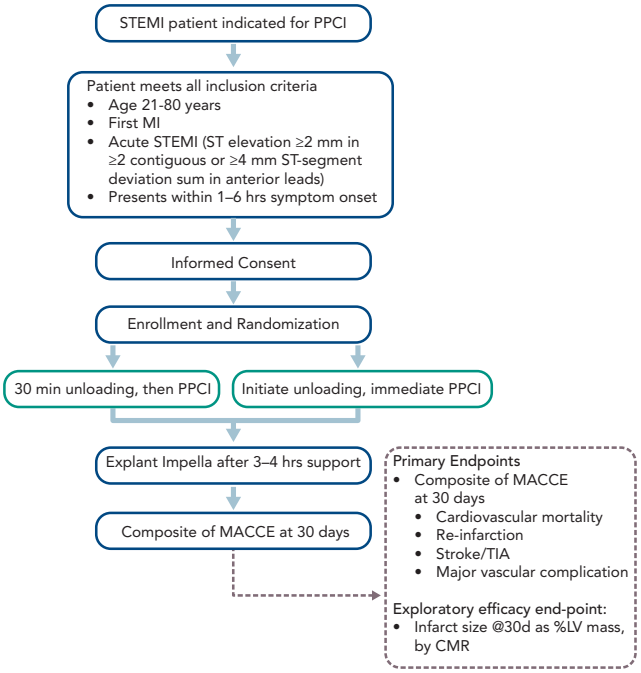
In late 2016 the US Food and Drug Administration gave approval for the Door to Unloading (DTU) in ST-segment elevation MI (STEMI) safety and feasibility study. This study is a prospective feasibility

study to evaluate the use of the Impella CP device for unloading of the LV prior to primary percutaneous coronary intervention (PPCI) in patients presenting with acute STEMI, without CS.[6] The main inclusion criteria are age 21–80 years, first MI and acute anterior STEMI with ≥2 mm in two or more contiguous anterior leads or ≥4 mm total ST-segment deviation sum in the anterior leads, and presentation between 1 and 6 hours of symptom onset.

Patients are randomised to two treatment arms: immediate Impella implantation followed by 30 minutes of mechanical unloading prior to PPCI, or immediate Impella implantation directly followed by PPCI. The Impella is explanted after 3–4 hours of support. This time was chosen as the optimal unloading time is not known and the implications for leaving in a 14 Fr sheath for longer than 4 hours may have safety implications. The primary endpoints are the composite of cardiovascular mortality, re-infarction, stroke or transient ischaemic attack, major vascular complication at 30 days, and also an additional exploratory efficacy endpoint of the infarct size as percentage of LV mass, evaluated by cardiac magnetic resonance (CMR) at 30 days post-PPCI (see *Figure 1).*

The first patient was enrolled in April 2017. To date, all patients have met the <90 min DTB times, including those who had delayed reperfusion. The DTU metric will be determined for each patient as the study continues. We will need an understanding of 3- to 5-day and 30-day magnetic resonance imaging (MRI) to guide optimisation of infarct size reduction. Results from these patients will be used to guide best practices for the pivotal study. Given the design of the study and its time-sensitive nature, enrolment decisions are based only on the patient history taken at the time of initial presentation. It can be difficult to explain the treatment and precisely ascertain clinical symptom start time. A radial approach is used for access for the non-large bore site to reduce unnecessary vascular complications. Patient screening should also be considered to enable adequate MRI; some patients may be claustrophobic and unable to undergo the procedure, an unanticipated complication of the study design. Other clinical considerations include the completeness of revascularisation in STEMI, use of adjunctive pharmacotherapy during Impella support, duration of Impella support after PPCI, and access site management, i.e. removal of the pump using manual compression or pre-close suture.

Figure 1: Design of the Door to Unloading (DTU) with Impella CP System in Acute Myocardial Infarction to Reduce Infarct Size study



MACCE = major adverse cardiac and cerebrovascular event; aMI = myocardial infarction; d = days; PPCI = primary percutaneous coronary intervention; STEMI = ST-elevation myocardial infarction; TIA = transient ischaemic attack.

In summary, this ongoing study has a strong focus on safety, using large bore access and device therapy. Appropriate patient selection is key to help us to understand the physiology and clinical correlates to DTU and how to use concomitant therapies to improve patient outcomes. ■

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Ventricular Unloading and Inflammation – The Role of Impella in Myocarditis

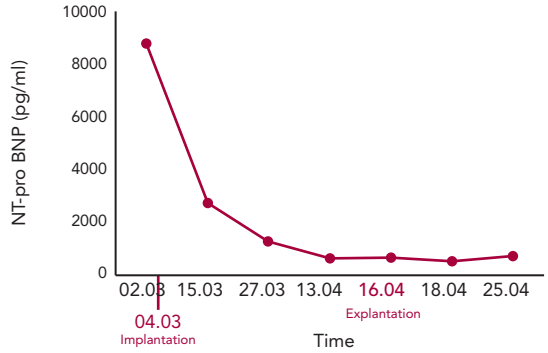
Presented by Carsten Tschöpe

Charité, CVK, Berlin, Germany

Dr Tschöpe is a Professor of Medicine and Cardiology and the Vice Director of the Department of Cardiology, Charité, CVK, Berlin, guiding the cardiomyopathy programme. His main research interests are the potential of cell therapies to cure heart failure and the role of the immune system in heart failure.

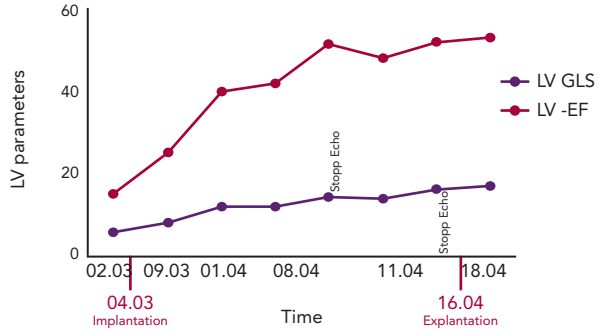
Acute fulminant myocarditis and giant cell myocarditis have a poor prognosis.[1] At present, short-term mechanical circulatory support (MCS) for myocarditis patients with refractory cardiogenic shock (CS) has predominantly used extracorporeal membrane oxygenation

Figure 1: Use of the Impella in a patient with myocarditis – NT-pro brain natriuretic peptide levels



NT-pro BNP = N-terminal pro-brain natriuretic peptide. Source: Tschöpe, 2017

Figure 2: Use of the Impella in a patient with myocarditis – left ventricle ejection fraction and strain

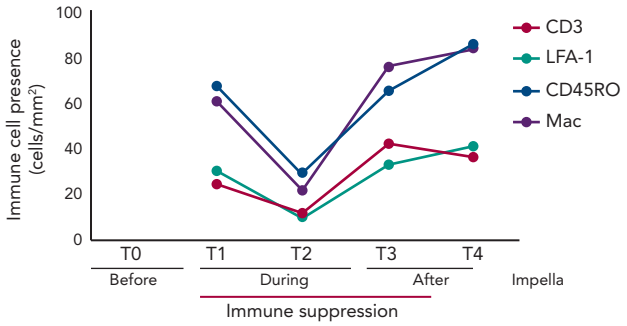


LV EF = left ventricular ejection fraction; LV GLS = left ventricular global longitudinal strain. Source: Tschöpe, 2017

(ECMO),[2] despite the use of Impella CP® for all other CS situations. Several case reports of successful short-term use of the Impella in fulminant myocarditis and giant cell myocarditis have been published.[3–7]

These reports have suggested that peripheral unloading with the Impella may not be merely providing circulatory support, but it also may be conferring additional anti-inflammatory effects that modify the disease state, thus allowing a bridge to recovery in patients with fulminant myocarditis. In order to explore this hypothesis further, Dr Tschöpe presented the known pathophysiological processes underlying myocarditis, including pro-inflammatory and fibrotic processes that lead to cardiac remodelling and failure during disease progression. In an overloaded myocardium such as is present during fulminant myocarditis, mechanical stress activates integrins (mechanoreceptors) in the heart, which are known to mediate pro-inflammatory and fibrotic processes. Furthermore, integrins are known to have direct detrimental effects on the contractile apparatus. These combined effects exacerbate myocarditis, and contribute to the observed poor patient outcomes. Therefore, the hypothesis is logically raised whether haemodynamically unloading the heart by means of MCS (thereby decreasing mechanical stress) is a sufficient means to overcoming these pathophysiological mechanisms.

Figure 3: Immune cell presence after unloading in a case of acute fulminant myocarditis



CD = cluster of differentiation; LFA-1 = lymphocyte function-associated antigen 1; CD4SRO = tyrosine phosphatase CD45. Source: Tschöpe, 2017

The hypothesis that mechanical unloading may improve reverse remodelling in fulminant myocarditis was tested in a 62-year-old patient recently admitted to the practice of Dr Tschöpe with severe myocarditis and pre-CS despite immunosuppressive therapy. An axillary Impella 5.0 was implanted, which remained in place for 40 days. After 2 days in bed, the patient was mobile. Steroid therapy and unloading gave a significant improvement in ejection fraction from 5 days after implantation. In addition, the patient's NT-pro brain natriuretic peptide levels reduced over time (see *Figure 1*), and increases were seen in EF and global longitudinal strain during short-time loading (see *Figure 2*). After 4 weeks, an echocardiogram showed the first signs of recovery.

Serial left ventricular biopsies taken at various time points during treatment to assess biomarkers of inflammation. These data demonstrate that the inflammatory response was significantly reduced during the time of Impella support. During this time steroids were also applied to decrease the inflammatory response. However, importantly, when the Impella was removed, the inflammatory response significantly increased, despite continued steroid use (see *Figure 3*). This suggests that Impella support may provide clinically important additional anti-inflammatory benefits beyond that observed with steroids alone. This pattern was seen for the levels of adhesion molecules ICAM-1 and VCAM-1, and also integrin receptors. Mass spectroscopic analysis of the biopsy samples revealed significant changes in protein composition, notably in the matrix proteins collagen and vimentin, which are important for integrin function. There was also a rapid improvement in titin function after unloading, which is essential for maintaining the elasticity of cardiomyocytes. Finally, energy consumption was assessed by measurement of glucose uptake and mitochondrial malate dehydrogenase. Again, a significant improvement was seen during the period of mechanical unloading.[8]

In conclusion, experience to date supports the hypothesis that prolonged unloading with an Impella device offers circulatory support with additional disease-modifying effects that are important for bridging fulminant myocarditis patients to recovery. ■

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Clinical Data and Experience With a Novel Right Ventricular Support Device, the Impella RP

Presented by Mark Anderson

Heart and Vascular Hospital, Hackensack Meridian Health Hackensack University Medical Center Hackensack, NJ, USA

Mark Anderson is the vice chair of cardiac surgery services and a cardiothoracic surgeon in the Hackensack University Medical Group. He is a leading expert in minimally invasive heart surgery, robotic techniques and mechanical assist devices. Dr Anderson is a founding member of the A-CURE Working Group.

Dr Anderson began his presentation by highlighting the high incidence of right ventricular (RV) failure during clinical interventions, including implantation with ventricular support devices.[1,2] The pathophysiology of RV failure includes impaired RV contractility, RV pressure overload, and RV volume overload.[3] Univentricular RV failure does occur, though biventricular involvement is commonly seen. RV failure increases morbidity and mortality rates in all clinical settings. Early management of RV failure is essential to improve survival.

The Impella RP is a modified version of the Impella CP that is designed for right heart support. One important difference is that, rather than pulling blood, it pushes blood from the inferior vena cava to the pulmonary artery. The Impella RP has received approval from the US Food and Drug Administration (FDA).[4] Approval was based on the findings of the RECOVER RIGHT study, which investigated the use of Impella RP support system in patients with RV failure (n=30).[5] Each study had two cohorts: patients with RV failure after left ventricular assist device implantation and patients with RV failure after cardiotomy or myocardial infarction, with a duration of support of 3 to 4 days. Haemodynamic improvement was seen following Impella implantation. There was also a decrease in the use of inotropes and vasopressors in all patients after Impella RP support. The primary endpoint was defined as survival at 30 days post device explant or hospital discharge (whichever is longer). The overall survival rate at 30 days was 73.3 %. All patients discharged were alive at 180 days. This endpoint was reached in 77 % of patients. The rate of device-related bleeding and haemolysis was low.

A continuous access protocol with same inclusion/exclusion criteria as those in the RECOVER RIGHT study was set up to continue the RECOVER RIGHT study during the initial FDA application. In addition, the Impella RP® Post Approval Study, a prospective, single arm, multi-centre study monitoring the safety and outcomes trends of the Impella RP device in patients with RV failure who require haemodynamic support (n=26), was completed in the last year.

Dr Anderson discussed some unresolved clinical issues that have been identified during these studies, primarily the challenge in accurately predicting and sometimes diagnosing RV failure. He also mentioned that there are still several practices that need further refinement and standardisation, including the anticoagulation approach and weaning protocols.

In conclusion, RV failure is associated with increased mortality rates and is difficult to predict and sometimes to diagnose. The Impella RP device is easy to use and consistently improves patient haemodynamics while providing ventricular unloading. The Impella RP has a favourable safety profile with low adverse events across all studies. The use of Impella RP in RVF has demonstrated improved survival. The Impella RP therefore represents a viable tool to enable recovery or as a bridge to other destination therapies. ■

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Impella Support Improves Pulmonary Congestion in Cardiogenic Shock

Presented by Ralf Westenfeld

Chief, Division of Cardiology, Pulmonology and Vascular Diseases, University Hospital Düsseldorf, Germany

Dr Westenfeld is head of the intensive care medicine and heart failure section at University Hospital, Dusseldorf, Germany. His research interests include the pathomechanisms of cardiovascular calcification, interventional treatment strategies in high-risk patients, and myocarditis and transplant rejection.

Dr Westenfeld began by describing the current state of understanding of pulmonary congestion in cardiogenic shock (CS). The evolution of systemic inflammatory response and multiple organ dysfunction syndrome following cardiopulmonary resuscitation may affect post-cardiac-arrest-syndrome.[1] Acute lung injury is an unrecognised problem in patients on extracorporeal life support (ECLS) who undergo implantation of a long-term mechanical circulatory support (MCS) device.[2] In addition, early progression of pulmonary oedema (within 24 hours) has been found to predict mortality in patients with extracorporeal membrane oxygenation (ECMO).[3] Increased pulmonary congestion in patients with ECMO carries the same mortality risk as dialysis. However, there have been no studies on the evolution of pulmonary congestion in CS.

Dr Westenfeld's team proposed the hypothesis that that pulmonary congestion in CS develops differently according to the type of MCS (Impella versus intra-aortic balloon pump [IABP]), and also that early increase of pulmonary congestion in CS is associated with adverse outcome and recovery. In order to investigate this hypothesis, a method of quantifying pulmonary congestion without the use of a CT scan was required. The Halperin score identifies six areas from chest X-rays and assigns scores according to the observed opacification. Congestion is then classified according to the Halperin score as mild (score 100), moderate (230) or severe (310).

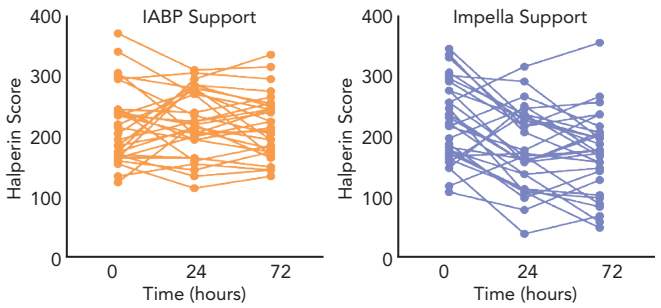
Dr Wentenfeld presented a retrospective study that identified 74 patients with CS who had received either IABP (January 2012–May 2015, n=43) or Impella (April 2014–June 2016, n=31) support.[4] After excluding patients who died during the blanking period or those who required ECLS, 60 patients remained for analysis; 30 who received IABP and 30 who received the Impella. On admission, patient characteristics were similar between groups (see *Table 1*). They had high serum lactate during MCS support, which was higher in the Impella group (see *Table 1*). Similarly, troponin levels, inotropic score, and levels of lactate dehydrogenase were also high, but not significantly different between groups. Data suggest that the patients treated with Impella may have been associated with increased tissue perfusion, which could lead to the observed higher lactate levels, or this group may have included sicker patients, supported by the data that an upgrade to ECLS or left ventricular assist device was needed in 10 % of the IABP group versus 33 % in the Impella group (P=0.03). Pneumonia was reported in 76 % of patients receiving IABP and 56 % receiving the Impella (P=0.18). Hospitalisation in the intensive care unit was required for 15±15 days and 24±14 days in the IABP and Impella groups, respectively (P=0.03). Total hospitalisation was 30±35 days and 48±30 days, respectively (P=0.03). At 30 days, survival was 42 % and 48 %, respectively (P=0.8).

Table 1: Patient characteristic on admission

	IABP (n=30)	Impella (n=30)	P value
Age (years)	69 ± 12	65 ± 14	0.12
Gender (f/m)	7/23	12/18	0.17
BMI (kg/m^2)	2 ± 5	27 ± 5	0.59
CPR (%)	47	50	0.8
STEMI (%)	47	37	0.44
Revascularisation (%)	80	60	0.09
SOFA score	9 ± 2.9	9 ± 2.8	0.72
APACHE score	23 ± 8.8	22 ± 6.2	0.55

APACHE = Acute Physiology and Chronic Health Evaluation; BMI = body-mass index; CPR = cardiopulmonary resuscitation; IABP = intra=aortic balloon pump; SOFA = Sequential Organ Failure Assessment; STEMI = ST-elevation myocardial infarction. Source: Wetsenfeld et al, 2017

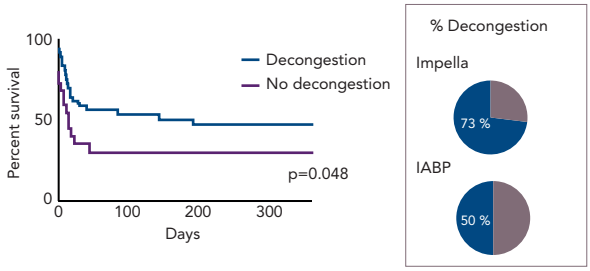
Figure 1: Ventricular unloading is associated with pulmonary decongestion in cardiogenic shock



IABP = intra-aortic balloon pump. Source: Westenfeld et al, 2017

Regarding the impact of ventricular unloading by the Impella on pulmonary congestion, a significant decrease in the Halperin score at 72 hours was observed in patients treated with Impella compared with those treated with IABP (see *Figure 1*). When the entire cohort was divided into patients who did or did not experience pulmonary decongestion as defined by the Halperin score, an association was seen between reduction of pulmonary congestion within the first 24 hours and improved survival in CS (see *Figure 2*). However, this Impella-dependent effect did not translate directly into a significant survival benefit in the overall cohort. Dr Westenfeld commented that in the cohort he examined, decongestion was achieved in 73 % of Impella-supported patients, but only 50 % of IABP patients.

Figure 2: Impact of congestion on survival in cardiogenic shock



Source: Westenfeld et al, 2017

In conclusion, in this single centre study, data suggest that early progression of pulmonary oedema is associated with poor outcome in CS. Left ventricular unloading by Impella may more effectively facilitate pulmonary decongestion in CS compared with IABP support. This study was limited by its small sample size and retrospective design. There is a need for a large-scale analysis of outcomes and confounders in large registry studies. In addition, prospective analysis is needed of pulmonary congestion in CS, using early assessment by ultrasound, guiding escalation strategies, and investigating weaning and haemodynamics. Finally, mechanistic studies in large animal models will help elucidate the effects at the molecular level in terms of mitochondrial function, reactive oxygen species production and the effects of unloading on inflammation. ■

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Plenary Lecture: The Evolution of Cardiovascular Disease Worldwide: New Frontiers

Presented by Valentin Fuster

Mount Sinai Medical Hospital, New York, USA

Dr Fuster is a distinguished figure in the cardiology field. Following his graduation from the University of Edinburgh he commenced work at the Mayo Clinic and Mount Sinai, where he is now physician-in-chief. In 1996 he received the Principe de Asturias Award of Science and Technology, the highest award given to a Spanish-speaking scientist. In 2010 Dr Fuster received an Honoris Causa from the University of Edinburgh, one of the 40 that he has achieved to date. As of December 2016 Dr Fuster has served as Program Director for the American College of Cardiology's Annual New York Cardiovascular Symposium for 22 consecutive years. He has also authored books and starred in a movie, The Resilient Heart, which focused on his work in prevention of cardiovascular disease (CVD). Dr Fuster is a member of the Institute of Medicine of the National Academy of Sciences.

The evolution of CVD therapy worldwide is moving towards identifying risk at early stages of life.[1] While recent advances in surgery, intervention, pharmacology, imaging and genetics have been impressive for the treatment and understanding of later stage CVD; mechanisms of disease differ at different life stages. The 2013 American College of Cardiology Foundation/American Heart Association (ACCF/AHA) Guideline for the Management of Heart Failure (HF) guidelines was based on advanced disease.[2] While recent work has highlighted the rapid advances that have been made in understanding dilated cardiomyopathy, a precursor to HF,[3] and assist devices have proven effective in end-stage disease,[4] Dr Fuster emphasised the need to focus on people at high risk for HF, but without structural heart disease.

He highlighted recent additions to the guidelines that have included biomarkers that may help identify an at-risk population.[5] These include screening assays based on levels of pro-brain natriuretic peptide[6] and troponin,[7] leading to high-sensitivity cardiac troponin (hs-cTn) assays.[8] Six-year increases in the levels of hs-cTn, suggestive of progressive myocardial damage, are independently associated with HF.[9] A risk model based on these biomarkers has been used to develop a robust tool for the prediction of cardiovascular death in patients with stable coronary heart disease.[10] Other aspects of changing approaches to CVD include a greater focus on the atherosclerotic disease burden rather than on features of individual plaques,[11] and the evolving paradigm of CVD as a systemic disease that is dependent on macrophage activity.[12] Imaging studies of patients after acute coronary syndrome (ACS) have demonstrated increased splenic metabolic activity after ACS and its association with proinflammatory remodelling of circulating leukocytes.[13] Evolving non-invasive technologies are also evaluating ischaemia at the microcirculation level.[14] In the future, Dr Fuster predicts that ischaemia of each artery will be assessed by non-invasive techniques.

Dr Fuster turned his focus to the evolving landscape of CVD and what he believed the future hold for its various treatments. Due to the increasing prevalence of diabetes, Dr Fuster predicts an increasing use of coronary artery bypass grafts and decreasing use of optimal medical therapy and percutaneous intervention. However, pharmacology may play a role in earlier disease stages. Of particular interest are the proprotein convertase subtilisin/kexin 9 inhibitors,[15] and the results emerging from cardiovascular outcome trials involving sodium-glucose

cotransporter 2 inhibitors and glucagon-like peptide 1 analogues.[16] In addition, new treatment modalities for HF that are employed at the early stages of the disease are emerging,[17] and cardiovascular regenerative medicine using genetic editing is advancing rapidly and offers considerable future potential.[18]

Dr Fuster turned his attention to the challenges of treating HF in older patients. Chief among his concerns was patient adherence to therapy, which has led to the development of the polypill for cardiovascular prevention.[19–21] Also important is the issue of cognitive degeneration due to microvascular disease. The cumulative burden of cardiovascular risk factors from childhood/adolescence has been associated with worse midlife cognitive performance independent of adulthood exposure.[22] Dr Fuster is currently undertaking a study known as the Trans-Atlantic Network to Study Stepwise Noninvasive imaging as a Tool for Cardiovascular Prognosis and Prevention (TANSNIP) heart to heart (H2H), to investigate the relationship between levels of dementia and cardiovascular risk factors.

Finally, Dr Fuster emphasised that of all the risk factors for CVD, behaviour is the most difficult to modify. However, a number of successful community interventions have illustrated the value of education.[25] Several studies and health programmes have independently indicated that behaviour modification, in terms of preventing CVD, is best achieved if the intervention is applied at early ages. Dr Fuster is personally involved in many educational initiatives that promote cardiovascular health during childhood.[26] Dr Fuster concluded by reinforcing the importance of identifying CVD at an early stage. ■

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Left Ventricular Support Using Impella Relieves Left Arterial Stretch and Inhibits Atrial Arrhythmias Through Reduced Oxidative Stress

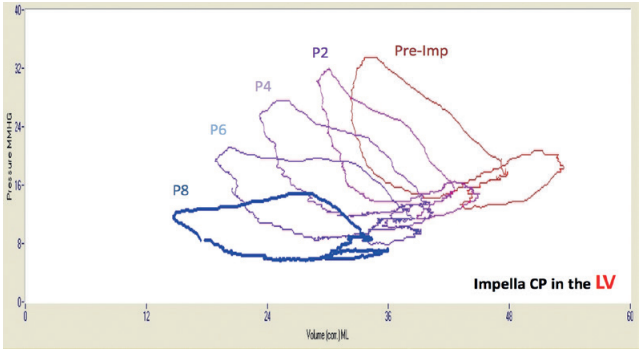
Presented by Kiyotake Ishikawa

Icahn School of Medicine at Mount Sinai, New York, USA

Dr Ishikawa is an assistant professor at Icahn School of Medicine at Mount Sinai, New York.

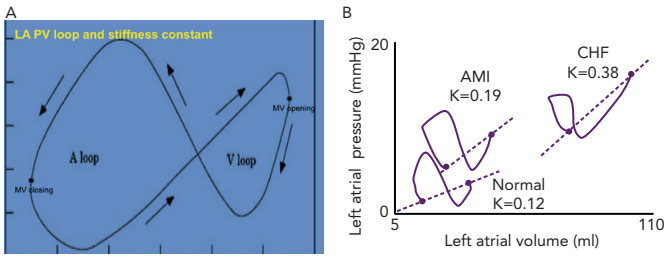
Dr Ishikawa's talk focused on his investigations into how left ventricular mechanical support affects left atrial haemodynamics. He recalled the common observation that following implantation of an Impella CP into the ventricle of a porcine model of myocardial infarction (MI), a dramatic reduction in left ventricular end diastolic pressure (LVEDP) is immediately seen. As flow is gradually increased, a further decrease in LVEDP follows. This led Dr Ishikawa to question how the unloading of the left ventricle would affect left atrium (LA) physiology, as the latter is closely linked to LVEDP. He investigated this by placing a pressure-volume catheter inside the LA through an atrial septostomy, and recording the effects of LV mechanical on atrial haemodynamics. In the same porcine model of MI, he observed a flow-dependent unloading of the LA (see *Figure 1*).[1] A characteristic LA-PV loop was seen (see *Figure 2*), in which the left side of the loop represents atrial contraction,

Figure 1: Flow-dependent LA unloading



LV = left ventricle. Source: Ishikawa et al, 2017

Figure 2: a) Left atria pressure-volume loop; b) Variation in left atrial pressure-volume loops in cardiac disease



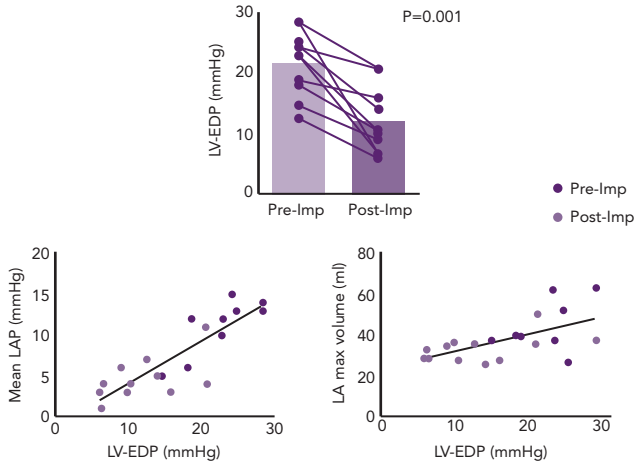
AMI = acute MI; CHF = chronic heart failure; LA = left atrial; PV = pressure-volume. Source: Ishikawa et al, 2017

giving rise to atrial pressure and a simultaneous decrease in volume as blood is expelled. When the mitral valve (MV) closes, the LA relaxes and we can observe the passive filling phase of the chamber by blood flow from the pulmonary veins. When the LA is stiff, the slope of the pressure–volume relationship is steeper because the same amount of volume increase will lead to a higher increase in pressure. This slope may, therefore, be considered as an index of LA stiffness. In patients with cardiac disease leading to a less compliant myocardium, steeper slopes are observed (see *Figure 2*).

Dr Ishikawa compared the slopes of these atrial pressure-volume loops in the same pigs before and after Impella LV support. The steepness of the slope, and therefore LA stiffness, was significantly decreased after LV Impella support. During MI, LVEDP increases together with LA pressure. This stretches the LA, making it more difficult to expand. Dr Ishikawa highlighted the interdependence of LA haemodynamics on those of the LV. The observed reduction in LVEDP while on Impella supported correlated well with the LA pressure as well as maximal LA volume (see *Figure 3*). In terms of LA function, LA ejection fraction was improved when the Impella was supporting the LV. Importantly, this was not associated with an increased atrial load, indicated by reduction of LA atrial work and developed pressure (dp/dt max) when the Impella was in place.[1] This suggested that atrial contraction was more efficient when the atrium was unloaded.

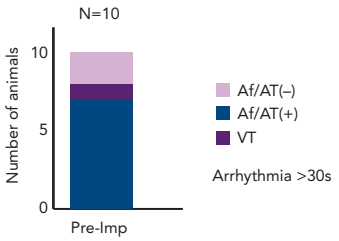
Since atrial stretch is a known mechanism for atrial arrhythmia, Dr Ishikawa's team investigated whether the use of the Impella reduced arrhythmogenesis. Using pacing of the right atrium, atrial tachycardia or atrial fibrillation was induced in the majority (70 %), while not unloaded by the Impella. By supporting these same pigs with an Impella in the LV,

Figure 3: Decreased LA pressure and volume with the Impella



LV-EDP = left ventricular end diastolic pressure; LAP = lest arterial pressure. Source: Ishikawa et al, 2017

Figure 4: Reduced arrhythmia inducibility and maintenance with the Impella



Af/AT = atrial fibrillation/atrial tachycardia; VT = ventricular tachycardia. Source: Ishikawa et al, 2017

the rate of atrial arrhythmia was reduced to only 30 % (see *Figure 4*). Furthermore, the duration of the arrhythmia events was found to correlate with the maximum LA volume, suggesting that LA stretch may play a key role in mediating the maintenance of atrial arrhythmias.[1]

Dr Ishikawa's team then explored the molecular mechanism underlying this effect. Earlier research found that stretching cardiomyocytes *in vitro* induces oxidative stress and increases spontaneous Ca^{2+} leak from the sarcoplasmic reticulum, which is a demonstrated arrhythmogenic trigger.[2] Dr Ishikawa's team therefore measured the expression level of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase 2 (NOX2), a stretch-dependent source of reactive oxygen species. He found levels of NOX2 to be increased in the LA after MI compared with controls, but NOX2 levels were remained unaffected in those animals that underwent LV Impella support for 2 hours. He demonstrated that increased NOX2 levels were associated with increased phosphorylation the ryanodine receptor 2, the source of diastolic Ca^{2+} leak. This increased phosphorylation was not observed in atria supported with the Impella.

In conclusion, LV unloading with the Impella CP also significantly affects the haemodynamics of the upstream LA. Directly unloading the LV with mechanical support leads to passive unloading of the LA, reduces LA stretch, and inhibits atrial arrhythmogenesis by modulating stretch-dependent oxidative stress. ■

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Utilisation of Support Device Hysteresis to Track Cardiac Function

Presented by Elazer R Edelman

Harvard University, Massachusetts Institute of Technology, Boston, MA, USA

Dr Edelman is the Thomas D and Virginia W Cabot Professor of Health Sciences and Technology at MIT, Professor of Medicine at Harvard Medical School, and Senior Attending Physician in the coronary care unit at the Brigham and Women's Hospital in Boston. His team has pioneered basic findings in vascular biology and the development and assessment of biotechnology. Dr Edelman directs the Harvard-MIT Biomedical Engineering Center, dedicated to applying the rigors of the physical sciences to elucidate fundamental biological processes and mechanisms of disease. Dr Edelman is a founding member of the A-CURE Working Group.

Dr Edelman commenced his presentation by reminding the audience that the Impella can be utilised not only as a therapeutic tool, but also as a diagnostic tool. Since it resides in the ventricle, it is uniquely positioned to provide insights into the function of the heart. It works in concert with the heart, is relatively non-disruptive, and its design allows the extraction of a substantial amount of information. The pump maintains a constant rotor speed by changing the motor current in response to the variable load caused by a pulsatile flow envirwonment. The motor current undergoes subtle variations in every beat. Dr Edelman's team therefore proposed the hypothesis that the relationship between a pump parameter (motor current) and a physiological parameter (pressure head) could be used to obtain diagnostic information on the function of the left ventricle (LV). The plotted relationship between the pressure head and the motor current forms a hysteresis loop which is asymmetric, non-linear and changes with each cycle, making extraction of information challenging. However, every pump exhibits the same hysteresis loop phases, making it possible to extract information about heart function such as the LV end diastolic pressure (LVEDP), peak pressure, slope of relaxation and slope of contraction.

In a recent study that aimed to validate this hypothesis, an Impella CP with both ventricular and aortic pressure sensors was implanted into a mock circulation loop.[1] The contractility was kept constant and the LVEDP was varied (see *Figure 1*). Similarly, it was possible to maintain a constant preload and vary the contractility. The motor current and aortic pressure were extracted from the console and plotted to illustrate the hysteresis relationship (see *Figure 1*). These inputs were then used to calculate LVEDP and contractility measurements. Using these techniques, multiple indices of LV function may be measured. Dr Edelman presented a flow chart describing the method for the use of device extracted metrics to predict physiological function, such as LVEDP during (see *Figure 2*).[1] It is hoped that this approach to estimating metrics of heart function will be placed into next generation of Impella devices.

Swan-Ganz catheters are used in patients regularly to estimation of LVEDP with real-time wedge tracing during end-expiratory hold. This new method of estimating heart function using device derived metrics would decrease the number of catheters in patients on Impella support by having one catheter residing in the LV that provides both circulatory support and heart function information.

In summary, understanding the dynamic changes of disease progression and its effect on cardiac state allows for standardised care of the patient, as well as improved outcomes using quantitative optimisation. From the clinician point of view, it also allows determination of the optimal Impella therapy in conjunction with other forms of therapy. ■

Figure 1: Hysteresis loop across different preload and contractility conditions

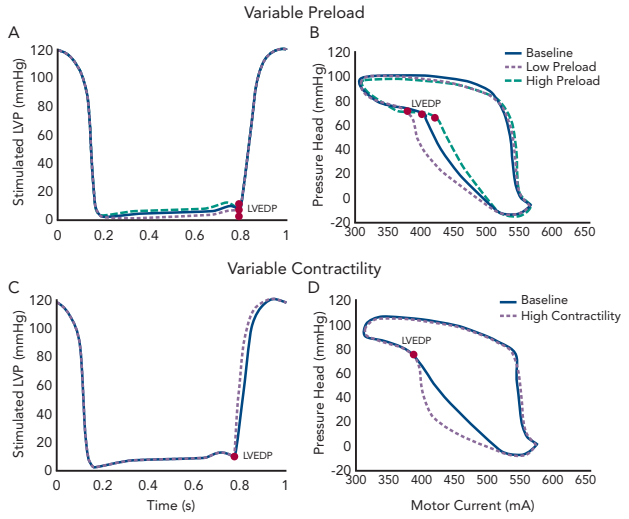
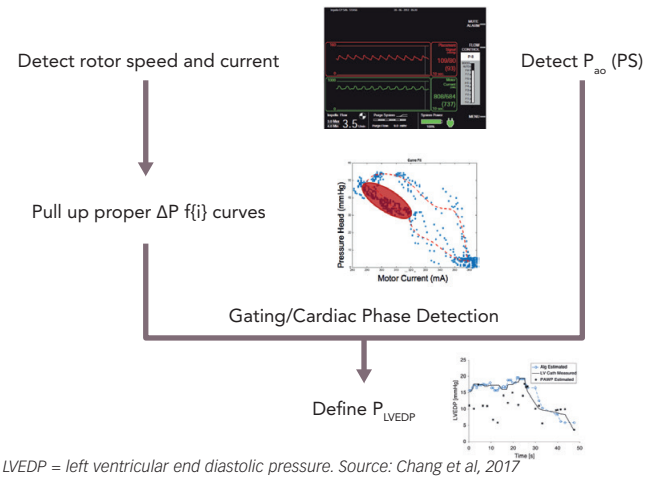


Figure 2: Flowchart for predictive use of the Impella



LVEDP = left ventricular end diastolic pressure. Source: Chang et al, 2017

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Optimal Haemodynamic Support during Cardiac arrest in the Cardiac Catheterisation Laboratory

Presented by Kapil Lotun, MD

University of Arizona, USA

Kapil Lotun is Associate Professor of Medicine, Associate Director Cardiac Cath Lab, Director of TAVR Program, Director of Vascular Medicine, Director of Structural Heart Disease, Sarver Heart Center, Division of Cardiology, University of Arizona, USA.

The goals of therapy for cardiac arrest in the catheterisation laboratory are to maintain vital end organ perfusion and correct the precipitating cause of cardiac arrest, usually achieved by percutaneous coronary intervention (PCI). However, these goals often compete with each other. Manual chest compression is very challenging in the catheterisation laboratory, partly because of space limitations, and can result in the provider experiencing excessive radiation exposure. Mechanical cardiopulmonary resuscitation (CPR) provides unique advantages over manual chest compression for treating cardiac arrest in the cardiac catheterisation laboratory.[1]

Mechanical circulatory support (MCS) has the potential to provide adequate end organ perfusion in this situation. It is readily available and can be initiated quickly. The available MCS devices have low complication rates and are inexpensive. Of the available devices, the TandemHeart is not practical to implant during cardiac arrest. Use of the Impella or extracorporeal membrane oxygenation (ECMO), however, hold more potential (see *Table 1*). A recent study found that the use of MCS during resuscitation of cardiac arrest in the catheterisation laboratory increases the rate of return of spontaneous circulation (ROSC).[2] A case series (n=8) found that use of the Impella was feasible in selected patients with cardiac arrest and gave a 6-month survival rate of 50 %.[3] The same survival rate was reported in a case series (n=14) that employed miniaturised ECMO systems.[4]

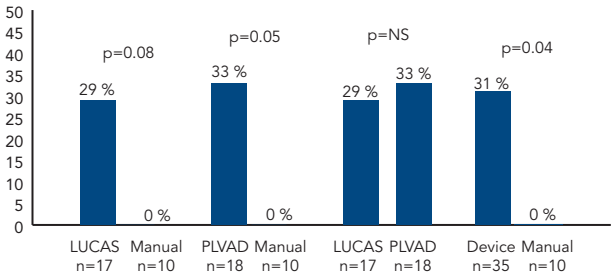
Recently, Dr Lotun's team conducted a study in which 30 pigs were randomly assigned to interrupted manual chest compressions (n=10) versus either a piston chest compression device (LUCAS™; n=10) or a percutaneously inserted Impella device (n=10), supporting systemic haemodynamics and perfusion during two clinically relevant time periods of cardiac arrest associated with a left main/proximal left anterior descending (LAD) coronary occlusion in the cardiac catheterisation laboratory.[5] The primary endpoint was favourable neurological function of survivors at 24 hours. Secondary endpoints included defibrillation success, ROSC and resuscitation-generated haemodynamics. The primary endpoint was achieved in 29 % of the LUCAS group and 33 % of the Impella group compared with none of the manual group.[5] ROSC was achieved in 78 % of the Impella group, compared with 50 % and 59 % in the manual and LUCAS groups, respectively.

Table 1: Comparison of mechanical support for cardiac arrest

	Mechanical CPR	Impella	ECMO
Level of support	?++	?++	++++
Time to initiation	<2 minutes	Longer	Longer
Readily available	+++	++	+ Institution dependent
Device complication rates	Low	Higher	Higher
Cost	$	$$$$	$$$$
Other		L-sided support only unless Impella RP also placed	Increases LVEDP, also oxygenate

CPR = cardiopulmonary resuscitation; LVEDP = left ventricular end diastolic pressure

Figure 1: Survival with 24 hour favourable neurologic recovery



NS = not significant; PLVAD = percutaneous left ventricular assist device.
Source: Truong et al, 2016

In conclusion, cardiac arrest in the catheterisation laboratory is a devastating event and will be more common with increasingly complex interventional procedures. The goal of circulatory support is to provide vital organ perfusion while the operator is correcting the underlying cause. Mechanical compression devices offer unique advantages over manual compression in this setting. The placement of percutaneous MCS devices can be considered but further studies are needed to define the optimal device and clinical outcomes. ■

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Myocardial Mitochondrial Reactive Oxygen Species Production is Reduced in the Left Ventricle of Mechanically Unloaded Hearts

Presented by Daniel Scheiber

Assistant Doctor, Section Intensive Care Medicine and Heart Failure, Division of Cardiology, Pulmonology and Vascular Diseases, University Hospital Düsseldorf, Germany

Dr. Scheiber is a practicing cardiac physician at Heinrich Heine Universität Düsseldorf. He was the recipient of the Young Investigator Scholarship for the 2017 A-CURE Symposium.

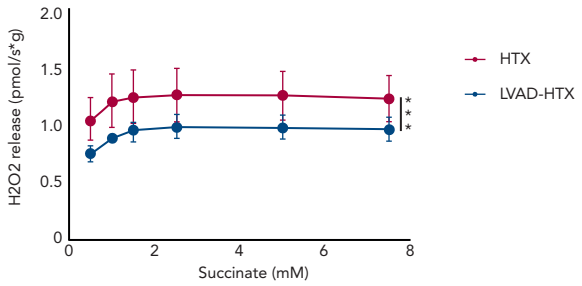
Dr Scheiber was the recipient of the Young Investigator Scholarship Award. He commenced his presentation with a discussion of mitochondrial energy metabolism in the failing heart. The heart consumes more energy than any other organ. To match this high energy demand, myocardial mitochondria cycle up to 6 kg of ATP every day, which is about 20 to 30 times the heart's own weight. Myocardial mitochondrial energy metabolism in the failing heart has, therefore, become a field of considerable interest.[1,2]

Increased ventricular filling pressure and volume are hallmarks of heart failure (HF) pathophysiology.[3,4] This pressure and volume overload is linked to alterations in myocardial substrate utilisation, mitochondrial energy production, and mitochondrial reactive oxygen species formation.[5,6] Clinical evidence suggests that ventricular unloading can reverse systemic and local metabolic dysfunction in patients with advanced HF treated with durable ventricular assist devices.[7] However, there are no functional data on mitochondrial respiration in the failing heart under these unloading conditions.

Dr Scheiber's team proposed the idea that chronic left ventricular unloading in terminal patients with HF would improve myocardial mitochondrial oxidative phosphorylation and reduce myocardial mitochondrial reactive oxygen species production. In order to investigate this hypothesis, a prospective study evaluated 13 patients undergoing heart transplantation between October 2016 and July 2017. Eight patients had a left ventricular assist device (LVAD) surgically implanted as a 'bridge to transplant' prior to heart transplantation. Myocardial tissue specimens were harvested from macroscopically scar-free areas of the left ventricular free wall of the explanted heart. Patients did not differ significantly in age or body mass index. The average time of unloading in the LVAD-supported patients was 20 months.

The *ex vivo* maximal myocardial oxidative phosphorylation capacity was analysed in tissue specimens. There was a similar maximum oxygen flux on fatty acids and tricarboxylic acid cycle derivates in chronically unloaded compared with standard heart explants. Interestingly, the respiratory control ratio, which is a surrogate marker of coupling efficiency, was significantly increased in the unloaded group compared with the standard transplant group, suggesting more efficient ATP production in these mitochondria. Analysis of myocardial mitochondrial hydrogen peroxide production between these two groups showed that reactive oxygen species production during mitochondrial respiration was decreased in tissue samples of the chronic unloaded hearts (see *Figure 1*).

Figure 1: Decreased hydrogen peroxide release in chronic unloaded explant hearts



H2O2 = hydrogen peroxide; HTX = heart transplantation. Source: Scheiber et al, 2017

In conclusion, this study found an increased mitochondrial coupling efficiency and decreased hydrogen peroxide production in chronically unloaded hearts, but no differences in maximal mitochondrial respiration when comparing those hearts haemodynamically unloaded by LVADs with hearts that were unsupported. Future research will investigate whether alterations of mitochondrial respiration occur during ventricular unloading in acute cardiogenic shock and, if so, how this may impact patient outcomes and heart recovery. Other planned studies include the impact of acute ventricular unloading on mitochondrial respiration and hydrogen peroxide production. ■

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Combining Extracorporeal Membrane Oxygenation and Impella for the Treatment of Cardiogenic Shock

Presented by Dirk Westermann

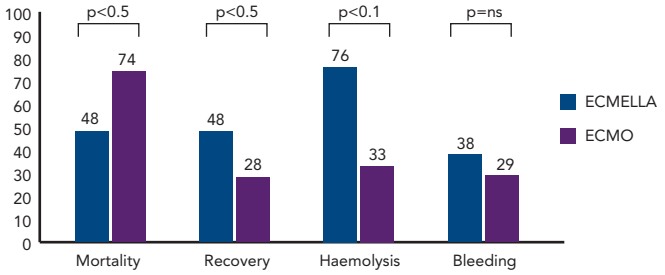
Department of General and Interventional Cardiology, University Heart Centre Hamburg, Germany

Dr Westermann is Deputy Director of the Department of General and Interventional Cardiology, University Heart Centre Hamburg. He is a specialist in Internal Medicine and Cardiology.

Dr Westermann opened his talk by reminding the audience of the surprising findings of the intraaortic balloon pump (IABP) SHOCK II study, which showed that the use of an IABP did not significantly reduce 30-day mortality in patients with cardiogenic shock (CS) complicating acute myocardial infarction.[1] Alternative methods of treating CS have, therefore, been sought. Many doctors have turned to using extracorporeal membrane oxygenation (ECMO) to support these patients. Dr Westermann presented unpublished data from a large study (n=9,258) that showed a rapid growth in the use of ECMO in Germany from 2007–2014.[2] Survival at 30 days was lower in patients over 65 years old and in those who required cardiopulmonary resuscitation (CPR). Using these data, an ECMO mortality score has been developed and validated.[2] However, prolonged use of ECMO (>2 days) is associated with greatly increased mortality.[3] The use of ECMO presents a number of clinical challenges. In particular, Dr Westermann highlighted that ECMO leads to an increased ventricular afterload. This increased afterload can become pathophysiological in ECMO patients causing vascular complications (bleeding, ischaemia, embolism), increased left ventricular (LV) filling pressures, increased in LV wall stress, pulmonary congestion, and the watershed phenomenon. The solution to this pathophysiological haemodynamic derangement is to vent the ECMO patient and relieve increased LV pressures and volume.

Recently, Dr Westermann's team has investigated a different LV venting strategy in ECMO patients. The addition of VA-ECMO leads to decreased stroke volume and a right-shift of the pressure-volume loop. This increased afterload is due to retrograde femoral flow in CS. This causes further ECMO-dependent increases in LV wall stress and LV pressures, conditions that are unfavourable to the patient. Therefore, there is a need to shift pressure-volume loops to the left, which can be achieved by unloading the LV. This can be achieved through transseptal methods (e.g. atrioseptostomy, TandemHeart) or the less invasive transvalvular route (e.g. Impella). Dr Westermann suggested that the use of the Impella in addition to VA-ECMO may improve outcomes in patients with CS due to LV unloading.

Figure 1: Outcomes using the concomitant use of ECMO and the Impella, or 'Ecmella'



ECMO = extracorporeal membrane oxygenation. Source: Westermann et al

This hypothesis was tested in a study that enrolled 157 patients with CS: 123 received VA-ECMO support and 34 had concomitant treatment with VA-ECMO and an Impella device. A propensity-matching analysis was performed in a 2:1 ratio, comparing 42 patients undergoing VA-ECMO alone (control group) with 21 patients treated with VA-ECMO and Impella. Patients in the VA-ECMO plus Impella group (termed Ecmella) had a significantly lower rate of in-hospital mortality (47 % versus 80 %; P<0.001) and a higher rate of successful bridging to either recovery or further therapy (68 % versus 28 %; P<0.001) compared with patients receiving VA-ECMO alone.[4] Similar findings have been observed in Dr Westermann's recent registry study in Hamburg (n=81).[5] There is increased haemolysis in the Ecmella group, but he indicated this did not lead to increased clinical complications. Those patients treated with ECMO/Ecmella also had significantly more rapid weaning from inotropes.

In conclusion, ECMO therapy may improve survival in CS; however, there is a lack of randomised controlled trial data. In addition, haemodynamic challenges remain with ECMO therapy in CS, including increases in afterload, LV wall stress, and pulmonary congestion. LV unloading with concomitant use of an Impella device may positively affect outcomes in patients with CS on VA-ECMO. It should be noted that data in support of

this new concept have been derived from a registry study. Randomised controlled trial data are required. Nevertheless, Dr Westermann's group have decided to use the Ecmella strategy as their clinical standard for future ECMO patients. ■

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Concluding Remarks

In the closing remarks, Dr Kapur commented that the work presented has provided a huge breadth of research related to acute unloading and myocardial recovery, acknowledging the support of the sponsorship from Abiomed. Dr Anderson commented that this meeting represents an advance from last year and exciting and inspiring to see new thoughts and investigations that will further advance the field. He made special reference to Dr Fuster, whose passion for the cardiovascular field has driven him to accomplish so much. Dr Anderson hopes that passion for this new field of cardiology will encourage investigators to think outside the box. Dr Burkhoff concluded the meeting by acknowledging the quality of the presentations and posters, which is unprecedented in an emerging field. While he recognised the unique advantages of being a small group in a unique setting, he encouraged future growth of the A-CURE group. ■

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Proceedings of the 3rd annual Acute Cardiac Unloading and REcover (A-CURE) symposium held on 8-9 November 2018 in Chicago, IL, USA

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MEETING REPORT Open Access

Proceedings of the 3rd annual Acute Cardiac Unloading and REcovery (A-CURE) symposium

Uma Chandrasekaran[1*], Daniel Burkhoff[2], Kiyotake Ishikawa[3], Lija Swain[4], Kenji Sunagawa[5], Jacob Møller[6], Carlos Santos-Gallego[3], Shiva Annamalai[4], James Udelson[4], Ralf Westenfeld[7], Navin Kapur[4], Xiaoying Qiao[4], Julian Wiora[7], Andreas Schäfer[8], Alexander Bernhardt[9], Ajar Kochar[10], Robert Kloner[11] and Haroon Faraz[12]

From The 3rd Annual A-CURE Symposium
Chicago, IL, USA. 8-9 November 2018

Foreword

Welcome to this special supplement devoted to the proceedings of the 3rd Annual Acute Cardiac Unloading and REcovery (A-CURE) Working Group meeting, which was held on November 9, 2018, in Chicago, USA. The A-CURE Working Group is comprised of leading academic experts in clinical and basic cardiac research who are dedicated to advancing the science and clinical application of acute cardiac unloading. This meeting brought together experts from multiple disciplines, including interventional cardiologists, heart failure specialists, cardiac surgeons, molecular biologists, and biomedical engineers. The 2018 Symposium featured talks and posters that highlighted cutting-edge advances in the field of acute cardiac unloading that have taken place since the conclusion of the 2017 A-CURE Symposium in Barcelona, Spain.

Cardiac disease states such as myocardial infarction (MI), myocarditis, cardiomyopathy, and cardiogenic shock impair the ability of the heart to pump blood, resulting in end organ failure and, ultimately, death. Pharmacological therapies for these disease states aim to maintain cardiac output but, in the process, impose further stress on the heart. Additional treatment strategies are needed. The A-CURE Symposium focused on the basic science and clinical application of new technologies. Acute cardiac unloading decreases myocardial oxygen consumption and maximizes the ability of the heart to rest and recover after damage. Mechanical unloading employs percutaneous ventricular assist devices such as the FDA-approved Impella family of devices, to decrease the physical workload of the heart.

This supplement features a number of presentations covering a broad range of subjects related to cardiac unloading. The first session of the symposium was devoted to the advances in basic and preclinical science of acute unloading and myocardial salvage. Topics discussed during the presentations ranged from influence of acute unloading on intercellular and inter-organ communication through exosome-based signaling to preservation of mitochondrial structure and function post-myocardial infarction (MI). New models of cardiogenic shock and investigations demonstrating enhanced collateral blood flow with acute unloading to reduce infarct size were also discussed.

In the keynote lecture, James Udelson focused on the physiologic and pathologic basis of left ventricular remodeling and the lessons learned from clinical trials in the field of chronic heart failure.

The second session of the symposium focused on clinical research programs of cardiac unloading. Wide spectrum of clinical studies presented included cardio-renal system interaction with effect of hemodynamic support on acute kidney injury, outcomes associated with adoption of standardized protocol for treatment in cardiogenic shock, and the first-in-man experience with the new Impella 5.5 heart pump.

The afternoon's presentations had a stronger focus on the clinical translation of left ventricular (LV) unloading. The temporal trends and patterns of the incidence of new heart failure (HF) post-MI and the potential of cardiac cell transplantation to fashion an external auxiliary circulatory pump were presented. The meeting concluded with two

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talks focused on the first exploratory study testing the safety and feasibility of LV unloading and delayed reperfusion, the door to unload (DTU) in ST-elevation in myocardial infarction (STEMI) pilot trial. The rationale, challenges, and learnings from the DTU in STEMI pilot trial were discussed.

The presentations highlighted the exciting new developments and represent substantial advances in the field of acute myocardial unloading and recovery that have developed in the last year. The A-CURE Working Group meeting is unique in involving a diverse group of experts from multiple disciplines within an open, constructive, and intimate public setting.

We hope that you find this supplement informative and interesting.

The state of the field: our current understanding of ventricular unloading

Presented by Daniel Burkhoff, MD, PhD

Dr. Burkhoff commenced the meeting by stating the mission of the A-CURE symposium, which is to advance the science and mechanistic understanding of acute cardiac unloading and support the translation of basic and clinical research into therapies aimed at heart muscle recovery. He noted that since the inception of the A-CURE Working Group 4 years ago, the mission and application of the science has rapidly progressed into the clinical setting, particularly in reference to the recent completion of the Door To Unload in STEMI clinical trial, an idea initially proposed at the first annual A-CURE Symposium in 2016.

Dr. Burkhoff presented a brief history of the A-CURE symposium, which began with the first faculty meeting in Paris in 2015. This was followed by the 1st Annual A-CURE Symposium in Rome (2016) and the 2nd Annual Symposium in Barcelona (2017). He added that following this year's meeting in Chicago (2018), the next meeting will be held in Paris in 2019. He highlighted the steady year-over-year growth in attendees of the Annual Symposia.

He guided the audience through a brief discussion of the proposed formal definition of left ventricular (LV) unloading. He put forth that LV unloading is defined as the reduction of total mechanical power expenditure of the ventricle which correlates with a reduction in myocardial oxygen consumption and hemodynamic forces that lead to ventricular remodeling [1]. He emphasized that myocardial unloading is not only about mechanics but also about metabolism and oxygen consumption. So, the goal of ventricular unloading is twofold: first to achieve myocardial salvage and second to prevent cardiac remodeling and subsequent heart failure. When the goal of myocardial unloading is achieved, it results in decreased left ventricular pressure and volume with the subsequent reduction in pulmonary capillary wedge pressure (PCWP), salvage of myocardium, improved coronary blood flow (CBF), and it limits remodeling (Fig. 1).

While the concept of unloading has been discussed for decades, he highlighted that the scientific investigation and application of unloading emerged from the seminal work by E. Braunwald and M. Pfeffer in 1985. This team first demonstrated the benefits of LV unloading using captopril, an angiotensin-converting enzyme inhibitor, in a rat model of myocardial infarction (MI) [2]. This pre-clinical finding was tested in a clinical trial that showed a significant reduction in end-diastolic pressure and PCWP with a resultant decrease in ventricular dilation with captopril [3]. These studies were followed by additional trials such

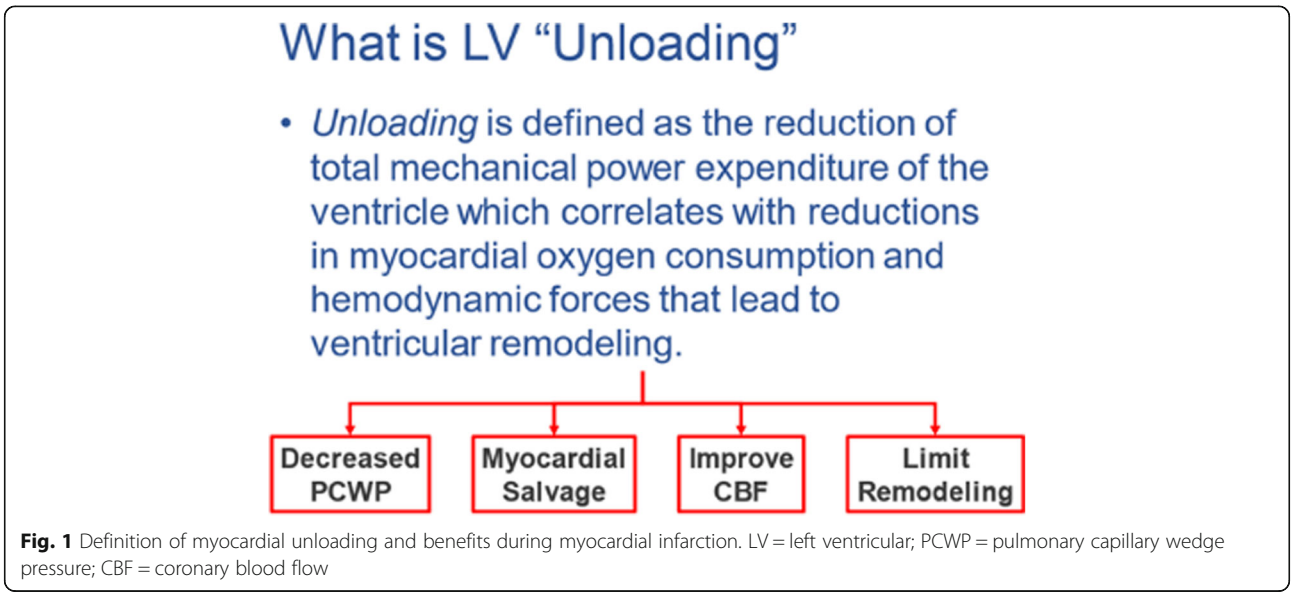

Fig. 1 Definition of myocardial unloading and benefits during myocardial infarction. LV = left ventricular; PCWP = pulmonary capillary wedge pressure; CBF = coronary blood flow

as SAVE that were critical in establishing pharmacological therapies for the treatment of MI.

However, there are inherent limitations to myocardial unloading using pharmacological therapies. Importantly, more unloading of LV pharmacologically to leads to more compromise in aortic pressure and cardiac output. Hence, the use of pharmacological therapies has been limited as a route to LV unloading. On the other hand, use of a percutaneous ventricular assist device (pVAD) like Impella can simultaneously unload the ventricle, reduce the workload of the heart, and increase the end-organ perfusion while maintaining cardiac output. As early as 1992, Smalling et al. showed improved regional myocardial blood flow, LV unloading, and infarct salvage using the Hemopump in a dog-model of MI [4]. Meyns et al. confirmed the above findings using Impella in a sheep model of ischemia-reperfusion [5]. They demonstrated that LV unloading using Impella during ischemia and reperfusion reduced myocardial oxygen consumption resulting in reduced infarct size.

Through the work of Dr. Suga and Dr. Sagawa, we have learned about the determinants of myocardial oxygen consumption (MVO_2) in the context of pressure-volume loops. MVO_2 is linearly related to pressure-volume area (PVA). PVA is the sum of the stroke work and the potential energy, i.e. the energy that is stored in the myocardial filaments after contraction rather than being released as external work. It is also important to note that even when the heart is producing no external work, it still consumes energy, largely due to calcium cycling, but also due to basal metabolism. As drugs increase contractility, they increase the mechanical work of the heart resulting in increased MVO_2, which is detrimental in the setting of MI where energy supply is limited. In addition, heart rate is another determinant of MVO_2. Recent work by Sunagawa et al. demonstrated that the combination of mechanical unloading and ivabradine (a bradycardic agent), synergistically reduces MVO_2 and significantly reduces infarct size in a dog-model of ischemia-reperfusion [6].

Right now, studies are underway in humans to see if mechanical unloading with devices will reduce infarct size. Once that is well established, it will be interesting to see if the combination of drugs such as beta-blockers and ivabradine with mechanical circulatory support devices will further reduce infarct size and improve outcomes. Finally, Dr. Burkhoff highlighted that the studies from the Kapur lab are not only reproducing the findings of a reduction in infarct size with LV unloading but also starting to unravel the underlying molecular mechanism of cardioprotection by LV unloading [7].

Dr. Burkhoff concluded with a mention that this year's meeting was a prelude to the results of the 1st randomized clinical study of unloading to reduce infarct size, the door to unloading (DTU) trial. He was delighted to be witnessing and playing a part in the dawn of a new era in clinical cardiology.

Cardiac uptake and release of exosomes during altered left ventricular load in ischemic HF

Presented by Kiyotake Ishikawa, MD

Dr. Ishikawa's lab is interested in the studying the non-LV effects of LV unloading. Although most of the effects of LV unloading can be explained by a change in hemodynamics, a potential role of humoral effects has not been studied and may play a vital role in cross-organ communication during LV unloading. Dr. Ishikawa's lab is investigating the exosomal microRNA-mediated regulation of local and remote communication [8] during LV unloading in a porcine model of percutaneously induced anterior myocardial infarction (MI). One week after MI, pigs underwent LV unloading using Impella CP for 2 h or LV over-loading following percutaneous induction of aortic regurgitation. MicroRNAs packaged in the exosomes extracted from blood samples collected from the coronary artery were compared with those from the coronary sinus, both before and after cardiac unloading/overloading.

A total of 127 microRNAs were identified among 3 pigs receiving LV unloading versus 220 microRNAs after LV overloading. Of the 127 microRNAs in the LV unloading group, 39 microRNAs were taken up by and 7 were released from the heart. Of the 220 microRNAs in the LV overloading group, 33 were taken up by and 32 were released from the heart. Six microRNAs showed an opposite transcardiac gradient after LV unloading versus LV overloading, that is increased uptake after overloading and increased release after unloading. In addition, they also performed a direct comparison of microRNAs in the coronary artery or coronary sinus blood before and after unloading or overloading and found significant difference in the microRNAs in the coronary sinus alone.

In conclusion, many exosomal microRNAs show transcardiac gradient and opposite changes in some of the microRNAs after unloading versus overloading suggests load-dependence, and may play a role in cross-organ communication. This is the first study investigating how acute ventricular unloading may regulate exosome-mediated cellular and organ communication. These preliminary results suggest that mechanical cardiac unloading may alter intra- and inter-organ communication. The direct consequences of this remains to be investigated.

Acute unloading and gene mitochondrial and Ca^{2+} gene regulation

Presented by Lija Swain, PhD

Dr. Swain presented her findings on how mechanical unloading of the left ventricle (LV) preserves myocardial

mitochondrial structure and function in acute myocardial infarction (AMI). In the past, Dr. Kapur's research group published in pre-clinical models that unloading the LV using Impella, a transvalvular pump before reperfusion (Primary unloading) reduces LV wall stress and infarct size compared to primary reperfusion [9]. In addition, in a recent study, they demonstrated that primary unloading activates cardioprotective cell signaling pathways that promote cell survival post-myocardial infarction [10]. Through the use of genomic approaches, the data presented by Dr. Swain at the A-CURE Symposium identified mitochondrial integrity/function as a potentially important mechanism by which primary unloading limits myocardial damage.

Interestingly, prior work by Esposito et al. showed that primary unloading preserves mitochondrial structure [10]. To further test and confirm this effect of LV load on mitochondrial function, adult male swine were subjected to left anterior descending artery (LAD) occlusion for 90 min followed by either immediate reperfusion (Primary Reperfusion); LV unloading for 30 min with an Impella CP and then reperfusion (Impella Group), or LV unloading for 30 min with VA-ECMO and then reperfusion (ECMO Group). Using RT-PCR, Dr. Swain confirmed that the expression of genes associated with electron transport chain (ETC) complexes were preserved within the infarct zone of Impella-treated pigs alone and not in ischemia-reperfusion injury or VA-ECMO treated pigs. Her data indicate that this gene regulation effect occurs simultaneously with primary unloading, suggesting an early effect of unloading on gene regulation post-MI.

Using the Agilent Seahorse Platform, mitochondria were isolated from the infarct zone of pigs subjected to the 3 different conditions, and oxygen consumption was quantified in response to various agonist and antagonists of the ETC complexes. The preliminary results suggest that compared to the primary reperfusion or ECMO groups, primary unloading using Impella CP preserves the function of Complex 1 in AMI.

In summary, these findings suggest that primary unloading using Impella may preserve mitochondrial structure and function in AMI. Future studies will confirm these findings and test novel approaches to protect mitochondrial function in AMI.

Automated Impella maximum unloading system (AIMUS): Exploration and development of first generation autopilot system (smart Impella system)

Presented by Kenji Sunagawa, MD, PhD

Dr. Sunagawa's talk focused on his investigations to develop an algorithm to automate control of the Impella (Smart-Impella) to maximally unload the left ventricle (LV). He reminded the audience that the left ventricular (LV) mechanical work and heart rate (HR) are major determinants of myocardial oxygen consumption (MVO_2) [11]. Also, the LV pressure-volume area (PVA) represents the total mechanical work of the heart and correlates linearly with MVO_2 [12]. Recent studies from his research group have shown that total support by Impella, in which the LV no longer ejects blood and the aortic valve remains closed, significantly reduces PVA and, subsequently, MVO_2 [13–15]. This reduction in MVO_2 results in a markedly reduced infarct size.

However, hemodynamics change with unloading conditions. In particular, Dr. Sunagawa focused on how the speed of the Impella pump, that is the level of mechanical support provided, impacted the unloading conditions. Based on the data from his studies, under total support, a little change in Impella speed results in a major change in LV systolic pressure (1 mmHg/50 rpm). Such a small change in rpm is difficult to achieve via manual control of the Impella and thus makes its clinical application impractical. To overcome this issue, Dr. Sunagawa's team developed a Smart-Impella algorithm that controls the instantaneous speed of Impella by incorporating left ventricular pressure and aortic pressure in feedback loops and evaluated its performance in a dog model of acute myocardial infarction (AMI).

Briefly, in 8 dogs AMI was induced for 180 min followed by reperfusion. The Smart-Impella algorithm was introduced 60 min after ischemia and continued for 60 min after reperfusion (I/R). The LV function and infarct size among dogs treated with or without Smart-Impella ($n = 4$ each) was evaluated four weeks after I/R. The results showed that the Smart-Impella treated dogs had nearly normalized LV end-diastolic pressure, LV end-systolic elastance, serum NT pro-BNP level and markedly reduced infarct size more than 60% compared to control. Future studies will focus on potential application of this automated control system to other parameters such as regulation of heart rate or oxygenation.

Dr. Sunagawa also presented the results showing combined use of ECMO and total Impella support during AMI significantly reduced infarct size via marked suppression of MVO_2. He concluded that these findings demonstrate that Smart-Impella is capable of auto-piloting LV unloading and reducing infarct size. Clinical translation of Smart-Impella combined with education may help improve the quality of care in medicine.

Mechanical circulatory support by VA ECMO or Impella CP and impact on left ventricular unloading and end organ perfusion in a porcine model of profound cardiogenic shock

Presented by Jacob Møller, MD, PhD, DMSc

Dr. Møller commenced his talk by stating that as a clinical cardiologist it is very important for him to

understand the evolving technologies and the whole concept of unloading the heart in a clinical setting, particularly in patients with cardiogenic shock (CS). Since it is close to impossible to conduct controlled hemodynamic studies evaluating the effect of mechanical circulatory support (MCS) in patients with CS, his research team has developed an animal model that mimics CS after myocardial infarction (MI). This model allows his team to acquire a detailed assessment of hemodynamics, while mimicking human anatomy which allows for the study of the placement of percutaneous MCS devices.

In an earlier study from Norway, investigators were able induce left ventricular (LV) failure by serial injections of 50 μm microspheres into the coronary artery. By doing so, they were able to titrate the degree of LV failure and CS [16]. Dr. Møller research team adopted this approach into their pig model and were able to induce profound CS by injecting microspheres stepwise into the left main coronary artery [17]. Profound CS was defined as cardiac output ≤2 L/min, mean arterial pressure (MAP) of about 30 mmHg, lactate of about 4 mmol/L, and/or a mixed venous saturation (SvO_2) ≤ 35%. Of note, his lab has been successful in establishing this model in pigs without losing a single animal. Using this model, they compared two MCS devices, the Impella CP and VA-ECMO, and their relative effect on LV end-diastolic pressure (LVEDP) and end-organ perfusion in 12 pigs. Immediately following implantation of both MCS device, cardiac output and SvO_2 normalized and the devices performed as expected.

The hemodynamic consequences of these devices diverged (Fig. 2). Treatment with Impella CP resulted in an immediate decrease in LV end-diastolic volume (LVEDV) and LVEDP. This significantly diminished the pressure-volume area (PVA), a measure of the mechanical work of the heart. In contrast, treatment with VA-ECMO resulted in immediate increase in LVEDV, LVEDP, and PVA, indicating increased mechanical work being conducted by the heart while on ECMO support. While the immediate impact of ECMO on PVA partially normalized after 1 h of support, PVA remained significantly elevated. This contrasted Impella-supported hearts in which PVA was immediately and significantly decreased, and this effected was maintained for the entire duration of support. This data supports the hypothesis that Impella CP efficiently unloads the heart compared to VA-ECMO during CS.

Based on these findings, Dr. Møller proposed as a next step to investigate the effect of different types of vasopressors in combination with Impella CP and titrate the dose optimally.

Left ventricular unloading with Impella causes cardiac metabolic remodeling with a significant reduction in myocardial glucose consumption and lactate production

Presented by Carlos Santos-Gallego, MD

Dr. Santos-Gallego presented results from his investigation into how left ventricular unloading using Impella may alter the metabolic remodeling in a model of sub-acute heart failure (HF). He began by providing the background of cardiac metabolism. Normal myocardium produces ATP mainly through free fatty acids (FFA) oxidation [18]. Any abnormalities in myocardial energetics can both cause and contribute to (HF). Since FFA oxidation requires more oxygen, during HF there is a metabolic switch to glucose consumption (which produces less ATP but also requires less oxygen) [18]. Recent studies have demonstrated that this increase in glucose consumption during HF is metabolized mostly through

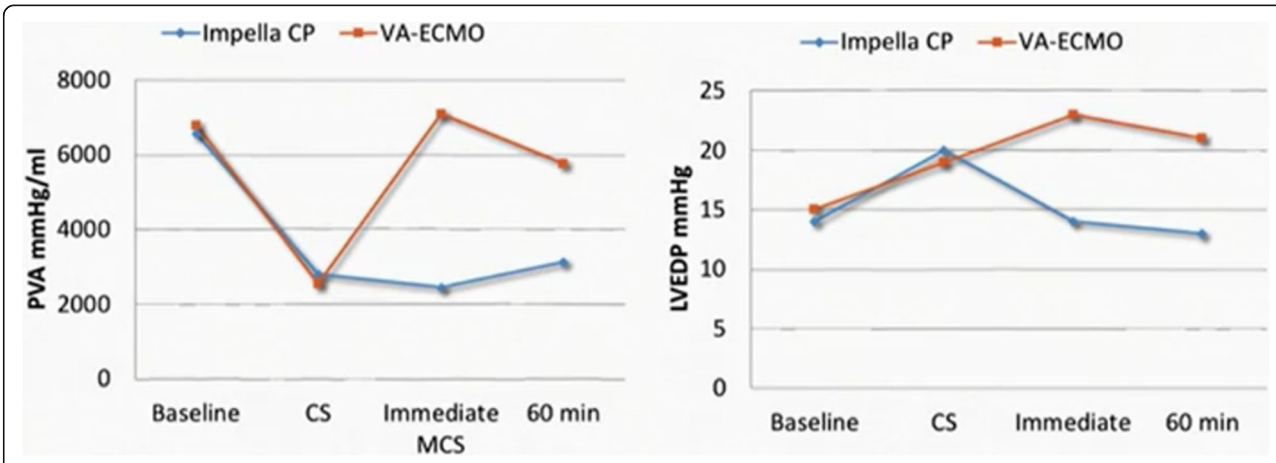

Fig. 2 Effect of MCS Devices on PVA and LVEDP in an Animal Model of Profound Cardiogenic Shock. CS = cardiogenic shock; MCS = mechanical circulatory support; PVA = pressure-volume area; LVEDP = left ventricular end-diastolic pressure; VA-ECMO = veno-arterial extracorporeal membrane oxygenation

the anaerobic respiration pathway and results in increased production of lactate [19].

Dr. Santos-Gallego investigated the effects of LV unloading and overloading on myocardial metabolism. He hypothesized that acute LV unloading using Impella would reduce myocardial glucose consumption and lactate production, thus reversing adverse metabolic remodeling. He measured the transmyocardial gradient (TG) of different metabolites using simultaneous catheterization of left anterior descending (LAD) and coronary sinus in pigs. Three experimental groups were compared: Sham animals with no myocardial infarction (MI), 1 week post-MI with acute unloading with Impella (before and 2 h after unloading), and 1 week post-MI with LV overloading due to severe aortic regurgitation (before and 2 h after overloading).

Results showed FFA consumption with low utilization of glucose and only mild lactate consumption in sham animals (Fig. 3). However, animals in HF showed reduced FFA consumption with increased glucose utilization and lactate production. LV overloading further exacerbated myocardial glucose consumption and lactate production. Contrarily, LV unloading reduced both glucose consumption and lactate production. No difference in myocardial uptake of FFA or ketones was found during LV unloading or LV overloading. These results support the hypothesis that LV unloading with Impella in HF rapidly shifts metabolic substrate utilization with reduced glucose consumption and lactate production.

Primary left ventricular unloading enhances collateral blood flow and reduces infarct size: A preclinical proof of concept study

Presented by Shiva Annamalai, MD

Dr. Annamalai began his presentation by recapping the findings of Kapur lab over the years that have demonstrated reduced infarct size with primary unloading prior to reperfusion, irrespective of the MCS device [9, 20]. One of the mechanisms of beneficial effect of primary unloading with Impella is the reduction in LV stroke work, thereby resulting in reduced myocardial oxygen consumption [21]. Another proposed mechanism is the functional reperfusion of the area at risk with Impella support. Dr. Annamalai proposed that the activation of a trans-valvular pump increases myocardial perfusion into the ischemic territory, despite persistent coronary occlusion. By increasing blood supply into the ischemic zone, this should translate into decreased cell death and a smaller infarct size. This concept was demonstrated by Smalling and Wampler in 1989 in a canine model, wherein use of a Hemopump resulted in improved perfusion into the ischemic territory despite persistent occlusion of left anterior descending artery (LAD) [22]. This improved myocardial perfusion to ischemic territory is likely due to improved collateral flow.

The collateral flow index (CFI) is a measure of microcirculatory blood flow and increased CFI has previously been shown to be a primary determinant of myocardial infarct size [23, 24]. Based on previous observations, Dr. Annamalai hypothesized that compared to primary reperfusion, primary unloading recruits collateral microcirculatory flow, thereby increasing 'functional perfusion' to the ischemic zone and decreasing infarct size. To test his hypothesis, he assessed CFI in a porcine model of acute myocardial infarction (AMI). The LAD was occluded for 90 min in adult Yorkshire swine ($n = 4$). Then the LAD was reperfused for 180 min in the primary reperfusion (PR) group. In the primary unloading (PU) group an Impella CP and in primary loading (PL) group, VA ECMO, was activated with LAD occlusion for additional 30 min, followed by 180 min of reperfusion. The CFI was calculated during LAD occlusion as (Pw-RA)/(Pa-RA), where Pa, RA, Pw are aortic, right atrial and coronary wedge pressure, measured using a pressure wire. The myocardial infarct size was quantified using 2,3,5-triphenyltetrazolium (TTC) staining.

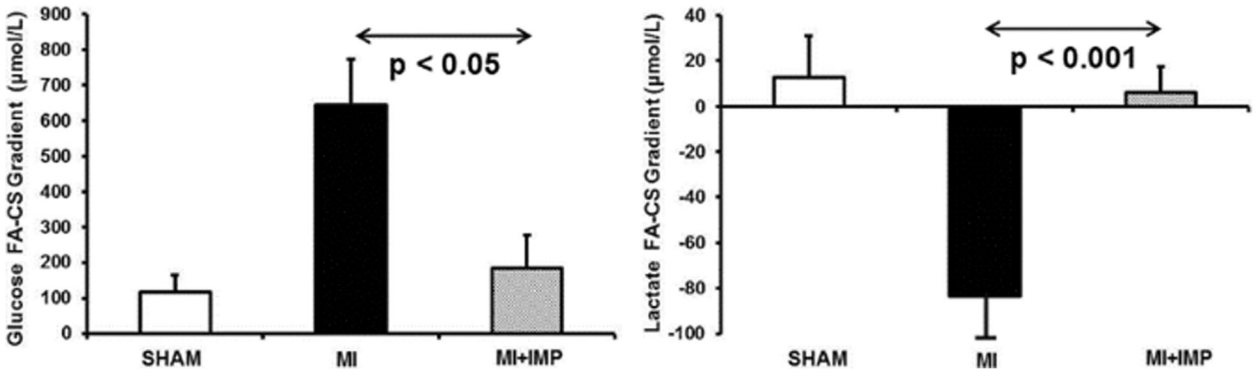

Fig. 3 LV Unloading With Impella During HF Reduces Myocardial Glucose Consumption and Lactate Production in an Animal Model. MI = myocardial infarction; IMP = Impella

Results showed that following 90 min of LAD occlusion, there was no difference in CFI among the groups as expected. However, after 30 min of PU, the CFI significantly increased compared to pre-activation as well as to the PR or PL groups. This suggests increased microcirculatory flow to the area at risk with 30 min of LV unloading with Impella prior to reperfusion (Fig. 4). In addition, the hemodynamic tracings showed a rise in distal coronary wedge pressure with Impella, likely contributing to increase in CFI. PU also reduced LV stroke work (LVSW) at 120 min compared to each of pre-activation, PR and PL. Among all the groups, the change in CFI between 90 and 120 min correlated inversely with the change in LVSW. Compared to PR and PL, PU reduced infarct size relative to the area at risk, and the change in CFI correlated inversely with infarct size.

In conclusion, this is the first study to show that reducing LVSW with Impella prior to reperfusion increases collateral flow to the infarct related artery in acute myocardial infarction. In contrast to Impella, activation of VA-ECMO does not augment collateral flow and does not reduce infarct size.

Keynote lecture

Left ventricular remodeling: Therapeutic effects, implications for trials and lessons from chronic heart failure

Presented by James Udelson, MD

Dr. Udelson's talk focused on his research interest in left ventricular remodeling and the lessons learned from clinical trials in the field of chronic heart failure. He began by highlighting the remarkable plasticity of the heart with the ability to grow larger by 50% during hypertrophy and shrink by 30% during atrophy [25]. Physiologic remodeling of the heart occurs in response to increased demand on cardiac output such as is associated with exercise training and pregnancy, and reverse remodeling occurs after birth or during deconditioning. Pathologic remodeling with hypertrophic growth occurs in response to hemodynamic stress such as hypertension or myocardial injury, and it increases the risk of heart failure (HF) [25]. Hence, the focus of many research teams over the years has been to understand the mechanisms of pathological remodeling following myocardial infarction (MI).

Early work by Pfeffer in 1991 demonstrated the schematics of LV volume change post-MI in a rat model [26]. During the early post infarction phase, there is infarct expansion but then the remaining normal myocardium undergoes hypertrophy and chamber dilation. This is initially an adaptive response to maintain stroke volume and hemodynamics. However, continuous unabated hypertrophy and dilation over time is maladaptive as cardiac function declines with increased dilation and volume overload. The pathological process of progressive ventricular dilation post-MI was demonstrated in humans as well by McKay and colleagues [27].

Later studies investigated the relation between post-MI remodeling and the incidence of cardiovascular adverse events. Results from the secondary analysis of SAVE trial showed higher rates of adverse cardiovascular events with greater increase in LV enlargement, independent of randomization to captopril [angiotensin-converting enzyme (ACE) inhibitor] or placebo [28]. Subsequent studies also demonstrated that the change in LV shape, size, volume, and architecture post-MI relates to subsequent adverse cardiovascular events.

Given the high rate of adverse events associated with ventricular remodeling post-MI, research efforts have focused on assessing the effect of drugs and devices in attenuating ventricular remodeling. Early work by Pfeffer et al. in a rat model showed that captopril therapy for 3 months post-MI attenuated LV remodeling and the deterioration of cardiac performance in chronic MI [29]. Further, they showed that long-term therapy with captopril

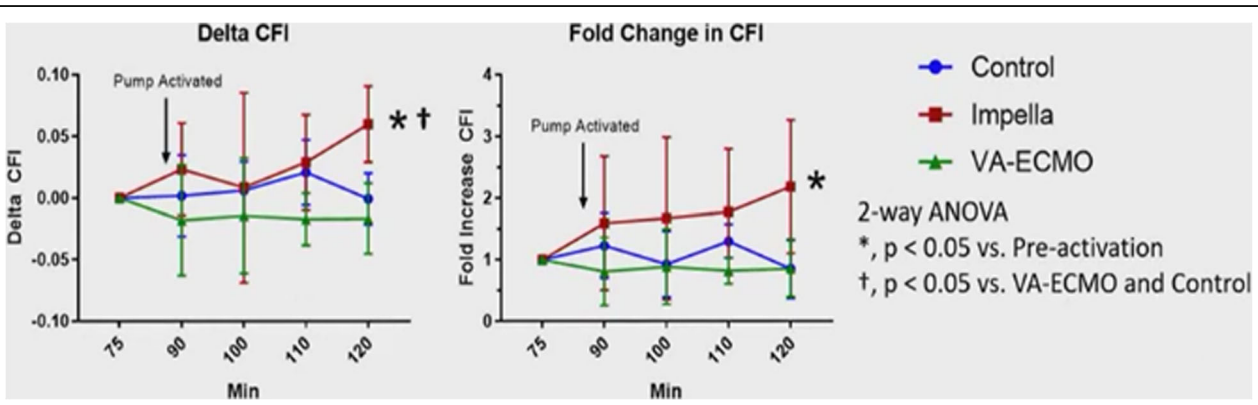

Fig. 4 LV Unloading With Impella for 30 min Increases Microcirculatory Flow to the Area at Risk. CFI = collateral flow index; VA-ECMO = veno-arterial extracorporeal membrane oxygenation

also improved 1-year survival [29]. Consistent with this finding, clinical data from the SAVE trial demonstrated a reduction in mortality with in patients with LV dysfunction after MI who were treated with captopril [30].

Results from additional trials with ACE inhibitors and beta-blocker therapy post-MI and in HF, including the SOLVD and CAPRICORN trials, suggested a pattern of reduced LV volume and concomitant decrease in mortality. Along the same lines, the PRIME-II trial that investigated the use of the dopaminergic receptor agonist, ibopamine, in patients with chronic HF also showed increased LV volumes to be associated with increased mortality. These findings led to the attractive supposition that LV remodeling was a fundamental feature of the post-MI or CHF disease process and progression, and the effect of the intervention on remodeling may act as a "surrogate" for its potential impact on outcome [31]. However, the RENEWAL trial with etanercept showed a decrease in LV volume with no difference in the mortality rates, thus questioning the use of variables of ventricular remodeling as a surrogate for patient outcomes.

Dr. Udelson discussed the use of biomarkers as potential surrogates for patient outcomes. Fleming and DeMets define a biomarker as a strong surrogate if: 1) it is in the causal path between an intervention and the outcome; 2) all intervention effects pass through the marker in the causal pathway; and most importantly 3), the effect of the intervention on the surrogate reliably predicts the overall effect on the clinical outcome [32]. Of note, sample sizes of recent clinical trials assessing the outcome of new HF drugs range from 3 to 8000 patients. This is mainly due to low event rates of the primary endpoint making the number of patients needed to adequately power the study to detect a clinically meaningful difference. This leads to long and costly clinical trials. Consequently, there is a lot of interest in identifying biomarkers surrogates in phase 2 clinical trials (involving few hundreds of patients) that can predict success or failure of phase 3 clinical trials (involving 1000 of patients).

However, results from the CAST and ILLUMINATE trial have demonstrated that biomarkers that are prognostic are not necessarily good surrogates. Premature ventricular contractions (PVCs) are known to associated with unfavorable prognosis post-MI; however, in CAST trial suppression of PVCs was associated with increased mortality. Similarly, ILLUMINATE demonstrated that increased HDL was associated with increased mortality, counter to prevailing thought. Dr. Udelson cautioned that this danger was not just limited to biomarker use. Even successful outcomes in a phase 2 trial don't necessarily predict successful outcomes in phase 3 trials. This was demonstrated by the opposite effect of vesnarinone on mortality in the phase 3 VEST trial compared to the preceding phase 2 trial. Since heterogenous pathways contribute to the progression of HF and resulting mortality, it is unlikely that any individual marker will be able to predict the clinical outcome of interest with precision. However, the magnitude of correlation of an intervention on a biomarker, and the effect of that intervention on longer-term outcomes should be quantifiable. Therefore, Dr. Udelson suggested that the change in a biomarker following an intervention should be viewed as a 'probability signal' of outcome effects, rather than as a precise surrogate. He highlighted the study by Kramer et al. that demonstrated a positive correlation between an intervention's short-term effect on LV remodeling and long-term mortality in HF. This study concluded that the effect of interventions on LV remodeling can serve as a probability signal of the likelihood of a favorable, neutral, or adverse effect on long-term mortality [33].

Dr. Udelson discussed strategies used by contemporary clinical trials to overcome the challenges such as huge sample size and contribution of only 10–15% of patients enrolled in the trial to the endpoint. He mentioned the use of hierarchical composites such as such as the Finkelstein-Schoenfeld method, and other analytic approaches including adaptive design and expedited access pathway to assess the outcome of an intervention using a reasonable sample size.

In conclusion, LV remodeling is a stereotypical response to injury underlying pathology. Remodeling is associated with adverse outcomes and is a fundamental driver of HF progression. The remodeling response to an intervention provides a probability signal of the intervention's response to the clinical outcome, and this concept can be leveraged into novel trial designs to enhance the likelihood of outcome response with smaller sample sizes.

The cardio-renal system: Acute kidney injury and MCS, opportunity for improved patient outcomes

Presented by Ralf Westenfeld, MD

Dr. Westenfeld began by referring to the recent PRESERVE trial showing a lack of benefit of bicarbonate and acetylcysteine for prevention of contrast-induced acute kidney injury (CI-AKI) [34]. This highlighted the unmet medical need to address CI-AKI in patients treated by percutaneous intervention (PCI) as it is associated with high mortality and increases mortality in patients with chronic kidney disease (CKD) [35]. In addition, CI-AKI ranks second among the causes of AKI [36]. An aversion to the risk of radiocontrast-associated nephrotoxicity has resulted in the less frequent use of coronary angiography among patients with CKD despite significant benefit in the odds of survival, also referred to as "renalism" [37].

The pathophysiology of CI-AKI is related to the decline in glomerular filtration rate (GFR) caused by renal

vasoconstriction, oxidative stress due to reduced renal blood flow, and renal tubular cell damage. Many interventions aimed at preventing CI-AKI have been tested but the protective effect has been observed only in studies of low quality, and no effect of the intervention was observed in high quality studies. According to a recent publication by Vanmassenhove et al., only volume loading for prevention of CI-AKI has proven to be of value [38]. Dr. Westenfeld further discussed the pros and cons of different biomarkers and imaging techniques used to detect or foresee AKI.

A recent study by Flaherty et al. was the first to demonstrate protection against CI-AKI by Impella 2.5. Interestingly, Impella 2.5 support was independently associated with a significant reduction in the risk of developing AKI during high-risk percutaneous coronary intervention (HRPCI) [39]. This led Dr. Westenfeld to question whether other mechanical circulatory support devices may be beneficial in preventing AKI during HRPCI. His research team investigated this by performing a retrospective analysis of 28 patients undergoing HRPCI with the support of Impella versus VA-ECMO. The results were consistent with the study Flaherty et al. with a lower incidence of CI-AKI in patients supported by the Impella versus VA-ECMO (12% vs. 54%, $p < 0.05$) (Fig. 5). In addition, they observed that with Impella support equally complex coronary interventions could be performed with shorter time and less bleeding events.

Dr. Westenfeld concluded by proposing a prospective "Protect Kidney Trial" to investigate the role of Impella in preventing CI-AKI in patients undergoing HRPCI.

Biomarkers of kidney injury in a preclinical model of acute myocardial infarction

Presented by Navin Kapur, MD on behalf of Xiaoying Qiao, PhD

Cardiorenal syndrome type 1 refers to the condition of acutely decompensated heart failure (ADHF) leading to kidney dysfunction. During heart failure (HF) the presence of venous congestion can increase renal vein pressure and interstitial pressure which compresses Bowman's capsule leading to a reduced glomerular filtration rate (GFR). A recent study from Ichiki et al. showed significant upregulation of several inflammatory cytokines, particularly in the renal cortex, in a canine model of HF, providing insights into the pathophysiology of kidney dysfunction in HF [40].

Since several hemodynamic parameters influence kidney function, Dr. Kapur's research team is investigating the effect of acute mechanical circulatory support devices on renal blood flow and function. Previously, Møller-Helgestad et al. compared the hemodynamics and blood flow to the kidneys with intraaortic balloon pump (IABP) versus Impella 2.5. They found higher renal blood flow (RBF) with Impella 2.5 and no change with IABP support [41]. Studies have reported up to 60% incidence of acute kidney injury (AKI) with VA-ECMO due to mechanisms such as nonpulsatile flow and inflammatory response resulting in reduced RBF [42, 43].

Based on these findings, Dr. Qiao hypothesized that compared to Impella, VA-ECMO would increase levels of renal injury biomarkers in acute myocardial infarction. To test this hypothesis, adult male swine were subjected to left anterior descending artery (LAD) occlusion

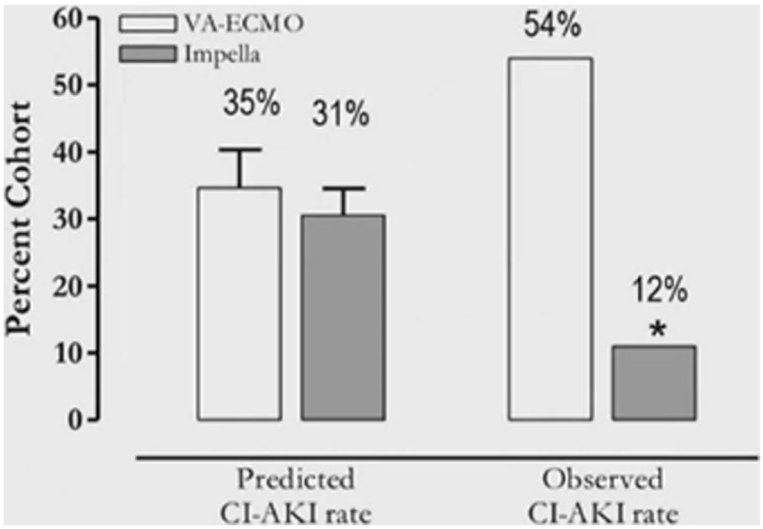

Fig. 5 Lower Incidence of CI-AKI During HR-PCI with Impella support versus VA-ECMO. CI-AKI = contrast induced acute kidney injury; HR-PCI = high risk percutaneous coronary intervention, VA-ECMO = veno-arterial extracorporeal membrane oxygenation

for 90 min followed by either immediate reperfusion (IRI), ventricular unloading with Impella for 30 min prior to reperfusion while on support, VA-ECMO support for 30 min prior reperfusion while on support, or sham-operated controls (n = 4/group). Renal injury biomarkers, kidney injury molecular 1 (KIM1) and NGAL, were measured. Results showed that the urinary KIM1 levels were elevated in the IRI and VA-ECMO groups, but not the Impella group. No changes in plasma KIM-1 levels were observed in any group. Compared to baseline values, VA-ECMO increased urinary NGAL levels but Impella did not. Compared to IRI, Impella reduced plasma NGAL levels after reperfusion. Further, Impella reduced urinary Cystatin-C (Cys-C) levels from the baseline but VA-ECMO did not. No change in plasma Cys-C levels was observed between groups.

In conclusion, this is the first study to identify IRI increases increases urinary levels of KIM-1, a highly sensitive biomarker of AKI. Impella, not VA-ECMO, may protect against this increase in urinary KIM-1 levels. Future studies will explore the mechanism underlying this observation.

Impella is associated with reduced incidence of contrast-induced nephropathy in patients undergoing high risk PCI

Presented by Julian Wiora, MD

Dr. Wiora presented results from his investigation into the effect of Impella support on contrast-induced acute kidney injury (CI-AKI) in patients undergoing high-risk percutaneous coronary intervention (HR-PCI). He reminded the audience that approximately 7% of all patients undergoing PCI experience AKI regardless of comorbidities [44], and the incidence of AKI and need for dialysis after PCI increases significantly with increasing severity of baseline chronic kidney disease (glomerular filtration rate, GFR < 30 ml/min/1.73 m^2).

A recent study by Flaherty et al. was the first to demonstrate protection against CI-AKI by Impella 2.5 compared to no support in high-risk PCI patients. Interestingly, Impella 2.5 support was independently associated with a significant reduction in the risk of developing AKI during high-risk PCI [39]. Dr. Wiora performed a similar analysis by comparing 35 patients who underwent HR-PCI with Impella support to 35 patients who underwent PCI without indication for Impella support in their institution. The patients in the two cohorts were propensity-matched for risk of contrast-induced nephropathy based on the Mehran risk score.

Patients in the non-Impella support group were older and had less compromised left ventricular ejection fraction (LVEF) than patients in the Impella support group. In the Impella group, the procedure time was longer with more number of lesions treated and stents implanted than the non-Impella group. Based on the Mehran risk score, CIN rates were predicted to be 25% with Impella support and 22% without Impella support. Interestingly, CIN was observed in only 11% of patients undergoing Impella-protected PCI compared to 31% in the non-Impella supported group (Fig. 6). In addition, serum creatinine levels were significantly lower in the Impella group over 4 days post-PCI. Furthermore, among the patients in the non-Impella group, CIN occurred more frequently in patients with lower LVEF and hemoglobin levels, but no such trends were observed in the Impella supported group. No difference in complication rates were observed between groups.

In conclusion, Impella use during HR-PCI was associated with a lower incidence of CIN compared to a propensity-matched unprotected control group. Use of Impella during HR-PCI is safe and feasible based on the low complications rates. Future studies will focus on the use of Impella during HR-PCI in patients with moderately reduced LVEF.

Impact of unloading during AMI-CGS: The Hannover cardiac unloading registry (HACURE) and European multicenter experience

Presented by Andreas Schäfer

Dr. Schäfer began by stating that acute myocardial infarction complicated by cardiogenic shock (AMICS) is a growing clinical challenge in clinical practice. Conventional therapeutic approaches using inotropic support with or without intra-aortic balloon pump have not improved outcomes. Retrospective studies have associated early identification and standardized treatment including early initiation of hemodynamic support with Impella followed by weaning

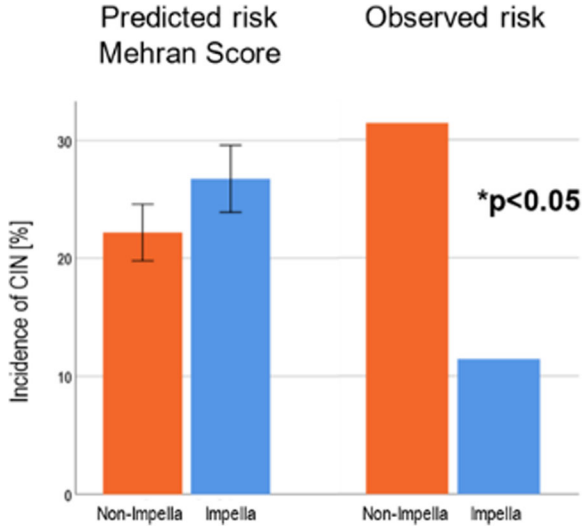

Fig. 6 Reduced Incidence of Contrast-Induced Nephropathy with Impella Support during HR-PCI. CIN = Contrast-Induced Nephropathy

of inotropes and complete revascularization with reduced mortality. Given the challenges of conducting randomized trials in CS and the lack of evidence on the efficacy of Impella from prospective trials thereof, Dr. Schäfer presented results from a retrospective analysis conducted by his research team in a contemporary cohort.

First, he highlighted the recently published Hannover Cardiac Resuscitation Algorithm (HaCRA) for patients presenting with Out-of-hospital cardiac arrest (OHCA) and/or cardiogenic shock [45]. The algorithm aims for early diagnosis and prompt treatment of life-threatening conditions such as cardiogenic shock. He emphasized the need to intervene using mechanical circulatory support (MCS) devices early during the "golden hour" of cardiogenic shock and not during later stages when multiorgan dysfunction and failure has already begun.

He then referred to a recent publication of 61 patients with cardiogenic shock (CS) supported using Impella CP for isolated left ventricular (LV) failure in the HAnnover Cardiac Unloading REgistry (HACURE) [46]. Comparison of survivors versus non-survivors showed that survivors had pronounced lactate clearance within 4 h of Impella initiation. This was also accompanied by a rapid reduction in vasopressors/inotropes. Importantly, a substantial reduction in 30-day mortality among the subgroup of patients (n = 25) fulfilling the inclusion/exclusion criteria of the former IABP-Shock II trial was observed (24% in HACURE using Impella CP vs. 40% in IABP-Shock II trial), highlighting the importance of a standardized algorithm for treatment of CS incorporating early use of active hemodynamic support using Impella.

He then presented the retrospective analysis of > 160 patients with AMICS treated at four dedicated European shock centers, fulfilling the inclusion criteria of the IABP-Shock II trial, mostly treated with Impella CP. Risk of mortality was calculated based on IABP-Shock II, CardShock, and SAVE scores. Cardiac arrest prior to Impella implantation was relatively common. Impella was implanted prior to percutaneous coronary intervention (PCI) due to the operator's discretion. While overall, 30-day mortality for the entire cohort was still slightly above 40%, mortality was higher among patients undergoing resuscitation and among those receiving Impella post-PCI. The predicted in-hospital mortality was 69% by SAVE score, 40% by CardShock score, and 49% by IABP-Shock II score, respectively. The observed 30-day mortality with use of Impella devices was lower than the predicted mortality. Furthermore, the observed mortality was lower than predicted mortality even among patients in the high-risk subgroup.

In conclusion, the results from these retrospective analyses encourage the use of active MCS by Impella devices in critically-ill patients with AMICS undergoing PCI and support the concept of early initiation of support prior to PCI.

First in man implantations of a newly designed transaortic axial flow ventricular assist device, Impella 5.5

Presented by Alexander Bernhardt, MD

Dr. Bernhardt began by reminding the audience of the features of the Impella 5.0. This device is an established transaortic axial flow ventricular assist device capable of providing forward blood flow of up to 5 L/min. It was originally designed for femoral access but axillary access is increasingly used as it allows for mobilization of the patient. Recently, a published meta-analysis of Impella 5.0 reported favorable survival outcomes and high rates of myocardial recovery in patients with cardiogenic shock [47]. Impella 5.0 has CE approval for a maximum to 10 days of support. However, more than 70% of patients at their hospital require Impella 5.0 support for > 10 days. Potential problems associated with longer duration of Impella 5.0 support include in-growth of the pig tail catheter, pump thrombosis, and arterial embolization due to the presence of a repositioning sheath in the axillary artery.

Impella 5.5 was developed to address the need for a longer duration of support with a low rate of complications. It is designed to provide hemodynamic support for up to 30 days. Like the the Impella 5.0, the Impella 5.5 device is an axial flow transaortic cardiac support device mounted on a 9 Fr steering catheter with a 21 Fr pump cannula (Fig. 7). The pump itself is shorter and stiffer than the Impella 5.0. Other improved features in the Impella 5.5 include an optical aortic pressure sensor distal to the outflow of the device and no pigtail at the tip of the catheter (eliminating the risk for in-growth of the pigtail and reducing the risk of thromboembolism and stroke), and improved kink resistance of the cannula. Importantly, the device provides maximum pump flow of 5.5 L/min against a pressure afterload of 60 mmHg, with observed flow up to 5.8 L/min. The device is designed for axillary insertion only and the repositioning sheath does not extend into the artery.

Dr. Bernhardt presented the first-in-man experience with the new Impella 5.5 in two critically ill patients [48]. The first patient was a 75-year-old male with a ten year history of ischemic cardiomyopathy and severe functional mitral regurgitation. The patient was treated with intravenous antibiotics for pneumonia and was on non-invasive ventilation. The left ventricular ejection fraction (LVEF) was 18%, and left ventricular end-diastolic diameter (LVEDD) was 75 mm. His N-terminal pro brain natriuretic peptide (NTproBNP) was 44 pg/ml at baseline. The Impella 5.5 was implanted via left axillary access. The implantation procedure was uneventful and the pulmonary function improved within 24 h. After further improvement in pulmonary congestion and pneumonia, a MitraClip procedure was performed successfully under Impella 5.5 support on post-operative day 10. During follow-up, the patient developed signs of an acute abdominal

Feature	Impella 5.5	Impella 5.0®
Catheter Length	70cm	135cm
Cannula Diameter	21Fr	21Fr
Motor Diameter	18Fr	21Fr
Rigid length (motor & outlet)	27mm	42mm
Pigtail	NO	YES
Sensor	Fiber optic	Differential Pressure

Fig. 7 Summary of Features of Impella 5.5 and Impella 5.0 Heart Pumps

pain due to an appendicitis. No signs of ischemia or thromboembolism were present. Initially, the patient recovered from this complication, but deceased on post-operative day 19 due to a recurrent septic episode. There were no pump related complications and no signs of a pump malfunction.

The second patient was a 52-year-old male patient with ischemic cardiomyopathy and a history of coronary artery bypass grafting and mitral valve repair. Three weeks prior, the patient suffered an acute decompensation that was treated with Impella CP support for five days. After that episode the patient needed dialysis. He suffered a second decompensation due to ventricular arrhythmia, was resuscitated and placed on a veno-arterial extra corporeal life support (ECLS) through femoral vessel cannulation. The Impella 5.5 was implanted during the same operation. The arrhythmias were treated using catheter ablation under ECLS and Impella 5.5 support, and the patient was extubated. The ECLS cannulas were explanted under local anesthesia the day after the ablation procedure. During Impella 5.5 support, renal function improved and the patient was mobilized. Impella 5.5 support was continued uneventful for 21 days. A durable LVAD (HeartMate 3) was implanted and Impella 5.5 was explanted. The patient is ambulatory at 7 months post-Impella 5.5 implantation with improved creatinine levels and off-dialysis. Two additional patients have been treated using Impella 5.5 since. No pump-related adverse events has been observed.

In conclusion, the Impella 5.5 expands the spectrum of available short-term mechanical circulatory support devices. New technical design features such as the absence of pig-tail helps minimize risk, and the optical pressure sensor aids in easy pump placement and monitoring. Early experience with Impella 5.5 in patients with no occurrence of pump-related adverse events indicate feasibility and safety of the new device.

Temporal trends and long-term outcomes of post-myocardial infarction heart failure

Presented by Ajar Kochar, MD, MHS

Dr. Kochar began by presenting the background of heart failure (HF) post-myocardial infarction (MI). Over half of contemporary MI patients are ≥65 years old. Despite decline in MI-related mortality in the past 2 decades, there has been an increase in the incidence of post-MI HF with significant long-term implications. The objective of Dr. Kochar's research study was to identify the temporal trends and patterns of the incidence of new HF among older MI patients and evaluate the association of post-MI HF with long-term mortality and major adverse cardiac events (MACE).

Dr. Kochar evaluated patients in the Medicare database between 2000 and 2013 who survived their first MI (based on ICD9 coding). Post-MI HF was defined as HF during index MI admission or a HF hospitalization within 1 year post-index MI admission. Outcomes assessed were HF hospitalization and all-cause death at 1 year and all-cause death and MACE (composite of all-cause death, MI and stroke hospitalization) at 5 years. The incidence of post-MI HF was calculated at 1 year based on estimates from the cumulative incidence function. The 5-year implications of HF post-MI was evaluated by comparing patients with HF post-MI with patients without any HF within 1 year post-MI.

The study population included 1,531,628 patients from 5948 hospitals. The mean age was 78 years, 49.7% were women, 64.6% had NSTEMI and 35.4% had STEMI. Among these patients, 36% had HF post-MI: 32.8% had HF during index MI and 10.4% had HF hospitalization post-MI within 1 year. The median time to first HF hospitalization was 66 days. The temporal trend from 2000 to 2012 suggests mild reduction in the incidence of HF during index hospitalization (34.7% in 2000 to 31.2% in 2012), HF hospitalization within

1 year (11.3% in 2000 to 8.7% in 2012), and 1-year mortality (22.5% in 2000 to 18.8% in 2012). Five-year mortality was 38.4% for patients without any HF, 66.2% for patients with HF during index admission only, 68.2% for patients with a HF hospitalization within 1 year only, and 79.7% for patients with HF at index admission and at least one HF hospitalization within 1 year (Fig. 8).

Given the high rates of HF post-MI, Dr. Kochar emphasized the importance of optimizing guideline directed therapies in older patients and the need to explore novel treatment dimensions. He added that the high 5-year mortality rates with HF post-MI should be communicated with patients to better inform shared-decision making.

In conclusion, the rate of mortality and HF post-MI has modestly declined over time among older MI patients treated in the US. Despite this decline, post-MI HF remains a common outcome in older adults, occurring in > 1 out of 3 patients. Compared to patients without HF, post-MI HF is associated with higher mortality and MACE.

Development of heart failure among survivors of STEMI and NSTEMI and long-term outcomes

Presented by Robert Kloner, MD, PhD

Dr. Kloner presented the results from his investigations aimed to develop a biologic left ventricular pump. He began by providing background for arterial counterpulsation. Arterial counterpulsation is a strategy used as a bridge to transplantation or recovery to treat patients with terminal heart failure. There are 4 different ways for arterial counterpulsation: intra-aortic, extra-aortic, para-aortic and enhanced external counterpulsation. His investigations were focused on determining whether it is feasible to develop a biologic extra-aortic counterpulsation device by cardiac cell implantation. Specifically, his research team tested if immature cardiac cells could be implanted into the outer wall of the aorta in rats, and if so, could they survive, differentiate, and contract [49, 50].

Female Fischer rats received either medium only (n = 22) or 5×10^6 neonatal cardiomyocytes each (n = 22). The aorta was exposed through a retroperitoneal approach, and cardiomyocytes isolated from 2 day old neonatal Fischer rats of both sexes were implanted at the outer wall of the abdominal aorta at a site 3 mm above the renal arteries. Histological analysis showed viable graft formation in the outer wall of the aorta at 2 weeks in 9 of 10 rats and at 6 weeks in 9 of 9 rats in the cell-treated group. In comparison, none of the rats in the medium-treated group showed viable graft formation in the outer wall of the aorta. In addition, neonatal cardiomyocytes in the graft formed compact, longitudinally oriented cardiac muscle bundles, and were differentiated with cross-striations and a high degree of vascularization. At 2 weeks after transplantation, spontaneous rhythmic beating was observed at the grafted site following excision of the native heart in 7 out of 10 rats in the cell-treated group versus none in the medium-treated group. Further, pacing in a cell-grafted aorta increased aortic pressure by 5-fold from the baseline.

These results suggest that grafted neonatal cardiomyocytes can survive, differentiate, and develop blood supply with the ability to spontaneously contract within the outer walls of the aorta in the rats. Encouraged by these results, his research team investigated whether it is feasible to develop a vein that rhythmically beats by implanting immature cardiomyocytes in the wall in aorta near the vena cava [51]. Female Fischer rats received either medium only (n = 6) or 5×10^6 neonatal cardiomyocytes

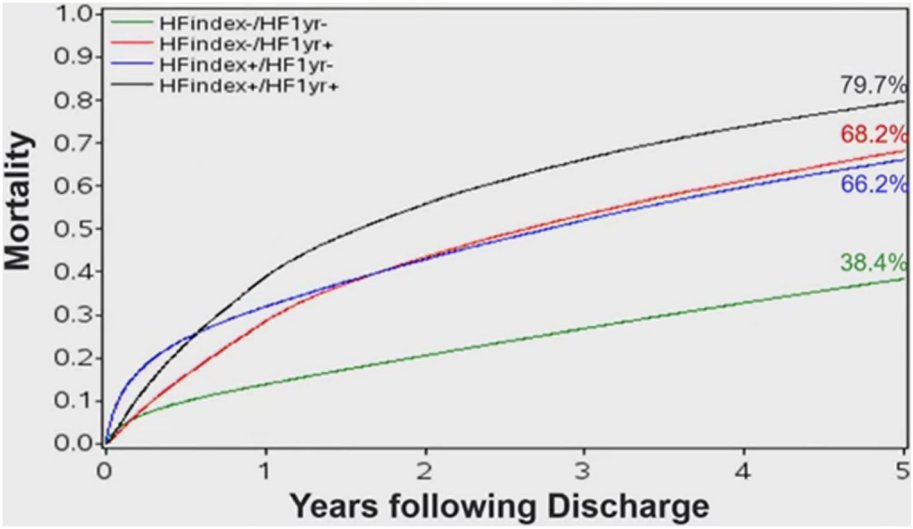

Fig. 8 Long-term Mortality Stratified by Heart Failure Status

each (n = 6). The vena cava was exposed through a midline incision of the abdominal wall and cardiomyocytes isolated from 2 days old neonatal Fischer rats of both sexes were implanted around the vena cava below the renal vein.

Histological analysis showed viable graft formation and maturation around the vena cava with cross striations at 3 weeks after transplantation. In addition, following aortic clamping and excision of the native heart, spontaneous rhythmic beating was observed at the grafted site at a rate different than the aortic rate in 100% of the cell-treated group versus none of the medium-treated group. The spontaneous beating rate of vena cava was 101 ± 7 beats at 1–3 min after excision of the native heart. Also, the diameter of the vena cava was reduced by 17.5 ± 5.4% when the grafted cardiac cells contracted. These results show that the grafted neonatal cardiomyocytes around the vena cava can survive, mature, and contract spontaneously.

In conclusion, Dr. Kloner suggested that the potential of cardiac cell transplantation to fashion an external auxiliary circulatory pump should be further investigated.

Should Door-To-Unload (DTU) replace Door-To-Balloon (DTB) for acute MI without shock

Presented by Navin Kapur, MD

Dr. Kapur presented the purpose and learnings from the Door-To-Unload (DTU) in ST-elevation in myocardial infarction (STEMI) pilot trial using Impella CP as the mechanical left ventricular unloading platform. He began by providing the background for this trial. By the year 2030, 1 out of every 33 individuals in the United States will have heart failure (HF), and the associated total costs will reach $70 billion per year [52]. For every 5% increase in myocardial infarct size, 1-year HF hospitalization increases by 20% [53]. Additional strategies are therefore needed to reduce myocardial infarct size.

Maroko and Braunwald in 1971 suggested "that measures designed for reduction of myocardial oxygen demands and improvement of coronary perfusion, when effected promptly might reduce the ultimate size of (a myocardial) infarction" [54]. Since 1978, multiple preclinical studies have tested whether reducing myocardial oxygen consumption by implementing a circulatory pump limits myocardial damage in an acute myocardial infarction (AMI). In addition, multiple attempts have been made using pharmacological approaches to reduce myocardial oxygen demand by reducing heart rate, left ventricular (LV) wall stress, and LV stroke work.

Several studies spanning 4 decades have tested mechanical unloading using mechanical devices and demonstrated that unloading before not after reperfusion is required to reduce infarct size [55]. Since 2012, multiple preclinical studies from the Kapur lab have supported the hypothesis that primary LV unloading and delaying coronary reperfusion for 30 min provides both cardioprotective signaling and myocardial salvage [10, 20, 56]. The central hypothesis of the DTU STEMI pilot trial was compared to LV unloading and immediate reperfusion, LV unloading followed by a 30 min delay to reperfusion is feasible and safe as defined by: successful enrollment and protocol completion (feasibility); no increase in major adverse cardiovascular or cerebral events (MACCE, safety); and no increase in infarct size between groups (safety).

In this phase 1, multi-center, safety and feasibility pilot trial, 50 patients with anterior STEMI were randomized (1:1) to LV unloading using the Impella CP followed by immediate reperfusion (U-IR) or delayed reperfusion after 30 min of unloading (U-DR) (Fig. 9). Impella CP was explanted after a minimum of 3 h of support. The technical feasibility of the DTU in STEMI pilot trial was highly dependent on optimal team dynamics. Dr. Kapur stated that the pilot trial was successfully completed and the results will be presented at the late breaking science session at American Heart Association (AHA) Annual Meeting 2018 with a co-publication in Circulation [57].

Dr. Kapur highlighted that the DTU STEMI Pilot trial is the first step towards developing a physiologically integrated approach to acute AMI therapy. He further stated that the success of the DTU STEMI pilot and pivotal trials may pave way for testing additional investigations in conjunction with primary unloading, targeting both the ischemic as well as reperfusion injury to further reduce infarct size such as intravenous beta-blockade [58] and intracoronary vasodilators.

Case report from the Door-to-Unload (DTU) in STEMI trial

Presented by Haroon Faraz, MD

Dr. Faraz presented a clinical case from the Door-To-Unload (DTU) in STEMI pilot trial. In this phase 1, multi-center, safety and feasibility pilot trial, 50 patients with anterior STEMI were randomized (1:1) to LV unloading using the Impella CP followed by immediate reperfusion (U-IR) versus delayed reperfusion after 30 min of unloading (U-DR). Impella CP was explanted after a minimum of 3 h of support.

The patient was a 62-year-old morbidly obese male with a history of smoking who presented with chest pains that started about an hour prior to presentation. The patient had experienced a vague epigastric discomfort two days prior that spontaneously resolved, but recurred with greater intensity and was associated with shortness of breath and diaphoresis. Baseline LV ejection fraction (LVEF) was 43%. This patient was enrolled in

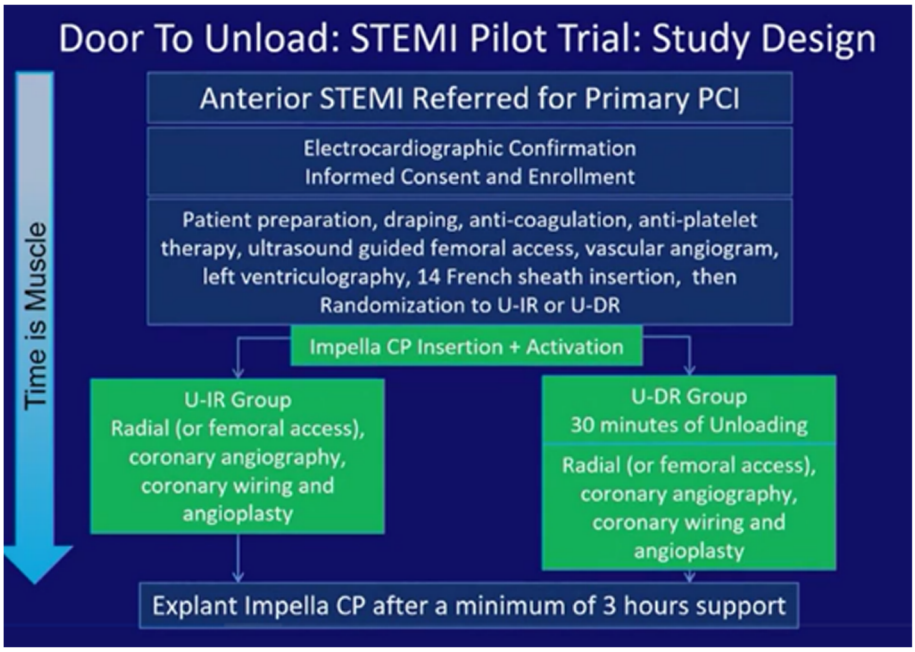

Fig. 9 Study Design of the Door-To-Unload in STEMI Pilot Trial. U-DR = delayed reperfusion after 30 min of LV unloading by the Impella CP; U-IR = immediate reperfusion after placement of the Impella CP; CP = cardiac power

the U-DR arm of the trial. Following successful LV unloading and percutaneous coronary intervention, the patient was discharged home on day 3. At 30 day follow-up, the patient's LVEF had improved to 55%. Dr. Faraz noted that immediately after initiating LV unloading with the Impella CP ST-elevation began to resolve and the intensity of chest pain experienced by the patient had reduced, which reassured him of the benefits of LV unloading.

Dr. Faraz highlighted the challenges with enrolling and obtaining informed consent from patients experiencing anterior wall myocardial infarction (MI) for participation in the first exploratory study in humans testing the safety and feasibility of left ventricular (LV) unloading and delayed reperfusion as a method to reduce infarct size. He emphasized that choice of words regarding the purpose of the trial and positive reinforcement from the emergency department staff regarding the interventional cardiologist's experience was vital in enrolling patients in the trial. He suggested a strategy of active 24/7 enrollment for the future pivotal trial and a dedicated champion at each clinical trial site to ensure coordination of multiple systems and processes needed for the successful completion of the trial.

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Consent for publication
Informed consent to publish had been obtained from the patients featured in the "First In Man Implantations of a Newly Designed Transaortic Axial Flow Ventricular Assist Device, Impella 5.5" and "Case Report from the Door to Unload in STEMI Trial"presentations.

Competing interests
The authors declare that they have no competing interests.

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Acute Cardiac Unloading and Recovery

Proceedings of the 4th Annual Acute Cardiac Unloading and REcovery (A-CURE) symposium held on 30 August 2019 in Paris, France

Session summaries by Uma Chandrasekaran, PhD, Senior Scientist, Abiomed

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Established in 2015, (in part due to the generous funding of our sponsor: Abiomed Inc.) the faculty of the A-CURE® Working Group meets annually to initiate scientific and clinical discussions on how acute cardiac unloading may increase myocardial salvage, prevent (or limit) myocardial and ventricular injury and remodeling, improve survival, and attenuate the development of heart failure after myocardial infarction. Many of the current A-CURE faculty members have been participants since the inception of the working group.

ICR Interventional Cardiology Review

Foreword

Welcome to this special supplement devoted to the proceedings of the 4th Annual Acute Cardiac Unloading and REcovery (A-CURE) Working Group meeting, which was held on 30 August 2019 in Paris, France. The A-CURE Working Group is comprised of leading academic experts in clinical and basic cardiac research who are dedicated to advancing the science and clinical application of acute cardiac unloading. This meeting brought together experts from multiple disciplines, including interventional cardiologists, heart failure specialists, cardiac surgeons, molecular biologists and biomedical engineers.

The 2019 symposium featured talks and posters that highlighted cutting-edge advances in the field of acute cardiac unloading that have taken place since the 2018 A-CURE symposium in Chicago, US.

Cardiac disease states, such as MI, myocarditis, cardiomyopathy and cardiogenic shock, impair the ability of the heart to pump blood, resulting in end-organ failure and, ultimately, death. Pharmacological therapies in these cases aim to maintain cardiac output, but in the process, impose further stress on the heart. Additional treatment strategies are needed. The A-CURE symposium focused on the basic science and clinical application of ventricular unloading using mechanical circulatory support technologies. Acute cardiac unloading decreases myocardial oxygen consumption and maximises the ability of the heart to rest and recover after damage. Mechanical unloading employs percutaneous ventricular assist devices, such as the Food and Drug Administration-approved Impella family of devices, to decrease the physical workload of the heart.

This supplement features a number of presentations covering a broad range of subjects related to cardiac unloading. The first session of the symposium was devoted to the advances in basic and pre-clinical science of acute unloading and myocardial salvage. Topics discussed ranged from the influence of acute unloading using Impella devices on the preservation of mitochondrial structure and function post-MI to improving intracoronary gene transduction efficiency. The impact of concomitant vasoactive treatment during active ventricular unloading in cardiogenic shock and a novel superior vena cava occlusion catheter system that reduces ventricular filling pressures while maintaining cardiac output in a model of congestive heart failure were also discussed.

In the keynote lecture, Douglas Mann shared insights on the cellular and molecular and mechanisms associated with left ventricular (LV) remodelling and reverse remodelling in a mouse model that combines clinically relevant comorbidities of moderate pressure overload and small ischaemic injury.

The second session focused on new frontiers and clinical translation of unloading. The wide spectrum of clinical studies presented included cardio-renal system interaction with the effect of haemodynamic support on acute kidney injury, the use of mechanical circulatory support for takotsubo syndrome with cardiogenic shock and clinical implications of prolonged use of Impella pumps for fulminant myocarditis with shock.

The afternoon's presentations had a focus on the clinical translation of LV unloading. William O'Neill provided an update on the outcomes associated with the adoption of a standardised protocol for treatment in cardiogenic shock, the key features of which include the early initiation of mechanical support prior to reperfusion. Jason Williams discussed preoperative identification of high-risk cardiac surgery patients who may benefit from LV unloading with Impella. Jaime A Hernandez-Montfort presented a study of the global epidemiology and survival outcomes of patients receiving temporary circulatory support before durable ventricular assist device implantation. In the concluding talk, Navin K Kapur provided the rationale and discussed the design of the ST-elevation MI Door-To-Unload pivotal trial.

The presentations highlighted the exciting new developments and represented substantial advances in the field of acute myocardial unloading and recovery that have developed in the past year. The A-CURE Working Group meeting is unique in involving a diverse group of experts from multiple disciplines within an open, constructive and intimate public setting.

We hope that you find this supplement informative and interesting. ■

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The State of the Field: Our Current Understanding of Ventricular Unloading

Presented by Daniel Burkhoff, MD, PhD

Cardiovascular Research Foundation and Columbia University, New York, NY, US

Dr Burkhoff is the Director of Heart Failure, Haemodynamics and Mechanical Circulatory Support Research at the Cardiovascular Research Foundation. He has authored more than 350 peer-reviewed publications and is a world expert in heart failure, haemodynamics and heart muscle mechanics. Dr Burkhoff is a founding member of the Acute Cardiac Unloading and REcovery Working Group.

Dr Burkhoff opened the meeting by reminding the attendees about the mission of the Acute Cardiac Unloading and REcovery (A-CURE) Working Group, which is to advance the science and mechanistic understanding of acute cardiac unloading and support the translation of basic and clinical research into therapies aimed at heart muscle recovery. He noted that the A-CURE symposium is the only scientific conference dedicated entirely to acute unloading and heart recovery, and clinicians have made great strides in accomplishing the mission.

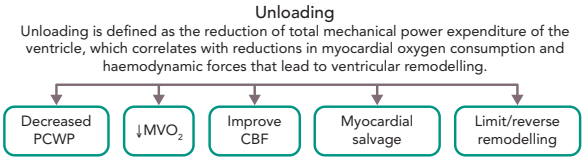
He presented a brief history of the A-CURE meetings, which began with the first faculty meeting in Paris in 2015. The annual A-CURE symposium started in Rome in 2016, followed by Barcelona in 2017, Chicago in 2018 and Paris in 2019. He highlighted the increasing number of abstracts (31 in 2016 to 63 in 2019) and accelerating science over the years, including the initiation and completion of the ST-elevation MI Door-To-Unload (STEMI-DTU) pilot trial in 2017 to the expected commencement of the STEMI-DTU pivotal trial in 2019.

Dr Burkhoff proposed a formal definition of left ventricular (LV) unloading as the reduction of total mechanical power expenditure of the ventricle, which correlates with the reduction in myocardial oxygen consumption and haemodynamic forces that lead to ventricular remodelling.[1] He explained the concepts of remodelling and reverse remodelling using pressure–volume loops (PVL), emphasising that the PVL is a graphical depiction of myocardial function that holds a wide range of physiologically relevant data. He highlighted that the PVL is bound by the end-systolic pressure–volume relationship and the end-diastolic pressure–volume relationship (EDPVR), indices of contractility and diastolic function, respectively. Following an acute insult to the myocardium, there is a reduction in contractility with a reduction in stroke volume and an increase in pulmonary capillary wedge pressure (PCWP). The sustained increase in haemodynamic load and neurohormonal activation leads to the initiation of ventricular remodelling.

Prolonged ventricular remodelling manifests as the rightward shift of the PVL representing haemodynamic stress and typically results in chronic heart failure. The goal of ventricular unloading is to prevent/reverse cardiac remodelling and subsequent heart failure. When the goal of myocardial unloading using mechanical circulatory support is achieved, it results in decreased PCWP, decreased myocardial oxygen consumption, improved subendocardial coronary blood flow, salvage of myocardium and limits/reverses remodelling (*Figure 1*).

He noted that the benefits of LV unloading are well-documented in basic and clinical literature. The seminal work by Pfeffer et al. in 1985 demonstrated the benefits of LV unloading using captopril, an angiotensin-converting enzyme (ACE) inhibitor, in a rat model of MI.[2] They showed that during a large untreated MI, the EDPVR is markedly shifted rightwards compared to normal conditions, reflecting acute pressure and volume overload in the LV. However, the degree of EDPVR rightward shift is blunted following treatment with captopril. This pre-clinical finding was tested in a clinical trial that showed a significant reduction in end-diastolic pressure and PCWP with the resultant decrease in ventricular dilatation with captopril.[3] These studies were followed by additional trials, such as the Survival and Ventricular Enlargement (SAVE) trial, that were critical in establishing ACE inhibitors as therapies for the treatment of MI.

Figure 1: Definition of Myocardial Unloading and Benefits During MI



CBF = coronary blood flow; LV = left ventricular; PCWP = pulmonary capillary wedge pressure.

However, there are inherent limitations to myocardial unloading using pharmacological therapies. Importantly, more unloading of the LV through pharmacological means leads to more compromise in aortic pressure and cardiac output. Hence, pharmacological therapies are inherently limited in their ability to unload the heart. On the other hand, the use of a percutaneous ventricular assist device, such as Impella, can simultaneously unload the ventricle and reduce the workload of the heart while increasing end-organ perfusion as perfusion pressure is maintained. In 2003, Meyns et al. demonstrated that LV unloading using Impella reduced myocardial oxygen consumption resulting in reduced infarct size in a sheep model of ischaemia–reperfusion.[4] The study by Kapur et al. of a pig model of ischaemia–reperfusion injury further demonstrated that mechanical pre-conditioning with acute circulatory support before reperfusion limits infarct size in acute MI.[5] These results led to the STEMI-DTU pilot trial in humans assessing the safety and feasibility of primary unloading with Impella followed by delayed reperfusion in patients with STEMI. The study confirmed the safety and feasibility of primary unloading, followed by delayed reperfusion, and showed that the infarct size was relatively independent of the area at risk. The results of the pilot study are the basis for moving forward with the STEMI-DTU pivotal trial, expected to start in December 2019.

Additional studies have shown that LV unloading in chronic heart failure can also induce reverse remodelling. Levin et al. showed that the EDPVR of hearts from patients with end-stage idiopathic cardiomyopathy were shifted rightwards towards markedly larger volumes compared to normal hearts.[6] However, chronic haemodynamic unloading with LV assist devices resulted in the leftward shift of the EDPVR towards lower volumes, similar to those of normal hearts. Additional studies have demonstrated that the unloading-induced reverse remodelling in chronic heart failure is both dose- and time-dependent.[7,8]

Dr Burkhoff concluded that this year's A-CURE symposium will showcase advances in the science of unloading and myocardial salvage from basic science and clinical research. ■

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A Novel Imaging Probe for the Detection of Autophagy in Pre-clinical Pig Models of Myocardial Ischaemia–Reperfusion Injury

Presented by Howard Chen, PhD

Tufts Medical Center, Boston, MA, US

Dr Chen is an assistant professor at Tufts Medical Center in Boston. His research focuses on the molecular imaging of cell death and survival pathways in the heart *in vivo*. His lab is particularly involved in the molecular imaging of autophagy, a catabolic cellular process that plays an important role in many cardiovascular diseases.

Dr Chen presented his findings on the role of autophagy in myocardial ischaemia–reperfusion (IR) injury based on a novel molecular imaging technique in a pre-clinical pig model. He began by highlighting that cardiomyocyte death is a hallmark of acute MI (AMI). He provided background by describing the three types of cellular death pathways (apoptosis, necrosis and autophagy), and the complex cross-talk between these cell death mechanisms.[1] Apoptosis is programmed, while necrosis is an irreversible cell death. Autophagy is an evolutionarily conserved catabolic cellular process, during which cells digest organelles in their cytoplasm and recycle the constituents. Autophagy is thought to play an important role in many cardiovascular diseases. The pathophysiological impact of autophagy has been shown to promote cardiomyocyte death or recovery. A major barrier in the study of autophagy is the inability to accurately detect and quantify autophagosomes within the area at risk during AMI.

Dr Chen proposed that *in vivo* imaging may aid in quantification and provide mechanistic insights of these different cell death pathways during AMI. He noted that the annexin V-magnetic nanoparticle AnxCLIO-Cy5.5 was previously demonstrated to detect apoptosis *in vivo* by MRI with good spatial resolution in a mouse heart following AMI.[2–4] More recently, a gadolinium–thiazole-based nanoparticle, which binds to the exposed DNA of ruptured cardiomyocytes, was demonstrated to detect necrosis *in vivo* by MRI in mouse heart following AMI.[5–7]

He stated that fluorescence imaging allows multiplexing, and thus plays an important part in understanding the fate of individual cells through the cell death pathways. Likewise, multiplexed imaging using nanoparticle probes is feasible and reveals additional insights, suggesting that early cardiomyocyte apoptosis may be reversible.

Dr Chen described in detail the molecular events during autophagy and emphasised that an expanded lysosomal compartment upon formation of the autolysosome is a hallmark of autophagy.[8] He described two autophagy imaging constructs that reflect lysosomal enzyme (cathepsin) activity: cathepsin-activatable fluorochrome (CAF) and autophagy-detecting nanoparticle (ADN).[9,10] ADN was rationally designed for enhanced sensitivity of autophagy detection and is based on a Food and Drug Administration (FDA)-approved drug, Feraheme (ferumoxytol), which is surface decorated with CAF peptides. The advantages of the ADN probe include dual near-infrared fluorescent and MRI readouts.

Dr Chen presented the results of ADN imaging of cardiomyocyte autophagy in a mouse model involving 24-hour starvation. Compared to the fed control mice, autophagy was induced in the starved mice and was detected by increased uptake of the ADN probe, both by MRI and fluorescent imaging. Systemic profiling of the ADN fluorescence showed increased autophagy (ADN levels) in the heart, spleen and small intestine compared to other organs, such as the lung, kidney or liver.

Next, Dr Chen presented his current hypothesis that the ADN, based on ferumoxytol, used to target lysosomal compartments during autophagy *in vivo*, could provide a robust fluorescent readout of autophagy levels in animal models of AMI. This hypothesis was tested using both mouse and pig models of IR injury.

Mice were subjected to 35 minutes of ischaemia by ligation of the left coronary artery, followed by 4 hours of reperfusion. At the onset of reperfusion, both ADN and CAF (internal control) probes were co-injected intravenously via the tail vein for *ex vivo* imaging. The results showed that ADN detects autophagy in IR mice (n=5) and is far more sensitive than CAF (n=5). Importantly, ADN activation was specific and localised in the ischaemic myocardium.

Treatment with rapamycin, a robust activator of autophagy through inhibition of the protein kinase mammalian target of rapamycin, led to a reduction in apoptosis by 23% and infarct size by 45%, thus providing molecular insights on the role of autophagy.[10]

In the pig model of AMI, adult swine were subjected to 2 hours of ischaemia by left anterior descending artery occlusion, followed by 30 minutes of mechanical support with Impella or extracorporeal membrane oxygenation (ECMO) and finally 2 hours of reperfusion. The ADN probe was injected intracoronary during reperfusion for *ex vivo* imaging. As expected from the results of the mouse model, a significant increase in ADN signal was seen in the area at risk compared to the uninjured (septal) myocardium. Of note, reperfusion significantly increased autophagosome formation (indicated by light chain 3B-II levels), which was attenuated by Impella (n=4), but not by ECMO (n=4).

In conclusion, this study demonstrates the feasibility of quantitative autophagy imaging in the heart following AMI and shows that unloading with Impella and ECMO differentially impacts autophagy. Future studies will focus on characterising additional molecular readouts of autophagy in unloaded swine hearts after AMI to further advance the translation of the novel autophagy imaging technology. ■

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Left Ventricular Unloading and Delaying Coronary Reperfusion Preserves Energy Substrate Utilisation and Protects Mitochondrial Integrity in a Pre-clinical Model of Acute MI

Presented by Lija Swain, PhD

Tufts Medical Center, Boston, MA, US

Dr Swain is a post-doctoral researcher with the Kapur Laboratory at Tufts University School of Medicine in Boston.

Dr Swain began by highlighting that haemodynamic load is a major determinant of acute and chronic ventricular remodelling.[1] This led her to question if acute ventricular unloading can be used as a therapeutic strategy to improve myocardial recovery. She recalled the observation by Mann et al. that the myocardial damage due to acute MI (AMI) is reversible following the reduction of left ventricular (LV) pressure and volume.[2] Studies have demonstrated that LV unloading reduces myocardial oxygen consumption, which is driven by myocyte cycling, excitation-contraction coupling and basal metabolism. Previous studies have shown that transvalvular pumps, such as Impella, rapidly unload the LV without the need for surgery.[3,4] In addition, emerging research comparing reperfusion alone to LV unloading prior to reperfusion has demonstrated that the unloading strategy reduces infarct size, despite delaying reperfusion by 60 minutes in a pig model.[4,5] The recent ST-elevation MI Door-To-Unload pilot trial demonstrated the safety and feasibility of LV unloading and delayed reperfusion (U-DR) in patients with ST-elevation MI.[6] The results of the subgroup analysis showed that U-DR reduced infarct size compared to unloading and immediate reperfusion.

Given the results of a previous study showing that LV unloading preserves mitochondrial structure and levels of genes associated with mitochondrial function,[5] Dr Swain hypothesised that LV unloading before reperfusion preserves mitochondrial structural and functional integrity in AMI. To test the effect of LV unloading on mitochondrial function, adult male pigs subjected to left anterior descending artery (LAD) occlusion for 90 minutes were divided into three groups. In the continued occlusion group, LAD was occluded for an additional

30 minutes, followed by 180 minutes of reperfusion. In the Impella pre-reperfusion group, Impella CP at maximal support was activated with LAD occlusion for an additional 30 minutes, followed by 180 minutes of reperfusion. In the veno-arterial extracorporeal membrane oxygenation (VA-ECMO) pre-reperfusion group, VA-ECMO at 7,500 rpm was activated with LAD occlusion for an additional 30 minutes, followed by 180 minutes of reperfusion.

The results showed that unloading with Impella CP before reperfusion compared to VA-ECMO reduced infarct size, despite equal exposure to LAD occlusion. Also, oxygen consumption rates measured using the Agilent Seahorse Platform on tissue harvested from within the infarct zone showed that primary unloading using Impella CP preserves the function of mitochondrial complex 1 in AMI compared to reperfusion alone. On the other hand, primary unloading with VA-ECMO led to a significant decrease in mitochondrial respiration via complexes I, II and III compared to reperfusion alone. Furthermore, unloading with Impella before reperfusion reduced the increase in complex I deactivation observed in the infarct zone due to ischaemia–reperfusion (IR) injury compared to VA-ECMO or reperfusion alone.

Along the same lines, oxidative stress biomarkers (catalase activity and glutathione levels) in Impella-treated animals were similar to sham-treated animals, indicating the prevention of oxidative stress and subsequent reactive oxygen species production following unloading with Impella in AMI. Dr Swain tested whether unloading with Impella impacted myocardial metabolism. Her findings suggested that unloading with Impella preserved glycolytic and Krebs cycle activity compared to IR injury alone or unloading with VA-ECMO.

Dr Swain also tested if LV unloading during ischaemia without reperfusion reduced infarct size and preserved mitochondrial function. To address this question, adult male swine were subjected to either 90 minutes of LAD occlusion, followed by an additional 120 minutes of occlusion (ischaemia), or 90 minutes of LAD occlusion, followed by 120 minutes of additional ischaemia with concurrent LV unloading with Impella (ischaemia and unloading). The results demonstrate that ischaemia and unloading significantly reduced the infarct size and preserved mitochondrial function compared to ischaemia alone. The results indicate that LV unloading may be able to limit ischaemia-dependent damage.

In summary, these findings suggest that LV unloading prior to reperfusion with Impella reperfusion versus VA-ECMO reduces infarct size and preserves mitochondrial function after IR injury. Also, the results indicate for the first time that unloading with Impella during ischaemia without reperfusion reduces infarct size and preserves mitochondrial function after prolonged ischaemic injury. ■

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Concomitant Vasoactive Treatment and Mechanical Unloading in an Experimental Porcine Model of Profound Cardiogenic Shock: Impact on Left Ventricular Function and End-organ Perfusion

Presented by Nanna Junker Udesen, MD, PhD

Odense University Hospital, Odense, Denmark

Dr Udesen is a doctoral researcher with the Møller Laboratory at Odense University Hospital in Denmark.

Dr Udesen opened her talk by stating the clinical relevance of testing vasoactive drugs concomitant with mechanical unloading in cardiogenic shock (CS). She highlighted that, according to the 2017 European Society of Cardiology guideline for the management of acute MI (AMI) in patients with ST-segment elevation MI, both inotropes and short-term mechanical support devices might be considered for haemodynamic stabilisation (Class IIb); however, the level of evidence is weak.[1,2] A recent publication assessing the temporal trends of CS in AMI in Denmark reported the increasing use of mechanical circulatory support with Impella devices, and the use of ≥1 vasoactive drug in about 90% of cases.[3] She described the clinical conundrum involving patients with CS and low perfusion pressure and the decision to use an inotrope or vasoconstrictor to increase end-organ perfusion. This increase in perfusion pressure comes at the expense of increased cardiac afterload, and hence an increase in left ventricular (LV) workload.

To aid in the choice of the vasoactive drug, Dr Udesen compared the effect of norepinephrine (NA), epinephrine (AD), dopamine (DA) and phenylephrine (PE) on pressure–volume area (PVA), LV workload (product of PVA and heart rate) and metabolism in a pig model of ischaemic cardiogenic shock supported by Impella CP (n=10).

CS was induced using stepwise injections of polyvinyl microspheres and was defined as mixed venous oxygen saturation (SvO_2) to <30% or ≤50% of baseline value and/or sustained cardiac index <1.5l/min/m2 for ≥10 minutes. The multiple steps of the experiment included instrumentation, development of CS, initiation of support with Impella CP for 30 minutes, administration of minimal NA (if the mean arterial pressure declined to <50 mmHg), blinded crossover to drug infusion for 30 minutes each (AD 0.1 µg/kg/min, NA 0.1 µg/kg/min and DA 10 µg/kg/min), PE infusion for 20 minutes and euthanasia. A linear mixed model was constructed using individual animals as subjects for random factors and sequential experimental stages as fixed repeated measurements. The reference time was set to 30 minutes after initiation of Impella CP support.

Concomitant administration of NA with Impella CP resulted in a leftward shift of the pressure–volume loop (PVL) with an increase in stroke work. Similar results were observed with DA (slightly more pronounced) and AD. However, concomitant administration of PE with Impella CP resulted in a rightward shift of the PVL, with an increase in end-diastolic pressure (LVEDP). Compared to treatment with Impella (reference), AD increased heart rate by 1.2-fold, DA and PE by about 1.4-fold, while no difference was observed with NA. LVEDP increased significantly only with PE and not with reference and other vasoactive drugs. In contrast, LV stroke work increased to different degrees with AD, DA and NA, with no difference with PE. Also, the PVA increased with all four drugs, compared to treatment with Impella. These data indicate that the total LV workload increased with all four drugs compared to treatment with Impella alone, and reached statistical significance in all drug treatment groups, except NA.

The arterial lactate concentration and renal and cerebral oxygen saturation were measured to assess the status of end-organ perfusion. Compared to reference, SvO_2 increased with AD, DA and NA, but decreased significantly with PE. Treatment with PE significantly increased arterial lactate levels and decreased renal venous oxygen compared to treatment with Impella. Treatment with DA significantly increased cerebral SvO_2 compared to treatment with Impella.

Taken together, the results suggest that if the perfusion pressure remains low after initiating support with Impella CP in CS, NA should be the first vasoactive drug of choice because it exhibits mild inotropic and potent vasopressor effects. The use of PE, which exhibits only vasopressor effects, should be avoided. ■

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Improving Cardiac Gene Therapy Efficacy Using Impella

Presented by Kiyotake Ishikawa, MD, PhD

Icahn School of Medicine at Mount Sinai, New York City, NY, US

Dr Ishikawa is an assistant professor at Icahn School of Medicine at Mount Sinai, New York.

Dr Ishikawa began by recalling that acute MI (AMI) was a deadly disease about 50 years ago, but advances in acute care, including early coronary revascularisation, have led to a significant decline in mortality.[1,2] However, it has led to a parallel increase in the prevalence of heart failure (HF) and the subsequent increase in costs of care.[3,4] In essence, the therapeutic advances in the management of AMI over the past few decades have led to a detour to the final destination of death that now goes through HF. He highlighted the research initiatives and publications by the Acute Cardiac Unloading and REcovery faculty in the past several years attempting to stem the development of HF following an AMI via mechanical unloading.[5–10] This raises the question of what therapies can benefit patients who have already developed HF and prevent them from premature death. Dr Ishikawa's team tested the idea of utilising mechanical left ventricular (LV) unloading to increase the efficacy of delivering cardiac gene therapy vectors in patients with established HF.

He highlighted the poor results of the phase IIb trial, Calcium Up-Regulation by Percutaneous Administration of Gene Therapy In Cardiac Disease (CUPID 2), which investigated the intracoronary administration of adeno-associated virus type 1 (AAV1)/*SERCA2a* gene in patients with Class III/IV HF.[11] Possible reasons for the failure of the trial include insufficient myocardial uptake of the transduced gene, as the AAV concentration was very low. He then described the antegrade intracoronary injection of the gene therapy vector, which is advantageous given the relatively low invasiveness and homogeneous distribution. However, data on this approach demonstrate that the cardiac uptake of the vector is low and so requires a high vector dose to compensate.

Studies suggest that efficient cardiac gene transfer efficiency with AAV vectors can be achieved with high perfusion pressure, coronary flow, vector dose and longer exposure times. Dr Ishikawa presented his hypothesis of improving gene delivery by using the Impella device to enhance viral uptake. He proposed that Impella support could affect uptake in two ways. First, LV unloading with Impella will

result in a decrease in LV wall stress and an increase in coronary flow and pressure. Second, Impella could be used to haemodynamically support the patient while the vector is delivered into the coronary system during temporary coronary balloon occlusion. This would allow for a longer dwell time by slowing the coronary perfusion rate and minimising the risk of haemodynamic collapse.

Dr Ishikawa tested the haemodynamic support approach with Impella in a pig model of subacute ischaemic HF. AMI is induced and the heart is allowed to remodel for 1 week. After 1 week, the AAV-6-Luc (5.0×10^{13}) is delivered intracoronary, with or without Impella support (n=3 each), and the hearts were analysed for luciferase activity after 4 weeks. No clear benefit of unloading with Impella alone was observed when using antegrade intracoronary delivery of the AAV vector with a luciferase gene construct.

Next, he tested gene delivery via coronary occlusion, with or without Impella. All pigs tolerated temporary balloon occlusion in the infarcted left anterior descending artery with no change in the systolic aortic pressure, both with and without Impella. However, the systolic aortic pressure dropped to <60 mmHg in all pigs treated with balloon occlusion in the non-infarcted left circumflex artery without Impella, while this was maintained in pigs receiving Impella support. The delivery of the AAV vector via coronary artery (CA) balloon occlusion with Impella resulted in approximately a 20-fold increase in the expression of the transduced gene. Moreover, delivery of the AAV vector using a combination of CA and coronary sinus occlusion with Impella support resulted in an up to 800-fold increase in the transduced gene expression, comparable to intramyocardial exposure via surgical approach. All animals supported with Impella during simultaneous CA and sinus occlusion were haemodynamically stable throughout the procedure.

In conclusion, these results demonstrate that haemodynamic support with Impella allows for safe and efficacious AAV gene delivery to the heart. Future studies include testing the above model with a therapeutic gene and delineating the mechanisms leading to high gene transduction. ■

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Reversal of MI-induced Changes in Gene Expression by Ventricular Unloading in Rats

Presented by Heimo Ehmke, MD

University Medical Center Hamburg-Eppendorf, Hamburg, Germany

Dr Ehmke is an institute director at University Medical Center Hamburg-Eppendorf, Germany. He was the recipient of the Best in Research Scholarship for the 2019 Acute Cardiac Unloading and REcovery symposium.

Dr Ehmke outlined that many studies have shown that mechanical unloading of the left ventricle (LV) may support the recovery of myocardium after an ischaemic insult, yet the molecular mechanisms underlying this reverse remodelling are largely unclear.[1] His team hypothesised that ventricular unloading leads to the normalisation of genes dysregulated after MI, and this normalised gene expression plays a role in reverse cardiac remodelling. The hypothesis was tested via an unbiased transcriptomic approach aimed at identifying relevant genetic pathways in 12-week-old male Lewis rats. MI was induced by coronary ligation of the left anterior descending artery or sham surgery was performed, followed by an assessment of LV function at 6 weeks. Cardiac gene expression was assessed at 8 weeks using the Affymetrix GeneChip. A subset of the MI-induced and sham rats received mechanical unloading using a syngeneic heterotopic transplanted heart at 6 weeks, followed by assessment of cardiac gene expression at 8 weeks.[2]

At 6 weeks post-MI, the LV ejection fraction in the MI-induced rats had decreased from 75% to about 25%, along with a significant increase in the LV internal diameter compared to the baseline. The gene expression profiling showed that, in infarcted heart MI, about 1,000 genes were dysregulated, with 874 genes being downregulated and 182 genes being upregulated compared to sham controls. Following

unloading, 101 of the 874 downregulated genes and 32 of the 182 upregulated genes were normalised. Further analysis showed that most of the genes normalised by unloading were involved in the Hippo signalling pathway, known to play a key role in cardiac development, cardiomyocyte homeostasis and regeneration.[3]

In conclusion, MI in rats led to dysregulation of about 1,000 cardiac genes, and mechanical unloading normalised the expression of about 10% of the dysregulated genes. Preliminary analyses suggest that modulation of the Hippo pathway may contribute to the beneficial effects of LV unloading in ischaemic hearts. ■

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A Novel Superior Vena Cava Occlusion System for the Treatment of Acute Congestive Heart Failure: Pre-clinical and Clinical Data

Presented by Daniel Burkhoff, MD, PhD

Cardiovascular Research Foundation and Columbia University, New York, NY, US

Dr Burkhoff is the Director of Heart Failure, Haemodynamics and Mechanical Circulatory Support Research at the Cardiovascular Research Foundation. He has authored more than 350 peer-reviewed publications and is a world expert in heart failure, haemodynamics and heart muscle mechanics. Dr Burkhoff is a founding member of the Acute Cardiac Unloading and REcovery Working Group.

Dr Burkhoff began by stating that the Acute Cardiac Unloading and REcovery symposium is focused on ventricular unloading using mechanical circulatory support devices to improve or maintain myocardial function. Laboratories around the world are investigating other novel methods for ventricular unloading and improving the haemodynamic status of other end-organs. He stated that congestion plays an important role in acute decompensated heart failure (ADHF) and is an important target of therapy.[1] It is characterised by elevated filling pressures, clinical signs of dyspnoea, peripheral oedema, ascites and end-organ dysfunction resulting in poor prognosis. Studies suggest that venous congestion reduces glomerular filtration and limits urine output, thereby attenuating the effects of diuretics and promoting HF.[2,3]

Existing approaches to reduce congestion are limited. Hence, there exists a need for rapid and effective cardiac decongestion in patients with ADHF. Dr Burkhoff highlighted a recent significant effort aimed at decreasing congestion: decrease central venous pressure and pulmonary capillary wedge pressure (DRIPPS). One of the components of DRIPPS includes a class of devices/drugs nicknamed 'pullers', whose mechanism of action is to decrease the central venous pressure or pulmonary capillary wedge pressure by 'pulling' volume out of the venous system. This effect of pullers should decongest the patient and promote increased end-organ perfusion by increasing the arterial-to-venous pressure gradient. Pullers also include devices that can transiently occlude the superior vena cava (SVC), leading to reduced cardiac filling pressures without reducing cardiac output (CO) or systemic blood pressure. Because SVC accounts for only about 30% of venous return, it was postulated that the SVC could be totally occluded, potentially with less impact on CO or systemic blood pressure, with a subsequent reduction in end-organ venous pressure.

The recent pre-clinical publication from Kapur et al. showed that while the inferior vena cava occlusion reduced CO, left ventricular end-systolic pressure (LVESP) and left ventricular end-diastolic pressure (LVEDP), SVC occlusion on the other hand led to a reduction in only LVEDP with no effect on CO or LVESP.[4]

The encouraging results of the pre-clinical studies led to the clinical proof-of-concept study to provide initial evidence of safety and feasibility of transient SVC occlusion in patients with ADHF and reduced ejection fraction (<40%), who were referred for cardiac catheterisation.[4] SVC occlusion was performed using a commercially available occlusion balloon in eight patients with systolic heart failure. Five minutes of SVC occlusion reduced biventricular filling pressures without decreasing systemic blood pressure or total cardiac output in five of the eight patients. In three of the eight patients, a second 10-minute occlusion period had similar haemodynamic effects. SVC occlusion was well-tolerated without the development of new symptoms, new neurological deficits or any adverse events, including stroke, heart attack or reported SVC injury or thrombosis at 7 days of follow-up. The favourable results of this proof-of-concept study have led to the prospective, multicentre early feasibility and safety study of the preCARDIA system in the SVC Occlusion in Subjects With Acute Decompensated Heart Failure (VENUS-HF) study.

In conclusion, venous congestion is an important prognostic indicator of ADHF and CS and contributes to impaired end-organ function. In an early clinical study testing transient SVC occlusion, this approach appears to be a safe therapeutic approach to rapidly reduce cardiac filling pressures in HF, while preserving blood pressure and CO and increasing urine output. ■

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Plenary Lecture: The Role of Haemodynamic Load in Left Ventricular Remodelling and Reverse Remodelling

Presented by Douglas L Mann, MD

Washington University School of Medicine, St Louis, MO, US

Dr Mann is the Lewin Chair and Professor of Medicine, Cell Biology and Physiology, at the Washington University School of Medicine, and Cardiologist-in-chief at Barnes Jewish Hospital in St Louis, Missouri, US. His research focus has been the molecular and cellular basis of heart failure, with particular emphasis on the role of innate immunity in disease progression and recovery of the failing heart. He is recognised for his outstanding contributions to the field of heart failure and has authored numerous peer-reviewed articles on the role of inflammatory mediators in cardiac remodelling and myocardial recovery. He is the editor of *Heart Failure, A Companion to Braunwald's Heart Disease*, co-editor of *Braunwald's Heart Disease* (the leading textbook in cardiovascular medicine) and the founding editor of *JACC: Basic to Translational Science*.

Dr Mann's talk focused on his investigations on the role of haemodynamic load in left ventricular (LV) remodelling and reverse remodelling. The biology of cardiac remodelling involves three main components in succession: myocyte and myocardial alterations resulting in alterations to LV geometry. His early work in 1989 provided the first evidence that an increase in load on adult mammalian cardiomyocyte can activate hypertrophy.[1] Numerous studies have since shown that cardiomyocyte stretch alone is sufficient to activate multiple growth pathways, although the exact stretch receptors are not known.[2] D'Angelo et al. provided evidence of recapitulation of the cardiac hypertrophy gene expression by the overexpression of a single component of the stretch-activated pathway (Gαq-protein signalling pathway).[3] Stretching of cardiomyocytes induces alterations in multiple pathways in myocyte biology in parallel, including sarcomeric changes, cytoskeletal proteins and mitochondria.

LV remodelling is classified based on the patterns of structural changes relative to normal (defined as normal LV mass [LVM] with normal mass-to-cavity [M-C] ratio): concentric remodelling (normal LVM with high M-C ratio); eccentric hypertrophy (high LVM with normal M-C ratio), typically observed with volume overload; and concentric hypertrophy (high LVM with high M-C ratio), typically observed with pressure overload.[4] Studies have proposed that a transition may exist between early 'compensatory' cardiac hypertrophy in the setting of prolonged and continuous pressure overload to a 'decompensated state' that leads to heart failure (HF).[5,6] However, emerging epidemiological studies suggest that this transition from concentric hypertrophy to HF does not occur in humans.[7,8] Also, the transition from concentric LV geometry to eccentric hypertrophy occurs in <10% of patients during long-term follow-up, suggesting that the concept of using extreme pressure overloads to produce eccentric hypertrophy to understand the biology of cardiac remodelling is not clinically relevant.

Drazner et al. proposed multiple potential pathways for the progression from hypertension (classic disease of pressure overload) to HF. He showed that concentric hypertrophy progresses to dilated cardiac failure most commonly via an interval MI.[9] Interestingly, clinical evidence shows that the concomitant occurrence of hypertensive and ischaemic heart disease may lead to the development of HF.[10,11] Hence, Weinheimer et al. developed a surgical approach that combined transverse aortic constriction (TAC; mimicking pressure overload) and distal left anterior coronary ligation (inducing MI) to produce a gradual and predictable progression of maladaptive LV remodelling that leads to HF.[12] Importantly, in this surgical mouse model, a small apical infarct (<25% infarct size) or moderate TAC alone did not lead to LV remodelling. In essence, this novel mouse model demonstrated that pressure overload acts synergistically with tissue injury to provoke LV remodelling. Dr Mann briefly discussed how tissue injury leads to LV remodelling. The inflammation initiated by tissue injury activates matrix metalloproteases, which prime the extracellular matrix to receive the increased haemodynamic load signal, leading to LV remodelling.[13]

This led to the question of how reverse LV remodelling happens. Dr Mann's research team developed a murine model wherein mice develop LV remodelling after TAC and a small apical MI undergo reverse LV remodelling after removal of the aortic band at 2 weeks post-TAC/MI.[14] De-banding normalised LV volumes, LV mass and cardiac myocyte hypertrophy at 6 weeks with no difference in myofibrillar collagen with or without de-banding. LV ejection fraction (LVEF) and radial strain improved after de-banding; however, both remained decreased in the de-banded mice relative to sham and were not different from non-de-banded mice at 6 weeks. Haemodynamic unloading in the de-banded mice was accompanied by a 35% normalisation of the HF genes at 2 weeks and 80% of the HF genes at 4 weeks.

Further, bioinformatic analyses showed that the reversal of the LV HF phenotype is accompanied by significant changes in the expression of multiple genes residing within each of the five different cardiac myocyte gene modules: extracellular matrix, integrin/cytoskeleton,

sarcomere, excitation-contraction coupling and metabolism. These analyses also suggested that the changes in myocyte function precede changes in the integrin/cytoskeleton during reverse LV remodelling. Interestingly, reverse LV remodelling was not merely a reversal of the functional pathways that become dysregulated during HF. Instead, reverse LV remodelling represented the summation of the complex interactions between multiple biological networks that adopt a novel less-pathological configuration when the inciting stress is removed. This observation raises the possibility that some of the changes that occur during reverse LV remodelling confer vulnerability to a subsequent stress. This concept of 'robust yet fragile' may explain, at least in part, the observation that stable patients whose hearts undergo reverse LV remodelling with normalisation of LVEF continue to experience recurrent HF events.[15,16]

Future studies will determine whether the re-tuning of gene networks during reverse LV remodelling represents a 'good enough solution' to accommodate biological function, or whether it represents an example of a 'robust yet fragile' biological system that has been optimised to maintain robustness (i.e. homeostasis following loss of cardiac myocytes) at the expense of increased fragility (i.e. increased myocardial fibrosis).[17] ■

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Impella Mechanical Circulatory Support for Takotsubo Syndrome with Shock

Presented by L Christian Napp, MD

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Dr Napp is a director at Hannover Medical School in Germany. He has authored more than 75 peer-reviewed publications. His research focuses on the basic and clinical science of acute heart failure.

Takotsubo syndrome (TS) is an acute heart failure syndrome with severely depressed left ventricular ejection fraction (LVEF) and increased left ventricular end-diastolic pressure, demonstrating the severe combined systolic and diastolic failure. Dr Napp described how TS is often misdiagnosed as acute coronary syndrome, as about 75% of patients present with angina and about 50% present with ST-segment elevation.[1] Both the short- and long-term prognosis is poor, with about 10% of patients developing cardiogenic shock (CS) and death in about 4%.[1,2] Catecholamine release is considered to play a causal role in TS, as it may aggravate outflow tract obstruction. Therefore, the management of TS with CS is often difficult because first-line therapies for CS are often inotropes and vasopressors, acutely worsening the severity of the disease.[3,4] Of note, the systolic function in TS often recovers as long as the shock is survived, that is, patients can be bridged to recovery. Thus, temporary mechanical circulatory support devices are an attractive option for therapy.[5–7] However, veno-arterial extracorporeal membrane oxygenation increases afterload with limited myocardial recovery, while intra-aortic balloon pump induces or aggravates left ventricular outflow tract obstruction in TS.

Dr Napp hypothesised that Impella support is effective as a bridge to recovery in TS-related CS. His team identified TS patients supported with Impella in Europe and the US, and analysed patient characteristics and in-hospital outcomes.

A total of 20 TS patients supported with an Impella pump (six with Impella 2.5, 13 with Impella CP and one with Impella 5.0) from 10 centres in Europe and the US were identified (age 61.5 ± 17.1 years, 80% female). Eleven patients had an apical TS type and seven patients had a physical trigger. Patients were on multiple catecholamines prior to Impella (average of 2.3 ± 0.6) and had a mean systolic blood pressure

of 100.5 ± 25.4 mmHg. Most patients (88.9%) were mechanically ventilated, and 38.9% sustained cardiac arrest requiring cardiopulmonary resuscitation prior to Impella. Of the 20 patients, 16 (80%) survived to discharge, with two of the non-survivors dying from causes unrelated to shock. Patients experienced myocardial recovery with a significant improvement of LVEF at discharge compared to baseline (22.5% ± 11.0% on admission versus 55.0% ± 4.8% before discharge, p<0.001).

This is the first case series to report the use of mechanical support with the Impella ventricular assist device in patients with TS. Despite the presence of refractory CS in the majority of patients, Impella support was associated with survival of 80% and myocardial recovery in surviving patients. Additional prospective studies on Impella support in TS with shock are needed to avoid the use of catecholamines and to increase survival. ■

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Cardiac Unloading and the Kidney Cross-talk in Real Time

Presented by Navin K Kapur, MD

Tufts Medical Center, Boston, MA, US

Dr Kapur is an Associate Professor and the Executive Director of Cardiovascular Center for Research and Innovation at Tufts Medical Center in Boston. His research focuses on acute and chronic heart failure, circulatory support device development, and cardioprotective mechanisms in the setting of MI. Dr Kapur is a founding member of the Acute Cardiac Unloading and REcovery Working Group.

Dr Kapur began by highlighting the impact of kidney injury on long-term outcomes in patients after acute MI (AMI). The study by Parikh et al. in 2008 showed that the long-term implications of mild acute kidney injury (AKI) in the setting of AMI are striking, with only about 20% of patients surviving to 10 years.[1] Also, severe AKI was associated with high mortality as early as 30 days. Another study by Goldberg et al. showed that even transient AKI after AMI is associated with a high probability of death in the long term.[2] The recent study by Chalikias et al. further emphasised the significantly higher mortality within 30 days in patients developing AKI after AMI than in those without AKI, which continued for more than 10 years.[3]

The underlying pathophysiological mechanisms in AKI is best validated in the heart failure model. The main determinants of decreased estimated glomerular filtration rate (eGFR) are a decrease in renal blood flow (RBF) and an increase in central and renal venous pressure.[4] The latter can be caused by intravascular congestion. Owing to increased renal venous pressure, renal interstitial pressure rises, resulting in the collapse of renal tubules, thus decreasing the eGFR. This eventually leads to decreased urine output, sodium retention and kidney congestion. Decreased RBF and low blood pressure trigger renal autoregulation, preserving the glomerular filtration rate by increasing the filtration fraction by increased efferent vasoconstriction. The use of certain drugs in heart failure may inhibit this efferent vasoconstriction, which leads to an increase in RBF, but may also result in a reduction in the eGFR (pseudo-worsening renal function).

Since several haemodynamic parameters influence kidney function, Dr Kapur's research team is interested in investigating the effect of acute mechanical circulatory support devices, such as Impella and veno-arterial extracorporeal membrane oxygenation (VA-ECMO) on renal blood flow and function. The study by Abadeer et al. showed that there is a 60% incidence of AKI in patients receiving VA-ECMO for cardiogenic shock, which also correlated with poor survival.[5] Patients who had severe AKI after initiation of VA-ECMO had lower survival than those with non-severe AKI. Villa et al. postulated that AKI with VA-ECMO might be related to haemodynamic, hormonal and patient-specific variables, leading to a reduction in renal oxygen delivery and/or inflammatory damage.[6]

A recent study by Flaherty et al. was the first to demonstrate renal protection by Impella 2.5 compared to no support in high-risk percutaneous coronary intervention patients.[7] Impella 2.5 support was independently associated with a significant reduction in the risk of developing AKI during high-risk percutaneous coronary intervention. Furthermore, unpublished results from Dr Westenfeld's research group shows that peri-interventional serum creatinine levels are stable only with Impella compared to VA-ECMO. Previously, Møller-Helgestad et al. compared the RBF with intra-aortic balloon pump (IABP) versus Impella 2.5.[8] The results suggest a signal of higher RBF with Impella 2.5 and no change with IABP support.

To understand haemodynamics in the kidney, researchers at Dr Kapur's laboratory performed pressure and flow measurements in the renal artery, renal vein and inside the renal parenchyma in the large animal, closed-abdomen experimental setup. The renal module setup was validated in healthy adult pigs treated with sham, Impella or VA-ECMO, followed by the measurement of cardiac and kidney haemodynamics over 6 hours. Preliminary results suggest that in the sham control animals, cardiac output and stroke volume (SV) were maintained over

6 hours, whereas the systemic vascular resistance (SVR) gradually declined. Treatment with Impella almost paralleled sham control animals. In contrast, the cardiac output and SV of the native heart dropped following initiation of VA-ECMO, along with a significant drop in SVR within 1 hour, which persisted throughout the treatment duration.

Dr Kapur introduced the concept that the reduction in kidney function may also be related to the role of the kidney as a sensor of damage- and pathogen-associated molecular patterns, culminating in a massive decline of function in diseases, such as sepsis.[9] AKI can be characterised using functional markers, such as creatinine and urine output, and biomarkers of kidney damage, such as neutrophil gelatinase-associated lipocalin (NGAL) and kidney injury molecule-1 (KIM-1).[10] This raised the question if any insight into AKI using biomarkers of kidney damage can be gained from the pre-clinical models of AMI supported with Impella or VA-ECMO. To address this question, adult male swine were subjected to left anterior descending artery occlusion for 90 minutes, followed by either immediate reperfusion (IRI), ventricular unloading with Impella for 30 minutes prior to reperfusion while on support, VA-ECMO support for 30 minutes prior reperfusion while on support or sham-operated controls (n=4/group). Renal injury biomarkers, KIM-1 and NGAL, were measured in urine, and plasma sample was collected at different time points throughout the study. The results showed that the urinary KIM-1 levels were elevated in the IRI and VA-ECMO groups, but not the Impella group. No changes in plasma KIM-1 levels were observed in any group. Compared to baseline values, VA-ECMO increased urinary NGAL levels, but Impella did not. Compared to IRI, Impella reduced plasma NGAL levels after reperfusion.

The mechanism for increased urinary levels of KIM-1 with VA-ECMO and IRI was investigated. The protein expression for both the cytoplasmic tail fragment and the extracellular domain (ECD) of KIM-1 was measured by western blot. Compared to sham and Impella, IRI and VA-ECMO had reduced levels of the ECD, but higher levels of cytoplasmic tail of KIM-1 within the renal cortex. KIM-1 is a known substrate of metalloproteinases (MMP). Higher levels of MMP-9 expression were observed in the IRI and VA-ECMO groups than the sham and Impella groups, both in the renal cortex and left ventricular infarct zone, suggesting cross-talk between the left ventricle and renal cortex. These results also suggest that IRI and VA-ECMO activate MMP activity and promote the shedding of the ECD of KIM-1 from the renal cortex, whereas Impella does not.

In conclusion, the results indicate there may be cross-talk between the heart and the kidney after an AMI via inflammatory pathways, and Impella support prior to reperfusion attenuates this effect. It would be interesting to assess the levels of the biomarkers of kidney injury in patients treated with Impella versus no support in the ST-elevation MI Door-To-Unload pivotal study. ■

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Impact of Microaxillar Mechanical Ventricular Support on Renal Resistive Index in Patients with Cardiogenic Shock after MI

Presented by Bernard Schieffer, MD

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Dr Schieffer is Director of Cardiology at the University Heart Center, University Hospital in Marburg, Germany. He has authored more than 50 peer-reviewed publications.

Dr Schieffer began by stating that his institution adopted a regionalised system of care in 2013, along the lines of the National Cardiogenic Shock Initiative.[1] The results of this initiative showed that networking improves patient outcomes. His institution also established one of the first cardiac arrest centres in Germany. As part of this initiative, 2,117 patients with out-of-hospital cardiac arrest between January 2013 and August 2019 were medically transported over a distance (range 23–97 km) and admitted to their institution. The overall survival was about 45% at 6 months and about 42% at 12 months. Among the 426 patients with post-cardiac arrest cardiogenic shock (CS) receiving Impella, the initiation of support pre-percutaneous coronary intervention (PCI) resulted in lower levels of lactate and lower vasoactive scores over 6–72 hours than post-PCI support. In addition, Impella support pre-PCI was associated with higher survival, a greater increase in left ventricular ejection fraction at 72 hours after support initiation and lower levels of creatinine (indicative of end-organ function).

Based on the above results, Dr Schieffer's team investigated whether Impella improves renal perfusion in CS. The renal resistive index (RRI) has been studied to gain diagnostic and prognostic insights into a variety of renal pathologies (such as the progression of chronic kidney disease and renal allograft rejection), but also for the prediction of renal outcomes in critically ill patients.[2,3] Therefore, Dr Schieffer's team evaluated if RRI, determined by intrarenal artery Doppler measurements, can serve as an indicator of haemodynamics during Impella support.

RRI, measured as the quotient of (peak systolic velocity – end-diastolic velocity)/peak systolic velocity, was obtained in 15 patients with CS supported with an Impella between May and October 2018 using Doppler ultrasound.[4] Simultaneously, blood pressure was determined invasively in the radial artery. RRI was determined in both kidneys in 13 patients and one kidney in two patients. The mean difference between right and left RRI was 0.026 ± 0.023 (p=0.72). When the Impella support was increased by a mean of 0.44 l/min (± 0.2 l/min), the systolic or diastolic blood pressure remained unchanged, whereas RRI decreased significantly from 0.66 ± 0.08 to 0.62 ± 0.06 (p<0.001) consistently in all patients, implying normalisation of renal perfusion.

This observation is consistent with the notion that Impella support may promote renal protection by enhancing renal perfusion. The RRI measurement serves as an early, easy and fast method for monitoring kidney function. The early detection of kidney hypoperfusion aids in prompt initiation of therapeutic manoeuvres, which are not possible when using alternative markers of acute kidney injury, such as low urine output or serum creatinine levels.

In closing, Dr Schieffer mentioned two ongoing studies investigating RRI-guided Impella treatment in high-risk PCI and CS due to acute MI. ■

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Prolonged Impella: Mode of Action and Clinical Implications

Presented by Carsten Tschöpe, MD

Charité, Campus Virchow Klinikum, Berlin, Germany

Dr Tschöpe is Professor of Medicine and Cardiology and the Vice Director of the Department of Cardiology, Charité, Campus Virchow Klinikum, Berlin, guiding the cardiomyopathy programme. His main research interests are the potential of cell therapies to cure heart failure and the role of the immune system in heart failure.

Patients with myocarditis may present with severe unexplained acute new-onset heart failure (HF). The specific causes and extent of inflammation are associated with varied prognosis. Acute fulminant myocarditis has a moderate prognosis, while giant cell and eosinophilic myocarditis have poor prognoses.[1,2] The known pathophysiological processes underlying myocarditis include pro-inflammatory and fibrotic processes that lead to cardiac remodelling and failure.

In an overloaded myocardium, such as during acute fulminant myocarditis, mechanical stress activates integrins (mechanoreceptors) in the heart, which are known to mediate pro-inflammatory and fibrotic processes. Furthermore, integrins are known to have direct detrimental effects on the contractile apparatus. These combined effects exacerbate myocarditis and contribute to the poor outcomes. This raises the question if haemodynamically unloading the heart by using mechanical circulatory support (thereby decreasing mechanical stress) is sufficient to overcome a severe cardiac inflammatory response.

Several case reports of the successful short-term use of Impella pumps in fulminant and giant cell myocarditis have been published.[3–7] Dr Tschöpe presented the case of an HIV-positive patient in cardiogenic shock (CS) due to viral-negative fulminant myocarditis, proven by endomyocardial biopsy. The patient was treated with temporary mechanical unloading using an Impella CP in the absence of immunosuppressive therapy.

The Impella CP support for >20 days resulted in the improvement of left ventricular ejection fraction (LVEF) to 40% from a baseline of <10%. Furthermore, Impella CP support in the absence of immunosuppressive support led to a significant drop in the mRNA expression of the integrins and innate immune cells. This was paralleled by the decrease in immune cell infiltration and an increase in protein kinase A and G activity (decreased left ventricular stiffness).

Dr Tschöpe further hypothesised that prolonged unloading with an Impella device (PROPELLA) might offer the circulatory support and disease-modifying effects that are important for bridging patients with fulminant myocarditis to recovery. This hypothesis was tested in a 62-year-old patient admitted with severe myocarditis and pre-CS, despite immunosuppressive therapy. An axillary Impella 5.0 was implanted, which remained in place for 40 days. The patient was mobilised after 2 days of Impella 5.0 support. Steroid therapy and ventricular unloading led to a significant improvement in LVEF from day 5 after initiation of support. After 4 weeks, an echocardiogram

showed the first signs of recovery. Serial left ventricular biopsies were taken at various time points during treatment to assess biomarkers of inflammation.

These data demonstrate that the inflammatory response was significantly reduced during concomitant treatment with Impella and immunosuppression. However, the inflammatory response significantly increased after removal of the Impella support, despite continued immunosuppression, indicating that ventricular unloading mitigates inflammation independent of immunosuppression. The patient was weaned off Impella support after 2 months and continued immunosuppressive therapy alone. However, the immunosuppressive therapy had to be stopped early due to the development of a life-threatening abscess. The patient developed recurrent myocarditis and CS and was bridged to a long-term left ventricular assist device (LVAD). Interestingly, unloading using an LVAD also led to a decrease in immune cell presence. This case provides proof of concept that unloading improves inflammation-induced remodelling.

Dr Tschöpe presented the case of another patient with fulminant myocarditis and severe impairment of the right ventricle (RV) and left ventricle (LV). The patient received concomitant therapy with extracorporeal membrane oxygenation (ECMO) and Impella (ECMELLA).[8] The RV function improved over time resulting in weaning of the patient from ECMO, whereas the Impella support was continued (PROPELLA). Again, serial LV biopsies showed a significant decrease in integrins and immune cell presence with PROPELLA support, and this effect was maintained by providing additional immunosuppressive therapy after the Impella's removal. This result suggests that additional pharmacological intervention is needed after cessation of unloading to maintain the immune-modulating effect until total myocardial recovery. Also, these results provide evidence of correlation between mechanical unloading (decrease in LV pressures) with molecular unloading (decrease in integrins).

Dr Tschöpe also presented a case of PROPELLA support in end-stage dilated cardiomyopathy without severe inflammation. In this case, the LV function did not improve with or without unloading with Impella. In addition, the mRNA expression level of integrins and immune cell presence increased, suggesting a mismatch of molecular and mechanical unloading. The failure of molecular recovery correlated with the persistence of HF, and the patient was bridged to an LVAD. This result suggests that a mismatch of mechanical and molecular unloading correlates with no myocardial recovery.

In conclusion, experience to date suggests that the PROPELLA approach in fulminant myocarditis can serve as a bridge to recovery, due to the correlation of mechanical unloading with molecular unloading, with the maintenance of these immune-modulating effects using additional pharmacological immunosuppression therapy until total myocardial recovery. In contrast, the PROPELLA approach in end-stage dilated cardiomyopathy can serve as a bridge to LVAD due to the mismatch of mechanical unloading with molecular unloading, leading to persistent HF with no myocardial recovery. ■

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Long-term Support Using Surgically Implanted Impella Devices

Presented by Alexander M Bernhardt, MD

University Heart and Vascular Center, Hamburg, Germany

Dr Bernhardt is a cardiac surgeon and surgical director of the heart transplantation and mechanical circulatory support programme at the University Heart Center Hamburg, Germany. His research interests include the pathophysiology of heart failure, ventricular unloading, mechanical circulatory support and the management of heart transplant recipients.

Dr Bernhardt began by reminding the audience of the features of the Impella 5.0. This device is an established transaortic axial flow ventricular assist device capable of providing forward blood flow of up to 5 l/min. It was originally designed for femoral access, but axillary access is increasingly used, as it allows for mobilisation of the patient. Recently, a published meta-analysis of Impella 5.0 reported favourable survival outcomes and high rates of myocardial recovery in patients with cardiogenic shock.[1]

The clinical uses of the surgically implanted Impella 5.0 include haemodynamic support for cardiogenic shock, safer weaning from extracorporeal membrane oxygenation (ECMO) devices, bridge-to-bridge (pre-left ventricular assist device and pre-heart transplant), bridge-to-recovery (myocarditis and peripartum cardiomyopathy) and controlled post-cardiotomy (mitral/aortic valve surgery, coronary artery bypass graft [CABG]/off-pump CABG with ejection fraction <20%).

Impella 5.0 has CE approval in Europe for a maximum 10 days of support. However, >70% of patients at Dr Bernhardt's hospital require Impella 5.0 support for >10 days. Potential problems associated with longer duration of Impella 5.0 support include in-growth of the pigtail catheter, pump thrombosis and arterial embolisation, due to the presence of a repositioning sheath in the axillary artery.

The Impella 5.5 was developed to address both the need for a longer duration of support and to avoid the complications associated with the Impella 5.0. It is designed to provide haemodynamic support for up to 30 days. Like the Impella 5.0, the Impella 5.5 device is an axial flow transaortic cardiac support device mounted on a 9 Fr steering catheter with a 21 Fr pump cannula. The pump itself is shorter and stiffer than the Impella 5.0. Other improved features in the Impella 5.5 include an optical aortic pressure sensor distal to the outflow of the device and no pigtail at the tip of the catheter (eliminating the risk for in-growth of the pigtail and reducing the risk of thromboembolism and stroke) and improved kink resistance of the cannula. Importantly, the device provides a higher maximum pump flow of up to 5.8 l/min. The device is designed for axillary insertion and the repositioning sheath does not extend into the artery. In addition, modification of the motor size (37% shorter motor housing and the outlet area) improves deliverability. Other modifications in the motor include a modified interior for long-term durability and low purge flows.

Dr Bernhardt mentioned that the first-in-man experience with the new Impella 5.5 in two critically ill patients was performed at his institution.[2] His experience is that the device is easier to implant and reposition. Until April 2019, a total of 32 patients at five German hospitals received Impella 5.5, with a survival rate of 68%.

Dr Bernhardt presented the case of a 63-year-old man receiving Impella 5.5 for post-cardiotomy failure. He had undergone aortic valve replacement (AVR) with a biological valve about 10 years earlier. The replacement valve had deteriorated and had an aortic valve opening of 0.8 cm^2. At presentation, the patient had a left ventricular ejection fraction (LVEF) of 26% and left ventricular end-diastolic diameter (LVEDD) of 68 mm. The patient underwent repeat AVR with a Perimount Magna ease valve of 23 mm. Due to the inability to wean him off the cardiopulmonary bypass machine, the surgical team placed an Impella 5.5. The patient was successfully extubated 4 hours after the surgery; he was fully mobile on postoperative day 1 and Impella 5.5 was weaned and explanted under anaesthesia on day 8. At discharge, the patient had an LVEF of 35% and LVEDD of 60 mm.

Dr Bernhardt also mentioned that his institution was the first in Europe to use the Impella Connect, a cloud-based, remote-monitoring platform. The Impella Connect enables hospital clinicians and staff, along with Abiomed's clinical support team, to view the Automated Impella Controller screen (showing ventricular pressure and Impella alarms, if any) through a secure website, allowing them to track, review and share that information from any internet-capable phone, tablet or computer.

He highlighted the new heart allocation system in the US that prioritises patients supported by temporary mechanical circulatory support (TMCS) devices, such as ECMO, over those with durable, continuous-flow left ventricular assist devices, which may increase the number of patients bridged to transplant with TMCS.[3] Furthermore, a recent study by Yin et al. showed that the survival is lowest among patients bridged to transplant with ECMO compared with durable left ventricular assist devices.[4] Dr Bernhardt proposed that the Impella 5.5 device may have beneficial outcomes after transplantation compared to ECMO, and should be considered for the potential lower adverse events and mortality rates during short-term device therapy on the waiting list.[5]

In conclusion, the Impella 5.5 expands the spectrum of available short-term mechanical circulatory support devices. New technical design features, such as the absence of pigtail, helps minimise the risk of thrombus formation, and the optical pressure sensor aids in easy pump placement and monitoring. Early experience with Impella 5.5 in patients shows promising outcomes. Future direction includes the design of the long-term bridge-to-recovery Impella heart pumps. ■

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Update from the National Cardiogenic Shock Initiative

Presented by William O'Neill, MD

Henry Ford Hospital, Detroit, MI, US

Dr O'Neill is the Medical Director of the Centre for Structural Heart Disease at Henry Ford Hospital, Detroit. He is an internationally recognised leader in interventional cardiology and structural heart disease, and a pioneer in research and new techniques to diagnose and treat heart disease. He has authored more than 300 peer-reviewed articles and was the founding member of the American Board of Internal Medicine interventional cardiology board.

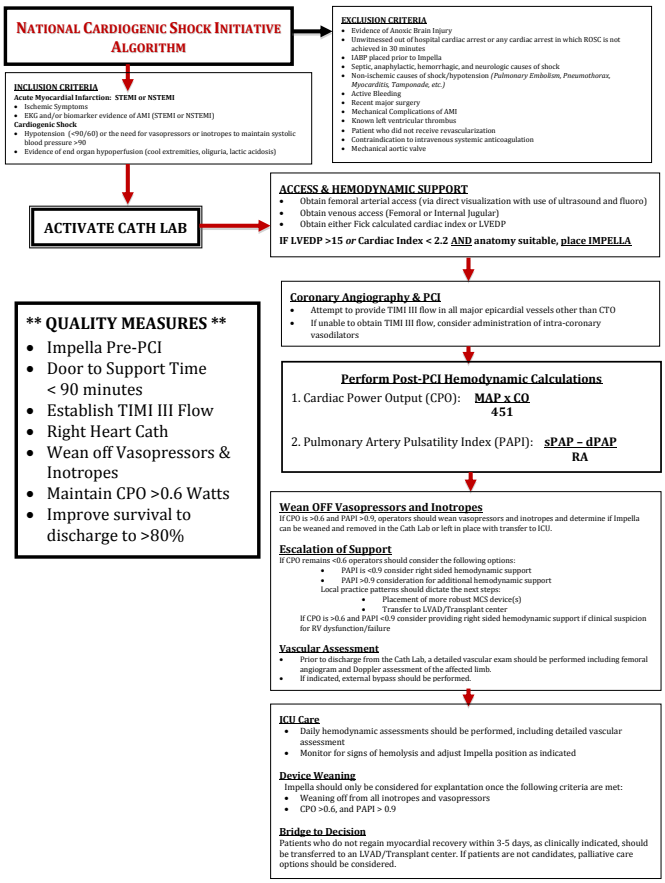
Dr O'Neill stated the causes of cardiogenic shock (CS) that ultimately influence patient outcomes. One of the main causes of significant variation in outcomes when comparing large retrospective registries of CS is the inclusion of patients with CS following an out-of-hospital cardiac arrest (OHCA). Typically, CS after OHCA is mostly due to arrhythmia rather than ischaemia, and these patients may also have neurological injury, leading to a worse prognosis. He emphasised that the National Cardiogenic Shock Initiative (NCSI) is a standardised protocol-based approach to treat CS due to acute MI (AMICS).

Dr O'Neill further highlighted that there are no Class Ia indicated therapy for AMICS in the European Society of Cardiology 2017 guidelines. Randomised controlled trials (RCTs) are challenging in AMICS, particularly in the US, given the need to obtain informed consent. A few RCTs have been conducted in Germany, where there is a system of prospective conditional approval. Therefore, in 2016, Dr O'Neill and colleagues designed a prospective registry to assess outcomes in patients with AMICS treated with Impella based on a standardised protocol. The protocol emphasises the early initiation of Impella support prior to reperfusion in patients with AMICS.

An analysis of data from more than 15,000 AMICS patients treated with Impella in the Abiomed Impella Quality (IQ) registry suggested a wide variation in survival outcomes across centres, based on the volume of Impella use.[1] Further analysis of the IQ registry identified three best practices associated with improved survival in AMICS: initiation of Impella support prior to percutaneous coronary intervention (PCI), haemodynamic monitoring using pulmonary artery catheter and the use of Impella CP. Dr O'Neill was excited about the increased adoption of these best practices over time, which was associated with a parallel increase in survival to Impella explantation from 51% in January 2009–December 2016 to 63% in April 2015–September 2018 (p<0.00001). The number of hospital sites in the registry that demonstrated a survival to explantation of >80% increased from 11% in January 2009–December 2016 to 19% in April 2015–September 2018.

The Detroit Cardiogenic Shock Initiative started in 2016 as a pilot study, with four Detroit sites agreeing to treat all patients with AMICS using a mutually agreed-upon, best-practice algorithm.[2] Of the 66 screened patients, 50 were included in the single-arm, prospective, multicentre study. The survival rate was 76%, compared with 53% in the Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock (SHOCK) trial and 53% in the IMPella versus IABP Reduces mortality in STEMI patients treated with primary PCI in Severe cardiogenic SHOCK (IMPRESS in Severe Shock) trial.[3,4]

Figure 1: National Cardiogenic Shock Initiative: Treatment Algorithm



AMI = acute MI; IABP = intra-aortic balloon pump; LVAD = left ventricular assist device; LVEDP = left ventricular end-diastolic pressure; MCS = mechanical circulatory support; NSTEMI = non-ST-elevation MI; PCI = percutaneous coronary intervention; ROSC = return of spontaneous circulation; STEMI = ST-elevation MI. Source: www.henryford.com/cardiogenicshock

The initiative has continued to grow. At present, more than 65 sites around the country are using the algorithm (*Figure 1*) and best practices, now referred to as the NCSI (NCT03677180).

As of 14 June 2019, a total of 423 patients had been screened for inclusion, of whom 214 were included in the initiative. A recent analysis of 171 patients included in the NCSI (lactate of 5.3 mmol/l and cardiac arrest in 42%) reported the survival rate of 72%.[5] This survival rate is higher compared to the SHOCK trial (53%) and Intraaortic Balloon Pump in Cardiogenic Shock (IABP-SHOCK) trial (60%).[3,6]

Dr O'Neill highlighted that the clinical sites in the NCSI are a combination of academic (38%) and community hospitals (62%). It is important to include community hospitals because 60% of CS patients present to a community hospital. He also emphasised the vital role of the 'hub and spoke' model to ensure prompt care for a wide range of patients.

The revascularisation strategy among patients enrolled in the NCSI was analysed. The survival among patients with one-, two- and three-vessel disease treated with a single vessel PCI was 71%, 72% and 75%, respectively. Interestingly, the survival was not significantly different among patients treated with a single-vessel or multivessel PCI, suggesting that the revascularisation strategy does not impact survival rates in this patient population. A potential reason for this effect could be a lower incidence of contrast-induced renal dysfunction in patients supported with Impella. In contrast, >70% of patients in the Culprit Lesion Only PCI Versus Multivessel PCI in Cardiogenic Shock (CULPRIT-SHOCK) trial did not receive haemodynamic support, which is the likely cause of the different outcomes.[7] In light of the above findings, Dr O'Neill suggested that the revascularisation strategy in patients with AMICS receiving haemodynamic support needs to be revisited.

Next, an attempt was made to identify important clinical and haemodynamic variables that aid in predicting outcomes post-PCI. Cardiac power output (CPO), cardiac output, cardiac index, pulmonary artery oxygen saturation, pulmonary artery pulsatility index, hepatic enzymes and lactate were found to be useful predictors of survival.[5]

Stratifying patients according to CPO (> or <0.6 W) and lactate (> or <4 mg/dl) at 12–24 hours post-PCI and Impella support provides a reliable and useful tool for predicting outcomes and the need for escalation of therapy. In addition, survival was lowest for patients with CPO ≤0.6 W and receiving ≥2 inotropes, while highest for patients with CPO ≥0.6 W and receiving 0–1 inotropes post-Impella and PCI.

In conclusion, the findings from the NCSI have demonstrated that a protocol-based approach emphasising best practices is reproducible in institutions across the country in both academic and community programmes and is associated with significant improvement in survival in AMICS compared to historical controls. Future studies will focus on identifying factors that will improve survival to >80% in AMICS. ■

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Peri-procedural Ventricular Unloading with Impella Optimises Outcomes in High-risk Patients at a Community Hospital

Presented by Jason Williams, MD

Ocean Springs Hospital, Ocean Springs, MS, US

Dr Williams is a cardiothoracic surgeon at Ocean Springs Hospital, Mississippi.

Dr Williams noted the limited available data on the use of Impella devices during cardiac surgery. RECOVER I was a prospective pilot study of Impella 5.0/left direct for postcardiotomy cardiogenic shock (PCCS).[1] The study demonstrated that safety and feasibility of the use of the Impella 5.0/left direct in PCCS with a favourable survival of 94% at 30 days. Immediately after the initiation of Impella support, cardiac index, mean arterial pressure and pulmonary artery diastolic pressure improved.

Lemaire et al. reported a single-centre study of 47 patients treated with Impella for cardiogenic shock (CS), including 32 patients with PCCS.[2] Survival at 30 days was 75% and 63.8% at 1 year. Of the 35 survivors, 88% had recovery of native heart and 11% were bridged to long-term ventricular assist devices.

Dr Williams highlighted study findings suggesting early initiation of Impella support prior to percutaneous coronary intervention was associated with improved survival. This led to the hypothesis that preoperative selection of high-risk patients for placement of Impella devices to haemodynamically optimise them before surgery and assist with recovery in the immediate postoperative period should allow faster recovery, reduced intensive care unit and hospitalisation days, improved end-organ function and reduced inotropic needs immediately postoperatively.

Dr Williams tested this hypothesis at his institution, which is a community healthcare system involving two hospitals, two catheterisation laboratories and four cardiac operation theatres. The cath lab Impella programme has been available since 2014, and the surgical Impella programme started in 2017. In the surgical programme, Impella support is used in three different subsets of patients: elective insertion of Impella preoperatively, haemodynamic optimisation group receiving Impella preoperatively (patients

presenting in CS receive Impella urgently to stabilise) and rescue insertion of Impella for PCCS.

The Impella device was used electively in patients based on frailty or surgeon gestalt, in addition to ejection fraction (EF) <20% and undergoing any procedure requiring cross-clamp, EF 20–30% undergoing off-pump coronary artery bypass grafting (CABG) or EF <25% undergoing major valve/CABG/double-valve procedures. Patients in the haemodynamic optimisation group receive Impella preoperatively to reverse end-organ damage, assist with diuresis and unload the ventricle while recovering from an acute event. Typical patients include those with acute MI and decompensation in need of urgent CABG and decompensated chronic heart failure with EF <25% requiring valve surgery. Impella use for PCCS was defined as ≥2 escalating doses of inotropes, inability to wean from cardiopulmonary bypass and failure to improve with an intra-aortic balloon pump.

A total of 149 patients received Impella devices at their institution. Of these, 35 patients underwent definitive surgical intervention following the initiation of Impella support; 23 patients received Impella electively, while 12 received Impella urgently. Patients receiving elective Impella support had a lower EF (19% ± 5%) compared to those receiving urgent Impella support (39% ± 17%). About 25% of patients in the elective group received high-dose inotropes, compared to 0% in the urgent group. The overall 30-day mortality was 9%, with no difference between the elective versus urgent Impella groups. The postoperative mortality was higher among patients with end-organ dysfunction, such as kidney or liver failure. There was a trend towards higher utilisation of blood products in patients receiving Impella CP versus Impella 5.0.

In conclusion, the results suggest that high-risk cardiac surgery with Impella support is safe, feasible and effective in the community hospital setting. Also, preoperative identification of high-risk patients who may benefit from left ventricular unloading with Impella is possible. Additional data might permit the development of a selection algorithm that would be broadly applicable to optimise outcomes in patients undergoing high-risk cardiac surgery. ■

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Longitudinal Impact of Temporary Mechanical Circulatory Support on Durable Ventricular Assist Device Outcomes: An IMACS Registry Analysis

Presented by Jaime A Hernandez-Montfort, MD

University of Texas Medical Branch, Galveston, TX, US

Dr Hernandez-Montfort is a cardiologist at University of Texas Medical Branch, Texas. His research interests include translational and clinical aspects of advanced heart disease, mechanical circulatory support and transitions to recovery.

Dr Hernandez-Montfort began by stating that acute heart failure (AHF) with cardiogenic shock (CS) remains a complex, heterogenous and time-sensitive disease entity that continues to challenge healthcare systems across the globe.[1,2] He drew attention to the fact that escalating doses of inotropes in AHF with CS are associated with exponential mortality.[3] He noted that contemporary care in AHF complicated with CS includes the use of temporary circulatory support (TCS) as a therapeutic bridge strategy that can potentially aid the transition to replacement therapies, such as durable ventricular assist devices (dVAD).[2]

There are limited data characterising longitudinal transitions for patients with AHF and CS receiving TCS prior to dVAD, despite its increased utilisation.[4,5] Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) patient profiles 1–3 are commonly utilised, although they also have shown to be heterogeneous descriptors of severity of illness prior to dVAD.[6] Hence, it is unclear whether a preimplant TCS strategy affects short- and long-term survival after dVAD. Also, specific TCS device/phenotype associated with recovery, replacement or palliation are yet to be characterised.

The aim of Dr Hernandez-Montfort's study was to describe the global epidemiology of patients receiving TCS (defined as preoperative use of extracorporeal membrane oxygenation [ECMO], intra-aortic balloon pump [IABP] and other TCS, including Centrimag, Impella and Tandem Heart) before durable left ventricular assist device (LVAD) implantation. In addition, to examine the short- and long-term survival of patients receiving TCS patients versus those not receiving TCS.

A total of 16,754 adult patients were implanted with dVAD in the International Society for Heart and Lung Transplantation Registry for Mechanically Assisted Circulatory Support (January 2013–November 2017). Of these, 13,813 patients had INTERMACS patient profile 1–3 and received a continuous flow LVAD (CF-LVAD) or biventricular assist device (BiVAD). A total of 5,632 patients received preoperative TCS before receiving CF-LVADs or BiVADs, while 7,879 belonged to the non-TCS group. The TCS support was classified as ECMO (1,138), IABP (3,901) and other TCS (593).

ECMO was used as TCS prior to dVAD mainly in Europe (17%), followed by Asia-Pacific (9%) and the Americas (8%). IABP was used mostly in the Americas (31%), followed by Asia-Pacific (26%) and Europe

(11%). Other TCS was used mostly in Asia-Pacific (13%), with similar utilisation in the Americas and Europe (4% each). The majority of patients receiving ECMO (77.6%) had INTERMACS profile 1. However, only 20.5% were bridged to transplant. All patients who received TCS had signs of right and left heart loading conditions and myocardial impairment, whereas patients on ECMO had elevated bilirubin levels, indicating liver congestion. Also, patients on ECMO were likely to receive BiVAD (22.1%), centrifugal pump (49.1%) and concomitant surgery (77.1%). The length of intensive care unit (ICU) stay (24 days) and implant-to-discharge duration (40 days) was longer with ECMO than IABP or other TCS support.

Importantly, patients receiving TCS support had lower survival than those not receiving TCS support at 2 years. Also, patients on ECMO had lower survival compared to patients treated with IABP or other TCS support. Multivariable analysis identified ECMO (versus other TCS) to be associated with increased risk of early death (HR 2.03, p<0.0001). Also, surrogates of kidney and liver function (such as creatinine and bilirubin) and right heart load (central venous pressure) were associated with early death. Similar results were obtained in the propensity-matched cohort of ECMO versus other TCS, ECMO versus IABP and ECMO versus non-TCS.

In summary, there are regional differences in pre-implant TCS, with ECMO being more commonly used in Europe than other regions. Patients requiring pre-implant TCS had lower longitudinal survival compared to patients without TCS.

Patients with pre-implant ECMO were less likely to receive dVAD as bridge to transplant and more likely to receive BiVAD. Patients on pre-implant ECMO had the highest median ICU length of stay and the lowest median time on dVAD. Further research in patients with INTERMACS profile 1–3 transitioning to dVAD is needed to better understand the differences in survival with ECMO versus other TCS. ■

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How to Unload the Heart on Extracorporeal Membrane Oxygenation

Presented by Bart Meyns, MD

Katholieke Universiteit, Leuven, Belgium

Dr Meyns is a professor and the Chief of Cardiac Surgery at Katholieke Universiteit, Leuven, Belgium. His research interests include clinical applications of mechanical support systems, congenital heart surgery and coronary surgery. He is a member of the Board of Governors for the International Society for Rotary Blood Pumps and European Society of Artificial Organs, and a member of many international societies.

Dr Meyns stated his intention to make a case for unloading in patients receiving extracorporeal membrane oxygenation (ECMO). He emphasised the increasing utilisation of ECMO in the treatment of acute cardiogenic shock (CS) due to technical ease of implantation at the bedside, transportability, oxygenation, immediate restoration of haemodynamics and the use as a bridge to decision. The survival to discharge of patients on ECMO varies from 41% for CS to 29% for extended cardiopulmonary resuscitation.[1]

He highlighted that incremental improvements in oxygenators, pumps, cannulas and management strategies have significantly reduced the incidence of adverse events with ECMO. Notwithstanding, major adverse events include bleeding and increased left ventricular (LV) afterload leading to LV distension of an already failing heart.

Unloading during ECMO helps avoid pulmonary congestion, improves myocardial recovery and reduces the risk of thrombus formation.[2] There are multiple strategies for unloading the failing LV during veno-arterial ECMO support, such as apical/pulmonary/transaortic drainage catheter, Impella and reducing ECMO flow. He presented multiple cases of patients unloaded with the strategies mentioned above, particularly with Impella.

Dr Meyns shared the management algorithm for acute CS at his institution. The Impella is the preferred LV unloading device before revascularisation in patients presenting with CS, defined as aortic blood pressure <90 mmHg for >30 minutes with plasma lactate > 2 mmol/l. Following revascularisation, if the cardiac index <2.5, then the escalation of therapy is considered. In patients requiring CPR or presenting with predominant right ventricular failure, ECMO is the preferred device for unloading followed by unloading with Impella, if needed.

In 2018, 31 patients with CS were treated at his institution using the management strategy mentioned above. Of these, 17 were treated with Impella alone and 14 with ECMO plus Impella. The Impella CP was implanted in 15 and Impella 5.0 in 16 patients. In the ECMO plus Impella group, nine patients died, two were bridged to left ventricular assist device (LVAD) and three had recovery. In the Impella alone group, three patients died, five were bridged to LVAD and nine had

myocardial recovery. The overall survival was 61%, which is better than historical controls. The mean duration of Impella support was 8.5 days with a maximum of 38 days, which is higher than the typical ECMO support. He further highlighted the advantage of axillary access for Impella 5.0, including long-term support with the ability to mobilise the patient. ■

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ST-elevation MI Door-To-Unload Pivotal Trial: Acute Cardiac Unloading and Myocardial Recovery

Presented by Navin K Kapur, MD

Tufts Medical Center, Boston, MA, US

In the concluding talk, Dr Kapur provided the rationale and discussed the trial design of the ST-elevation MI Door-To-Unload (STEMI-DTU) pivotal trial. He stated a few facts from the American Heart Association about MI and its prognosis. Nearly every 40 seconds, an American will have an MI, and the estimated annual incidence of new MI is 605,000.[1] The estimated average number of years of life lost because of an MI death is 16.2. Approximately 35% of people who experience a coronary event in a given year will die as a result of it, and about 14% who experience an MI will die. He highlighted that the Swedish Web-system for Enhancement and Development of Evidence-Based Care in Heart Disease (SWEDEHEART) study shows that heart failure (HF) after MI increases mortality, and this is one of the reasons why the STEMI-DTU trial is needed.[2,3] Studies have also shown that the size of the infarcts matter. For every 5% increase in myocardial infarct size, 1-year all-cause mortality increases by 19% and HF hospitalisation by 20%.[4]

He discussed the paradox of reperfusion therapy in MI by highlighting that reperfusion therapy to limit myocardial damage in STEMI may itself promote myocardial damage. A fundamental component of the paradox is the mandate for rapid reperfusion in STEMI.[5,6] Data suggest that every 30-minute increase in ischaemic time is associated with increased 1-year mortality and infarct size. This raises the question of whether the ischaemic time increases in the STEMI-DTU trial due to delayed reperfusion in the Impella arm. Studies have suggested that during ischaemia without reperfusion, 100% of the area at risk (AAR) is infarcted.[7] On the other hand, only 50% of the AAR is infarcted with ischaemia with timely reperfusion, and ischaemia with timely reperfusion with cardioprotection may reduce the infarct size to 25% of the AAR.[7,8]

Dr Kapur noted that the current approaches of management in STEMI have focused on reducing reperfusion injury, not ischaemic injury.[9] He highlighted that left ventricle (LV) unloading with Impella uncouples ischaemia and reperfusion, thus reducing the fear of delaying reperfusion.[10] He showcased the pre-clinical development of primary unloading from 2012 to 2019, which demonstrated that transvalvular LV unloading limits myocardial ischaemia and promotes a cardioprotective shift in myocardial biology.

Dr Kapur emphasised that in STEMI-DTU, delayed reperfusion is not equal to delayed treatment. He hypothesised that unloading the LV prior to reperfusion limits the potential ischaemic damage, thus the point of inhiation of haemodynamic support may be considered the onset of treatment. To test this hypothesis, adult male pigs subjected to left anterior descending artery (LAD) occlusion for 90 minutes were divided into two groups. In the no unloading group, LAD was occluded for an additional 120 minutes without reperfusion. In the unloading group, LAD was occluded for an additional 120 minutes with unloading using Impella and no reperfusion. The infarct size was 10% of the AAR in the no unloading group without reperfusion compared to 2–3% of the AAR in the unloaded group without reperfusion. Interestingly, the infarct size in the no unloading group increased from 10% to 30% of the AAR following reperfusion. Likewise, the infarct size also increased in the unloaded group from <3% to 18% of the AAR after reperfusion, but was significantly less than the no unloading group. These results suggest two important things. First, ischaemia-dependent damage is independent of reperfusion-dependent damage, and second, that unloading with Impella prior to reperfusion may differentially limit both.

The STEMI-DTU pilot trial assessing the feasibility and safety of primary LV unloading and delaying reperfusion was conducted before attempting a randomised control trial evaluating the efficacy of this approach.[11] In the STEMI-DTU pilot trial, 50 patients presenting with anterior STEMI at 14 centres in the US were randomised to mechanical unloading with the Impella CP, followed by immediate reperfusion (U-IR) or LV unloading with a 30-minute delay to reperfusion (U-DR). The majority of the patients enrolled in the pilot trial had large anterior MI with high left ventricular end-diastolic pressure (LVEDP). Notably, no patient in the trial experienced no reflow after the percutaneous coronary intervention (PCI) compared to the expected rate of 25%. The successful STEMI-DTU pilot trial established safety, feasibility and compliance with no bailout PCI in the U-DR arm. A subgroup analysis of infarct size normalised to the myocardial AAR was performed in patients stratified by sum ST-segment elevation. A stepwise increase in infarct size normalised to the AAR was observed in the U-IR group compared with no such effect in the U-DR group. This result suggests that unloading and reperfusion limits infarct size, irrespective of the AAR by sum ST-segment elevation.

He further outlined the current trial design of the upcoming STEMI-DTU pivotal trial. When a patient with anterior STEMI presents to a DTU site, an iliac and femoral angiogram, LV-gram and LVEDP measurement are

performed. The patients are then randomised to either the DTU arm (LV unloading with Impella CP, followed by reperfusion using PCI) or the door-to-balloon (DTB) arm (reperfusion as per current standard of care). In the DTU arm, Impella CP support is initiated first, followed by PCI. The patient will be supported with Impella CP for 4–6 hours post-PCI, and the subject will be taken to the catheterisation lab for Impella explant. In the DTB arm, patients will receive PCI after a coronary angiogram. The primary endpoint of the trial is infarct size as a percentage of LV mass at 3–5 days.

Secondary endpoints include clinical safety evaluation at 30 days, 6, 12, 18 and 24 months. The subjects will be followed up yearly until 60 months.

In conclusion, Dr Kapur emphasised that there is no delay to treatment in the STEMI-DTU trial. The biggest difference is that the treatment in STEMI-DTU begins with LV unloading with the ultimate goal to prevent HF after an acute MI by limiting infarct size and aid the process of myocardial recovery. ■

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Acute Cardiac Unloading and Recovery

Proceedings of the 5th Annual Acute Cardiac Unloading and REcovery (A-CURE) symposium held on 14 December 2020

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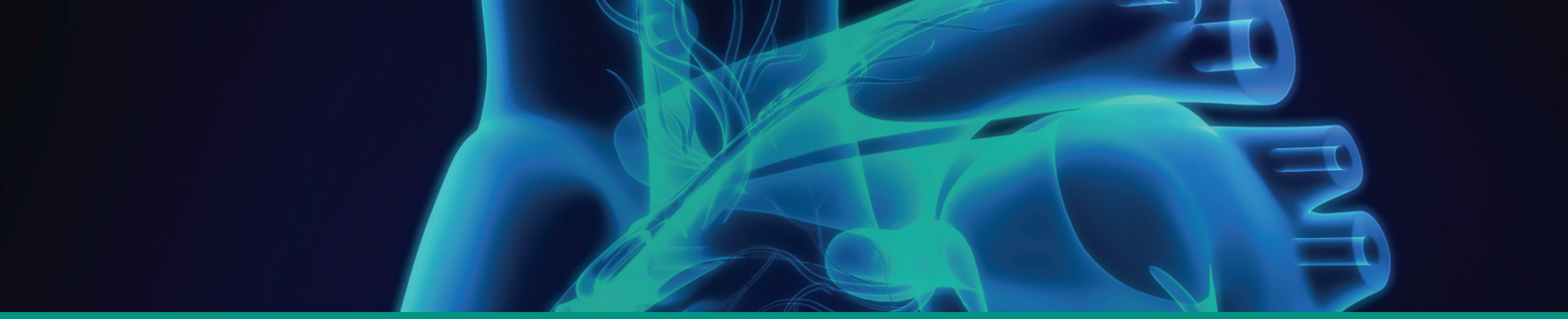
Established in 2015, (in part due to the generous funding of our sponsor: Abiomed Inc.) the faculty of the A-CURE® Working Group meets annually to initiate scientific and clinical discussions on how acute cardiac unloading may increase myocardial salvage, prevent (or limit) myocardial and ventricular injury and remodeling, improve survival, and attenuate the development of heart failure after myocardial infarction. Many of the current A-CURE faculty members have been participants since the inception of the working group.



Foreword

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Welcome to this special supplement devoted to the proceedings of the 5th Annual Acute Cardiac Unloading and REcovery (A-CURE) Working Group meeting on 14 December 2020. The A-CURE Working Group comprises leading academic experts in clinical and basic cardiac research who are dedicated to advancing the science and clinical application of acute cardiac unloading. This meeting brought together experts from multiple disciplines, including interventional cardiologists, heart failure specialists, cardiac surgeons, molecular biologists and biomedical engineers.

The 2020 symposium featured talks and abstract presentations that highlighted cutting-edge advances in the field of acute cardiac unloading that have taken place since the 2019 A-CURE symposium in Paris, France. Due to coronavirus disease 2019 and the associated travel restrictions, this year's symposium was held remotely, and all content can be accessed at https://a-cure.org.

Cardiac disease states, such as MI, myocarditis, cardiomyopathy and cardiogenic shock, impair the ability of the heart to pump blood, resulting in end-organ failure and, ultimately, death. Pharmacological therapies administered to maintain or increase cardiac output and/or blood pressure in these cases impose further stress on the heart; therefore, additional treatment strategies are needed.

The 2020 A-CURE symposium focused on the basic science and clinical applications of ventricular unloading using mechanical circulatory support technologies. Acute cardiac unloading decreases myocardial oxygen consumption and maximises the ability of the heart to rest and recover after damage. Mechanical unloading can be achieved using percutaneous ventricular assist devices, such as the Food and Drug Administration-approved Impella family of devices, to decrease the physical workload of the heart.

This supplement features presentations from the 2020 A-CURE virtual symposium covering a broad range of subjects related to cardiac unloading. Dr Dan Burkhoff's state-of-the-field address highlighted left ventricular (LV) unloading as an enabler for other kinds of therapies. Herman Reichenspurner demonstrated the viability of Impella LV unloading as a bridge to decision treatment from extracorporeal membrane oxygenation (ECMO). Impella support enhanced survival, decreased bleeding complications and improved neurological recovery time in this multicentre feasibility study of LV assist device (LVAD) after ECMO. Dr Bob Kloner presented preclinical and clinical data demonstrating that therapeutic hypothermia after ischaemia onset (with a target temperature of <35°C prior to reperfusion) decreases infarct size and microvascular obstruction and improves vascular recovery. Dr Kiyo Ishikawa concluded Dr Kloner's presentation with a research proposal to investigate LV unloading in combination with therapeutic hypothermia to limit reperfusion injury.

Drs William O'Neill and Mark Anderson presented outcomes from clinical studies investigating the effect of Impella unloading prior to reperfusion in cardiogenic shock and cardiorenal patients. The National Cardiogenic Shock Initiative (NCSI) protocol for the treatment of acute MI complicated by cardiogenic shock includes early initiation of Impella support prior to reperfusion, and improves native heart recovery. Survival rates among shock patients treated with the NCSI protocol are the highest reported in any modern cardiogenic shock trial or registry conducted in the US or Europe. Data presented by Dr O'Neill demonstrated that use of the NCSI protocol improved patient outcomes through aggressive down-titration of inotropes, identification of inadequate LV support and appropriate escalation, identification and support of right ventricular dysfunction, and the systematic use of right heart catheterisation to guide therapy. A retrospective chart review by Dr Anderson indicated that Impella support safely improves cardiac and renal function and prevents progressive renal deterioration in acute heart failure patients with cardiorenal syndrome who are refractory to diuretics and inotropes. Additionally, Dr Elric Zweck introduced three distinct phenotypes of cardiogenic shock that may enable the conception of more targeted clinical trials instead of a one-size-fits-all solution.

Dr Navin Kapur presented new data from a preclinical acute MI model showing that Impella unloading prior to reperfusion decreased infarct size and preserved mitochondrial structure and function in the myocardium, while venoarterial ECMO did not. Zach George presented a patient case from the currently enrolling STEMI-Door-to-Unload pivotal trial as an example of trial enrolment, MI resolution immediately after unloading, single-access technique and post-closure technique.

Two panel discussions highlighted the collaborative approach necessary to improve clinical utilisation of cardiac unloading. The ongoing collaboration between Massachusetts Institute of Technology and Abiomed aims to elucidate the impact of Abiomed's Impella transvalvular mechanical support pump on cardiac function, as well as the impact of end-organ function on the behaviour of Impella. Initiating the collaboration with a shared goal of improving patient outcomes has been fundamental to building a strong, productive relationship. A panel of paediatric cardiologists recommended a multidisciplinary approach to assessing cardiogenic shock to ensure selection of the least invasive and most effective surgical techniques and LV unloading method. Continued collaboration between physicians and industry partners will drive development of paediatric-specific mechanical unloading devices.

This year's A-CURE symposium also featured a fellowship opportunity for young investigators. Three 1-year research grants of US$20,000–US$25,000 each were awarded to the top three submitted abstracts, as judged by the A-CURE faculty. Topics included basic research and clinical investigations addressing left and right heart failure, cardiogenic shock and potential mechanisms for therapeutic intervention. A blinded panel of A-CURE faculty members selected the top six abstracts to be virtually presented by the investigators. After live presentations to the faculty, Drs Lija Swain, Kay Everett and Renata Mazurek were awarded research grants for their abstracts investigating LV unloading for protection against both ischaemic and reperfusion injury, acute haemodynamic effects of LV unloading prior to ECMO and the negative impact of subsequent acute reloading, respectively.

The presentations at this year's virtual A-CURE symposium highlighted exciting new developments and substantial advances in the field of acute myocardial unloading and recovery. The A-CURE Working Group meeting continues to bring together a unique and diverse group of experts from multiple disciplines in an open, collegial and constructive setting to build knowledge and drive clinical advances in the field of acute cardiac unloading.

We hope you find this supplement informative and interesting. ❑

The State of the Field: Our Current Understanding of Ventricular Unloading

Presented by Daniel Burkhoff, MD, PhD

Cardiovascular Research Foundation and Columbia University, New York, NY, US

Dr Burkhoff is the Director of Heart Failure, Haemodynamics and Mechanical Circulatory Support at the Cardiovascular Research Foundation. He has authored more than 380 peer-reviewed publications and is a world expert in heart failure, haemodynamics and heart muscle mechanics. Dr Burkhoff is a founding member of the Acute Cardiac Unloading and REcovery Working Group.

Dr Burkhoff opened the meeting by providing an overview of the Acute Cardiac Unloading and REcovery (A-CURE) symposium. The mission of the A-CURE group is to advance the science and mechanistic understanding of acute cardiac unloading and support, and the translation of basic and clinical research into therapies aimed at heart muscle recovery. He noted that the A-CURE symposium is the only scientific conference dedicated entirely to acute unloading and heart recovery.

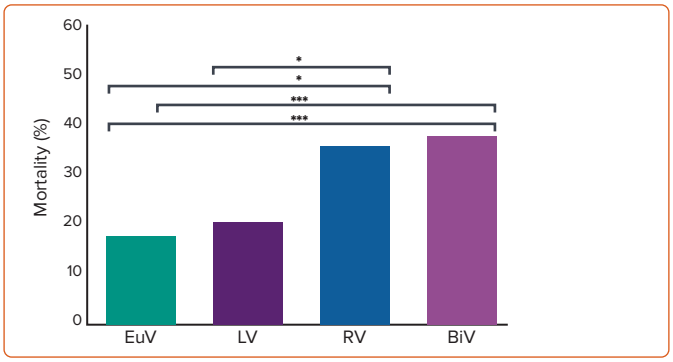
He described the history of the A-CURE symposium, which began in 2015 with a group of interested investigators in Paris, France. The first annual symposium occurred in 2016 in Rome, Italy, with Dr Eugene Braunwald as the keynote speaker. The commencement of the ST-elevation MI Door-to-Unload (STEMI-DTU) pilot trial was announced in 2017 at the second A-CURE symposium held in Barcelona, Spain, with Dr Valentin Fuster as the keynote speaker. Results of the STEMI-DTU trial were released as a late-breaking abstract at the American Heart Association annual meeting in 2018. The third A-CURE symposium was held in Chicago, Illinois in 2018, with Dr James Udelson as the keynote speaker. The commencement of the STEMI-DTU pivotal trial and PROTECT kidney trial was announced in 2019 at the 4th symposium held in Paris, France, with Dr Douglas Mann as the keynote speaker. This year's symposium was virtual due to coronavirus disease 2019 (COVID-19) and the associated travel restrictions, and featured a competition for three US$20,000–US$25,000 research grants awarded to the best submitted abstracts, as judged by the A-CURE faculty. In addition, as a response to the global COVID-19 pandemic, Dr Burkhoff announced that A-CURE has developed cardiac-specific educational resources relevant to COVID-19, which are available on the website.

Dr Burkhoff defined ventricular unloading as the reduction of total mechanical power expenditure of the ventricle, which correlates with reductions in myocardial oxygen consumption and the haemodynamic forces that lead to ventricular remodeling.

This year's symposium focused on cardiac unloading can act as an enabler for other kinds of therapies. Specifically, unloading the heart and assuming its role to support the circulation provides haemodynamic stability, and may enable the application of additional therapies aimed at further protecting the heart or other end-organs. which may otherwise not be possible.

Dr Burkhoff provided examples of such potential future therapies. He described how an implanted unloading device, such as Impella, can provide the cardiac output necessary to support adequate perfusion of end-organs. In the case of acute MI (AMI) complicated by cardiogenic shock, high-dose beta-blockers or ivabradine can be used to slow heart rate and further spare myocardial energetics beyond what may be achievable by unloading alone. The presence of haemodynamic support would minimise the risk for haemodynamic collapse that may result from the use of such drugs during AMI. Similarly, haemodynamic support could be deployed in the setting of therapeutic hypothermia, enabling more rapid cooling of a patient while simultaneously minimising the risk of hypothermia-dependent arrythmia and haemodynamic collapse. In addition, unloading the heart and enhancing end-organ perfusion may be a means of treating cardiorenal syndrome and diuretic resistance in acute decompensated heart failure. Finally, long-term unloading support may also promote reverse remodelling and enhance recovery in patients who otherwise may receive permanent left ventricular assist devices or a heart transplant.

Figure 1: Congestion Profiles as Indicators of Mortality and Cardiogenic Shock Severity



**p<0.05; ***p<0.001. BiV = biventricular; EuV = euvolemic; LV = left ventricular; RV = right ventricular.*

Another goal of this symposium is to advance the current understanding of the role of right ventricular unloading in various clinical settings. Consistent with prior studies, mortality increases markedly in cardiogenic shock patients once central venous pressure or right atrial pressure increases, whether in isolation or in combination with elevations to pulmonary capillary wedge pressure (*Figure 1*).[2] Dr Burkhoff stated that such correlations are also true in patients presenting with acute MI shock and those with acute decompensated heart failure-related shock. Prior A-CURE symposia primarily focused on left ventricular unloading, but a large part of future efforts is to better understand the indications, timing and role of right ventricular support in such patients.

Dr Burkhoff concluded by encouraging virtual attendance at this year's nine symposium talks and six additional talks selected from the submitted abstracts, as well as in-person attendance at the 6th Annual A-CURE symposium next year. ❑

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A Successful Industry Academic Collaboration: A Panel Discussion

Moderated by Jerry Curran, PhD[1]

Presented by Elazer Edelman, MD, PhD,[2,3] Steven Keller, MD, PhD,[3] Christian Moyer, PhD,[1] Ahmad El Katerji, PhD[1] and Noam Josephy, MD[1]

1. Abiomed, Danvers, MA, US; 2. Massachusetts Institute of Technology, Boston, MA, US; 3. Brigham and Women's Hospital, Boston, MA, US

Dr Elazer Edelman is Professor in Medical Engineering and Science at Massachusetts Institute of Technology and Professor of Medicine at Harvard Medical School and Brigham and Women's Hospital. Dr Steven Keller is Medical Director of ECMO at Brigham and Women's Hospital and an Instructor of Medicine at Harvard Medical School. Dr Jerry Curran, Dr Christian Moyer, Dr Ahmad El Katerji and Dr Noam Josephy are employees of Abiomed.

The ongoing collaboration between Massachusetts Institute of Technology (MIT) and Abiomed aims to elucidate the bidirectional impact of Abiomed's Impella transvalvular mechanical support pump on cardiac function, as well as the impact of end-organ function on the behaviour of Impella. Dr Edelman described a linear format of patient care prior to the collaboration, in which physicians provided mechanical support without any detailed feedback on performance. Impella is a combined sensor and pump, providing left ventricular (LV) mechanical unloading while simultaneously querying patient state. This bidirectional feedback enables titration of support to optimise care in cardiogenic shock patients, in contrast to the intermittent monitoring approach provided by the current standard of care.

Collaboration between MIT and Abiomed began in 2015 to further understand how the Impella device impacts cardiovascular physiology and how end-organ function impacts device performance *in vivo*. Dr Josephy spurred Abiomed engineers to include haemodynamic information on the device display after recognising similarities in appearance between an LV pressure tracing and Impella's motor current signal. Abiomed and MIT then formulated a goal to enable Impella to provide both haemodynamic support and meaningful patient-specific physiological information to the team managing the patient. This academic-industry partnership set out to fill the information void that often exists between devices and patients.

Early studies by Dr Edelman identified LV end-diastolic pressure (LVEDP) as a key cardiac marker of the interaction between patient physiology and Impella device function. Research teams lead by Dr El Katerji and Dr Keller subsequently developed algorithms for Impella to calculate cardiac output and measures of vascular impedance. Cardiac output is determined by novel calculations not used on any device approved by the Food and Drug Administration (FDA). Abiomed is currently working with the FDA to establish the first regulatory submission of this sensor type. Patient-specific measures of cardiac output and LVEDP make the Impella attractive for clinical studies, and device commercialisation efforts are currently underway.

Identifying a common goal of improving patient outcomes is key to the success of this industry and academic collaboration. Starting the collaboration with a shared goal in mind was fundamental to building a strong, trusting relationship. Weekly meetings between Abiomed and MIT

ensured open communication, keeping the group informed and efficient. The framework for all animal testing and clinical testing must be agreed upon by the group. Honest bidirectional feedback and criticism help to stress test concepts and produce the best ideas. The FDA is considered a third partner in this team, providing key insight on how to propel mechanical support devices into the clinic.

Impella's unique position within the patient's circulation, specifically within the heart, provides local, regional and systemic circulatory feedback. Future directions include the use of non-intuitive advanced metrics to assist support timing and elucidating mechanical support device-to-device interactions, such as Impella with extracorporeal membrane oxygenation.

Industry and academic collaboration are the hallmarks of great medical interventions, including antibiotics, genomics and medical devices. The amalgamation of academic ideas and industrial engineering enables innovation from bench to bedside. ❑

Unloading in a Paediatric Population: A Panel Discussion

Moderated by Vivian Dimas, MD[1]

Presented by Sebastian Tume, MD,[2,3] Iki Adachi, MD,[2] Brian Morray, MD,[4] Athar Qureshi, MD,[2,3] Christina J VanderPluym, MD[5] and Ryan Davies, MD[6]

1. Medical City Children's Hospital/Medical City Heart and Spine Hospital, Dallas, TX, US; 2. Baylor College of Medicine, Houston, TX, US; 3. Texas Children's Hospital, Houston, TX, US; 4. University of Washington School of Medicine Seattle, WA, US; 5. Harvard Medical School, Boston, MA, US; 6. UT Southwestern Dallas, TX, US

Dr Vivian Dimas is Medical Director of the Adult Congenital Heart Disease Program at Medical City Dallas in the Heart and Spine Hospital. Panel attendees included Dr Sebastian Tume, Assistant Professor of Pediatric Critical Care at Baylor College of Medicine and Director of Cardiac ICU at Texas Children's Hospital; Dr Iki Adachi, Associate Professor of Congenital Heart Surgery at Baylor College of Medicine and Co-Director of the Mechanical Circulatory Support Program at Texas Children's Hospital; Dr Brian Morray, Pediatric Interventional Cardiologist and Associate Professor of Pediatrics at the University of Washington School of Medicine at Seattle Children's Hospital; Dr Athar Qureshi, Professor of Pediatrics at Baylor College of Medicine and Medical Director of the Catheter Lab at Texas Children's Hospital; Dr Christina J Vanderpluym, Co-director of the Stroke and Cerebral Vascular Center and Medical Director of Cardiac Antithrombosis Management and Monitoring Program at Boston Children's Hospital, as well as Assistant Professor of Pediatrics at Harvard Medical School; and Dr Ryan Davies, Associate Professor of Cardiovascular Thoracic Surgery at UT Southwestern and Surgical Director for Heart Transplantation and Mechanical Circulatory Support at Children's Hospital Dallas.

The aetiology of paediatric acute cardiogenic shock (CS) varies more than that in adults, and may include coronary artery disease, myocarditis, congenital heart disease, cardiomyopathy, diastolic heart failure and systolic heart failure. Unlike in adults, ischaemic coronary artery disease is not a common CS aetiology in children. Paediatric CS patients often possess a single ventricle, or have undergone a Fontan procedure or biventricular repair. Treatment options are limited by smaller patient size, reduced ventricular dimensions and lack of mechanical support devices approved for use in children. Percutaneous circulatory support options, such as balloon pumps, may enable haemodynamic support for adults, but are often more harmful in children.

Left ventricular (LV) unloading is necessary to decrease ventricular size and pressure in paediatric CS patients. The standard LV unloading approach at many centres is static balloon atrial dilation of the septum, balloon atrial septostomy, stenting the atrial septum or left atrial venting with extracorporeal membrane oxygenation (ECMO) support. ECMO is often used due to ease of access and rapid oxygenation of the blood; however, lack of optimal coronary reperfusion compromises long-term patient recovery. After ECMO placement, immediate echocardiogram imaging to assess canula position and ventricular ejection status can help determine whether additional LV unloading is required.

The panellists recommend additional haemodynamic support modalities, such as the Impella transvalvular pump, to achieve LV unloading. The panellists discussed specific patients, in which the Impella 5.5, used in combination with ECMO, improved recovery in ischaemic CS patients by decreasing LV end-diastolic pressure. The Impella device provides greater ease of placement, acute decompression and a bridge to weaning the patient off ECMO, reducing ECMO-associated morbidity. Discussion also focused on the utilisation of LV unloading, followed by right ventricular support prior to resorting to ECMO in paediatric CS patients. Dr Adachi and Dr Morray further discussed using Impella-mediated LV unloading for single-ventricle paediatric CS patients with failed Fontan circulation, as it decreases central venous pressure, improves cardiac output and increases survival.

A multidisciplinary approach to assess paediatric CS patients ensures selection of the least invasive and most effective surgical techniques and LV unloading method. Determination of CS aetiology by monitoring the (lack of) response to therapies, biventricular dysfunction, chronicity of heart failure and lactate levels can assist with appropriate device selection. Vascular access techniques, such as hybrid access and trans-cable access, together with reduced sheath and catheter size, can decrease surgical complications. Timing of placement and removal of mechanical support devices should be optimised. Physician collaboration with industry partners is critical to driving development of paediatric-specific mechanical unloading devices. ❑

A New Role for Circulatory Support Devices to Limit Ischaemia–Reperfusion Injury

Presented by Navin Kapur, MD, FACC, FSCAI, FAHA

The CardioVascular Center for Research and Innovation, Tufts Medical Center, Boston, MA, US

Dr Navin Kapur is an Associate Professor in the Department of Medicine and Executive Director of The CardioVascular Center for Research and Innovation at Tufts Medical Center.

Dr Kapur began his talk by describing the global burden of heart failure (HF), which affects over 23 million individuals worldwide. Acute decompensated HF is currently the leading cause of hospital admissions and rehospitalisation for persons over the age of 65 years in the US.[1,2] Approximately 1.8 million people are admitted for HF each year, with annual treatment and readmission costs of US$31 billion and US$7 billion, respectively.[3–6] Patients who have a heart attack are at high risk for developing HF, generating a major healthcare burden.

Rapid coronary reperfusion or opening a blocked artery after acute MI can reduce the risk of HF. However, the size of the infarct impacts the magnitude of potential benefit from reperfusion. Larger infarcts drive mortality and HF. Data from patients receiving primary reperfusion after a heart attack indicate that 18% of total left ventricular mass remains infarcted after reperfusion.[7] The same dataset also demonstrated that 1-year all-cause mortality and hospitalisation for HF increase by approximately 20% for every 5% increase in myocardial infarct size.

Time to treatment is also critical for ST-segment elevation MI (STEMI). Every minute of delay from symptoms of chest pain to the point that a coronary artery is opened with angioplasty counts towards mortality, as well as infarct size. Every 30-minute delay in total ischaemic time, or time from symptom onset to reperfusion, is associated with a 7.5% increase in 1-year mortality and a 30% increase in infarct size.[8,9]

Rapid reperfusion is one option to try to terminate ischaemic injury, yet may contribute to approximately 50% of myocardial damage in the setting of a heart attack.[10] As a result, a significant volume of research has been conducted to identify the molecular mechanism(s) of reperfusion injury. Activation of the reperfusion injury salvage kinase and survivor activating factor enhancement signalling pathways prevents reperfusion injury in cardiac muscle cells by protecting mitochondria.[11] Mitochondria provide energy to the cell, thus protection of mitochondria prevents energy loss and subsequent cell death. Ischaemia disrupts these pathways, reducing mitochondrial structural and functional integrity to produce reperfusion injury.[12] Clinical trials to identify cardioprotective pharmacological agents targeting the ischaemia–reperfusion injury cascade remain inconclusive.[13]

Dr Kapur's research hypothesis is that primary mechanical unloading could be a potential cardioprotective strategy to reduce ischaemia–reperfusion injury. In the past 15 years, his team demonstrated that mechanical devices, such as the Impella CP transvalvular pump, unload the heart, decreasing stress during a heart attack and reduce infarct size by approximately 50% in preclinical models.

Dr Kapur also demonstrated that 30 minutes of left ventricular (LV) unloading before reperfusion is necessary and sufficient to reduce infarct size.[14] In addition, a meta-analysis of preclinical studies from around the world over the past 40 years established that LV unloading reduces infarct size using a variety of different pump configurations.[15]

Reperfusion without unloading is the current MI standard of care. Dr Kapur's STEMI-Door-to-Unload (DTU) pilot clinical trial was designed to assess whether mechanical unloading for 30 minutes prior to reperfusion would increase or decrease infarct size.[16] Fifty anterior STEMI patients received an Impella CP device to assess device safety and feasibility during a heart attack. The patients were randomised to receive unloading with immediate reperfusion or unloading for 30 minutes prior to reperfusion. The results confirmed the safety, feasibility and technical performance of the Impella CP in STEMI patients, and demonstrated that unloading with delayed reperfusion by 30 minutes limits infarct size, irrespective of the MI area at risk.

Additional data from the STEMI-DTU pilot trial indicated that mechanical unloading reduces myocardial ischaemia prior to reperfusion. Increased exposure time to unloading prior to reperfusion time correlated with a decrease in infarct size in patients with large anterior MI.[16,17] These data correlate with anecdotal evidence of chest pain resolution and decreased ST-segment elevation after mechanical unloading. These encouraging data from the STEMI-DTU pilot trial enabled the initiation of Dr Kapur's currently enrolling STEMI-DTU pivotal randomised clinical trial to compare the impact of unloading and delayed reperfusion against reperfusion without unloading on infarct size in a larger patient population.

Dr Kapur's team is currently investigating the mechanism by which LV unloading improves blood flow, reduces ischaemic injury and protects cell function to promote heart recovery after infarction. Hypoxia, or lack of oxygen, characterises the ischaemic phase of a heart attack before reperfusion. Dr Kapur's team demonstrated that, LV unloading with Impella CP prior to reperfusion in a preclinical ischaemic model of coronary artery occlusion, improves myocardial oxygen delivery by decreasing levels of hypoxia-inducible factor-1 alpha.[17] Further data, pending publication, indicate that mechanical unloading reduces infarct size, both with and without subsequent reperfusion. Mitochondrial function is also improved with or without reperfusion, as indicated by retention of mitochondrial structural integrity, increased levels of critical complex I proteins, increased adenosine triphosphate production and stabilised calcium handling.[17] LV unloading also increases microcirculatory collateral flow and reduces the area at risk in acute MI models pre-reperfusion.[18]

Interestingly, the protective effects of mechanical unloading against ischaemia–reperfusion injury differ according to pump type. Comparison of the Impella CP transvalvular pump to the venoarterial (VA)-

extracorporeal membrane oxygenation (ECMO) pump demonstrated that use of ECMO was associated with increased infarct size and did not provide mitochondrial structural protection prior to reperfusion.[17] This suggests that transvalvular unloading with Impella protects mitochondrial function in acute MI, whereas VA-ECMO does not. Unpublished data from Dr Kapur's laboratory, in collaboration with Dr Divaka Perrara, also suggest that VA-ECMO decreases coronary blood flow and increases myocardial oxygen consumption, resulting in increased infarct size, vascular pressure, vascular injury and poor myocardial recovery.

Dr Kapur's laboratory will continue to advance the field of mechanical circulatory support and LV unloading as a vital approach to prevent ischaemia–reperfusion injury. At the forefront of these efforts is the STEMI-DTU pivotal trial, a landmark study to further understand the benefits of transvalvular unloading in patients with acute MI. ❑

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A New Strategy for the Treatment of Patients with Type 1 Cardiorenal Syndrome with Impella

Presented by Mark Anderson, MD, MHA, FACS

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Dr Mark Anderson is Chief of the Department of Cardiac Surgery at the Hackensack University Medical Center and Professor of Surgery at the Hackensack Meridian School of Medicine.

Dr Anderson began his talk by defining cardiorenal syndrome (CRS) as a pathophysiological disorder of the heart and kidney, whereby acute or chronic dysfunction of one organ may induce acute or chronic dysfunction in the other. The focus of his study was CRS-1, cardiorenal syndrome characterised by rapid worsening of cardiac function, such as acute decompensation of heart failure, leading to acute renal injury.[1] A feedback loop of neurohormonal and molecular signalling ensues between the kidney and heart, further promoting organ damage. The rate of decline in renal function predicts mortality in these patients, even after adjusting for baseline kidney function. The current standard of care for acute decompensated heart failure (ADHF) is a loop diuretic. If the loop diuretic is not effective in removing excess fluid volume, it is followed by or combined with additional diuretics, vasoactives, ultrafiltration and ultimately renal replacement therapy (RRT). Heart failure patients with CRS who are on RRT have poorer outcomes, as they are often declined for advanced therapies, such as a left ventricular assist device (LVAD).

Dr Anderson's research hypothesis is that cardiac unloading with an Impella transvalvular mechanical support device in CRS-1 patients can have a favourable impact on neurohormonal activation and haemodynamics to mitigate the need for RRT. Potential benefits of Impella support include increasing cardiac output and haemodynamic stability, decreased neural sympathetic drive, renal unloading (resulting in decreased central venous pressure [CVP]), decreased renin–angiotensin–aldosterone system activation and decreased inflammatory response.

A retrospective chart review of 13 CRS-1 patients diagnosed with ADHF and acute kidney injury, who received the Impella 5.0 or Impella 5.5 device prior

to RRT, demonstrated positive outcomes. All 13 patients survived with no serious adverse events and were successfully bridged to LVAD, transplant or native heart recovery, with none requiring RRT. Impella support improved haemodynamics with decreased CVP, maintenance of mean arterial pressure (MAP) and increased mixed venous oxygen saturation (SVO_2) to normal levels. Normalisation of SVO_2 levels indicate overall improved end-organ perfusion. Several patients were weaned off vasoactives/inotropes by day 7 of treatment. Impella support also improved renal function with significantly increased 24-hour urine output at days 1 and 7 of treatment, and significantly decreased blood urea nitrogen levels by day 7.

Dr Anderson concluded that Impella support safely improves cardiac and renal function and prevents progressive renal deterioration in ADHF patients diagnosed with CRS-1 who are refractory to diuretics and inotropes. A putative mechanism includes unloading the renal circulation by decreasing CVP and maintaining MAP. Impella may also be an effective bridge therapy to improve the candidacy of CRS-1 patients for LVAD or transplant by preventing the need for RRT. Future directions include a larger, prospective study with longer-term follow-up to confirm findings and understand whether observed improvements in renal function persist, especially in heart recovery patients. ❑

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Impella 5.5 as an Ideal Bridge to Left Ventricular Assist Device

Presented by Herman Reichenspurner, MD, PhD

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Dr Herman Reichenspurner is Professor and Chief of the Department of Cardiovascular Surgery at the University Heart and Vascular Center.

Implantation of a left ventricular assist device (LVAD) after extracorporeal membrane oxygenation (ECMO) can compromise the survival of heart failure patients.[1,2] Dr Reichenspurner's research hypothesis is that axillary implantation of an Impella 5.0 or Impella 5.5 transvalvular pump after extracorporeal life support (ECLS), such as ECMO, and before LVAD implantation could serve as a bridge-to-decision treatment, enhancing survival by enabling patient mobility, decreasing complications and facilitating evaluation of right ventricular (RV) function to assist ECLS weaning. The Impella 5.0 is a 21 Fr microaxial pump providing up to 5 l per minute of antegrade blood flow from the left ventricle (LV) to the aorta for up to 10 days. The device is placed using a 9 Fr catheter with axillary access, enabling patient mobility. Additional features of the Impella 5.5 include fibre optical pressure sensing, a modified motor size for improved deliverability, increased pump output to 5.5 l/min, increased ease of positioning and extended usage for up to 30 days.[3]

Dr Reichenspurner demonstrated the viability of Impella bridging with a multicentre feasibility study of LVAD after ECMO and Impella 5.0 implantation.[4] Nine patients with Interagency Registry for Mechanically Assisted Circulatory Support 1 heart failure received venoarterial-ECMO on day 0, Impella 5.0 implantation on day 8, ECMO removal on day 9, continued Impella bridge support to day 17 and LVAD implantation on day 17. The study was a success, with no in-hospital mortality and only one death approximately 7 months after treatment. A recent study of 19 heart failure patients who received Impella 5.5 as a bridge to LVAD after implantation with short-term device support, such as ECMO, also experienced a 90% survival rate with few complications nearly 6 months after treatment.[5]

Other recent studies have demonstrated that using Impella 5.0 as a bridge to LVAD decreases bleeding and thromboembolic complications, while providing neurological recovery time. Sixteen heart failure patients who received axillary Impella 5.0 treatment after percutaneous femoral ECMO treatment experienced fewer thromboembolic complications, no access site bleeding requiring revision and reduced administration of blood products compared with those receiving ECMO alone.[6] Impella 5.0, used as a bridge to decision in patients on ECLS with unclear neurological outcomes, resulted in significant improvement in quantitative measures of cerebral performance after 30 days.[7]

Dr Reichenspurner concluded that Impella 5.0 is an established and successful therapy for LV failure. Impella 5.0 support allows mobilisation and optimisation of patients before LVAD implantation, and enables evaluation of RV function after weaning from ECLS. Results after LVAD implantation are excellent in patients bridged with Impella 5.0. Impella 5.5 is a further improvement, with initial success demonstrated in bridging patients to LVAD. ❑

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Updates from the National Cardiogenic Shock Initiative

Presented by William O'Neill, MD

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Dr O'Neill began by introducing the National Cardiogenic Shock Initiative (NCSI), a group established in April 2016 to address mechanical support management of patients with acute MI (AMI) with cardiogenic shock (CS). No protocols for mechanical support management existed at the time of NCSI inception, with great disparity in device use in the context of angioplasty. Survival after angioplasty supported with an intra-aortic balloon pump (IABP) has remained at 50% for the past 30 years. Dr O'Neill formed the Detroit Cardiogenic Shock Initiative with cardiologists in the Detroit metro area with the goal of establishing a single mechanical support protocol that would increase AMI CS survival to >70%.

NCSI is a prospective, non-randomised, single-arm, multicentre nationwide study assessing the impact of early mechanical circulatory support (MCS) in AMI CS patients treated with percutaneous coronary intervention (PCI). Partial funding is provided by Chiesi and Abiomed, but neither company had direct involvement in the study design or data analysis. More than half of the 70 sites currently participating in NCSI include non-academic, teaching or community hospitals, ensuring broad protocol applicability to AMI CS patients.

The NCSI treatment protocol consists of rapid identification of CS, catheterisation lab activation, femoral access, AMI CS confirmation and implantation of an Impella CP transvalvular support device prior to PCI within a target door-to-support time of less than 90 minutes. Angioplasty is then performed, followed by an assessment of the patient's status by right heart catheter (RHC) monitoring of cardiac power output (CPO) to assess left heart performance and pulmonary artery pulsatilty index (PAPI) or a right atrial pressure-to-wedge pressure ratio to assess right heart performance. Higher numbers for both values indicate normal heart performance. If CPO is ≥0.6 and PAPI is >0.9, left and right heart performance are doing well, and the patient can be down-titrated off of inotropes or vasopressors and the Impella device removed within 48 hours. If CPO is <0.6, the patient is still in shock and requires further left or right heart support. If PAPI is >0.9 and CPO is <0.6, the right ventricle (RV) is considered normal and increased left ventricular (LV) support should be strongly considered. If CPO is <0.6 and PAPI is <0.9, then RV failure is possible and increased RV support should be considered.

Preliminary data of 300 AMI CS patients enrolled at 57 centres demonstrated a 70% survival rate and >90% native heart recovery using the NCSI protocol.[1,2] Implantation of IABP prior to referral, no AMI or anoxic brain injury were the primary reasons for patient exclusion. Comparing the NSCI result with those of five other major AMI trials and studies revealed that the NCSI survival rate of 70% is the highest reported of any modern trial or registry conducted in the US or Europe (*Figure 1*). Taken together, these data suggest MCS with Impella prior to PCI greatly improves patient outcomes.

Figure 1: Variable Comparison Between Acute MI Cardiogenic Shock Studies and Clinical Trials

Variable	Sample Size	Age	Inotropes	Cardiac Arrest	HR	BP	Lactate	Lactate ≥2 mmol/l	Survival %
SHOCK	302	66	99	28	102	89/54	N/A	N/A	53%
IABP SHOCK	600	70	90	45	92	90/55	4.1	74%	60%
Culprit SHOCK	686	70	90	54	91	100/60	5.1	66%	49%
DanGer	100	68	94	0	N/A	76/50	5.5	100%	N/A
NCSI	**300**	**64**	**86**	**43**	**88**	**78/51**	**5.3**	**75%**	**70%**

The NCSI protocol improves patient survival by early identification of shock and initiation of mechanical support with Impella prior to PCI. A golden hour of care exists for AMI CS patients with a treatment delay of every 10 minutes associated with a 3.31% increase in mortality in PCI-treated patients.[3] Ineffective support for AMI CS, such as primary use of IABP, can cause further treatment delays.5,6 Mechanical unloading of the heart by Impella CP pre-PCI is associated with improved AMI CS survival, and should be considered as a support option.[4,7–14]

Inotrope usage greatly increases mortality in AMI CS patients, with use of more than two inotropes being associated with a near doubling of the mortality rate.[4,15] Increased inotrope use also correlates with poor mortality outcomes, predicted by CPO levels of <0.8.[16,17] The NCSI protocol includes down-titration of inotropes to further improve survival in AMI CS patients.

Dr O'Neill concluded that improvements in mechanical support protocols, such as those implemented in the NCSI study, improve survival and native heart recovery. Best practice protocols include early identification and support of patients with cardiogenic shock, aggressive down-titration of inotropes, identification of inadequate LV support and escalation, identification and support of RV dysfunction and the systematic use of RHC to guide therapy.[2,17–19] RHC provides the data critical for the optimisation of treatment. The NCSI dataset has also demonstrated functional application to the Society of Cardiovascular Angiography and Interventions shock staging system and multivessel versus culprit vessel PCI.[20,21] Future studies include a large-scale randomised clinical trial of optimal MSC compared with standard of care in AMI CS. ❑

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Investigating Treatment with Therapeutic Hypothermia for Ischaemia of the Heart

Presented by Bob Kloner, MD, PhD

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Mechanical Left Ventricular Unloading and Therapeutic Hypothermia

Presented by Kiyo Ishikawa, MD

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Dr Bob Kloner is Chief Science Officer and Director of Cardiovascular Research at Huntington Medical Research Institutes and Professor of Medicine at the USC Keck School of Medicine. Dr Kiyo Ishikawa is Assistant Professor of Medicine at the Icahn School of Medicine at Mount Sinai.

Dr Kloner's two decades of research demonstrate that therapeutic hypothermia (TH) reduces myocardial damage in the setting of acute MI. Topical cooling of the heart to a target a temperature <35°C prior to ischaemia or coronary occlusion, followed by reperfusion, or opening of a coronary artery, significantly decreased infarct size in rabbits and sheep.[1,2] Mild regional hypothermia prior to ischaemia also preserved metabolic activity in the ischaemic or occluded area by retention of adenosine triphosphate stores, glycogen stores and creatine phosphate.[3]

TH after ischaemia onset also reduced infarct size in rabbits and rats if administered immediately prior to reperfusion.[4–6] TH induction by intracoronary injection of chilled saline prior to reperfusion limits the no-reflow or microvascular obstruction (MVO) area of the infarct.[6] TH initiated after reperfusion also substantially reduced the extent of no-reflow, but did not decrease infarct size.[7,8]

TH using a non-invasive convective-immersion cooling ThermoSuit produced a similar cardioprotective decrease in no reflow, cardiac scar length and infarct size of ischaemic animals.[9,10] TH also assisted healing after MI, with increased infarcted wall thickness, decreased inflammatory gene expression and improved left ventricular (LV) fractional shortening and ejection fraction.[11] TH also improved long-term survival and blunted inflammation in rats exposed to haemorrhagic shock.[12]

Dr Kloner concluded his talk with a summary of TH clinical studies. Few have been successful due to difficulties decreasing temperature to a sufficient degree, delaying conventional therapy.

Four clinical studies demonstrated that TH reperfusion with a target temperature of <35°C prior to reperfusion decreases infarct size and MVO in patients with ST-segment elevation MI (STEMI).[13–16]

Dr Ishikawa proposes TH in combination with LV mechanical unloading as a treatment for STEMI patients. TH, during the 30-minute period of LV unloading prior to reperfusion, as recommended by the STEMI-Door-to-Unload pilot clinical trial, could enhance the impact of both treatments.[17] A meta-analysis of preclinical studies from around the world over the past 40 years established that mechanical unloading reduces infarct size.[18] Mechanical LV unloading decreases pressure–volume area, reducing myocardial oxygen consumption (MVO_2) for mechanical work, whereas MVO_2 for non-mechanical work remains unchanged.[19] TH improves myocardial energy efficiency by decreasing heart rate and MVO_2 for non-mechanical work.[20,21] LV unloading stabilises haemodynamics and prevents lung congestion through increased blood flow, mitigating TH complications of increased arrhythmia and impaired diastolic function.[22,23] Combination therapy may also limit reperfusion injury by LV unloading-mediated reduction in wall stress and TH-mediated decrease in myocardial temperature. The appropriate TH method of cooling, administration timeline and potential side-effects of combined therapy, such as thrombogenesis, should be determined in future clinical studies. ❑

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Identification of Three Phenotypes of Cardiogenic Shock

Presented by Elric Zweck, MD

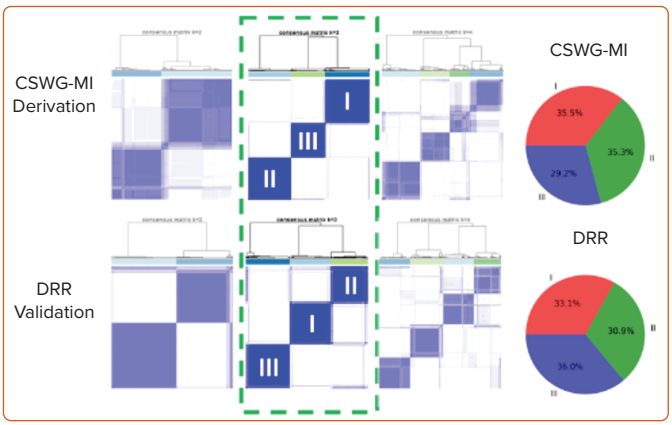
German Center for Diabetes Research, Heinrich-Heine-Universität, Düsseldorf, Germany

Dr Elric Zweck is a doctoral researcher in the Westenfeld laboratory at the German Center for Diabetes Research.

Dr Zweck began his talk by defining cardiogenic shock (CS) as a heterogenous clinical syndrome with unacceptably high mortality. Despite numerous innovations, in-hospital mortality for CS remains at 30–60%. Dr Zweck proposed that recent clinical trials in CS have been unable to identify superior new treatment strategies due to the heterogeneity of included patients. Current CS classifications, such as the 2019 classification released by the Society for Cardiovascular Angiography and Interventions (SCAI), are primarily derived through expert consensus, instead of being data driven.[1]

Dr Zweck's research hypothesis is that a data-driven machine learning analysis could identify distinct phenotypes of CS with clinical applicability. Semi-supervised analysis using consensus K means clustering on clinically relevant mortality-driving variables identified by machine learning was applied to 1,835 CS patients from three international cohorts: the Danish Retroshock Registry (DRR), a two-centre registry of patients in CS after MI; the Cardiogenic Shock Working Group–Myocardial Infarction Registry (CSWG-MI), a US multicentre cohort of patients in CS after MI; and the Cardiogenic Shock Working Group–Heart Failure Registry (CSWG-HF), a

Figure 1: Consensus K Clustering Producing 3 Phenotypes (I, II, III) Derived from the Cardiogenic Shock Working Group–Myocardial Infarction Registry (CSWG-MI) and Validated by the Danish Retroshock Registry (DRR)



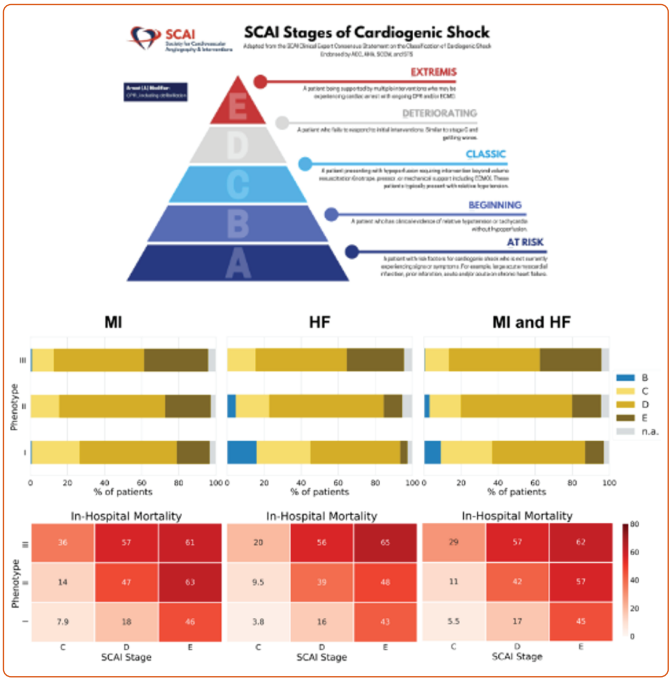
US multicentre group of CS patients with acute-on-chronic heart failure. Clusters were derived from the CSWG-MI and cross-validated in the DRR and CSWG-HF.

Clustering techniques with many variables may provide granularity, but often lack generalisation to their applied disease states. Dr Zweck's research team limited cluster variables to those driving patient mortality to generate a clinically actionable phenotype. Fitting a random forest model to the CSWG-MI cohort identified six variables driving mortality to cluster based on availability, variable orthogonality and predictive importance: glomerular filtration rate (GFR), alanine aminotransferase (ALT), lactate, HCO_3, platelets and white blood cell (WBC) count.

Independent consensus clustering of GFR-CKDEPI, ALT, lactase, HCO_3, platelets and WBCs to the CSWG-MI and DRR data identified three distinctly different CS clinical profiles (*Figure 1*). A three-cluster model provided stable or well-defined boundaries in visual representations of the data, as opposed to a two- or four-cluster model for both data cohorts.

Each cluster differs clinically in congestive profiles, haemodynamics, metabolic variables, cardiac function and in-hospital mortality. The key features of each cluster lead to their identification as non-congested CS/phenotype I, cardiorenal CS/phenotype II and cardiometabolic CS/phenotype III. Each phenotype demonstrated distinct in-hospital mortality profiles and applicability to CS patients with heart failure.

Figure 2: In-hospital Mortality Differentiated by Machine Learning Phenotypes (I, II, III), MI, Heart Failure (HF), Combination of MI and HF and Society for Cardiovascular Angiography and Interventions (SCAI) Stage



Application of all three CS phenotypes within the SCAI shock classification scheme provides further stratification for mortality (*Figure 2*). SCAI stage and mortality associated with MI, HF or a combination of both primarily increased with phenotype classification number; non-congested/phenotype I CS patients often exhibit a classic SCAI stage with the least in-hospital mortality, whereas cardiometabolic/phenotype III CS patients exhibit an extreme SCAI stage with the greatest in-hospital mortality.

Dr Zweck concluded that an unbiased machine learning approach identified three distinct clinically applicable phenotypes of cardiogenic shock.[2] These phenotypes exhibit different metabolic and haemodynamic profiles, and show a reproducible association with mortality. Each phenotype was classified by their defining features of non-congested shock, cardiorenal shock and cardiometabolic shock, and are compatible with, and enhance, SCAI stages. Future studies may further characterise these phenotypes and apply them in the conception of more targeted clinical trials, instead of a one-size-fits-all solution. ❑

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ST-segment Elevation MI-Door-to-Unload Trial Updates

Presented by Zach George, MD, FACC, FSCAI

Prisma Health Carolina Cardiology, Greenville, SC, US

Dr Zach George is an interventional cardiologist at Prisma Health Carolina Cardiology.

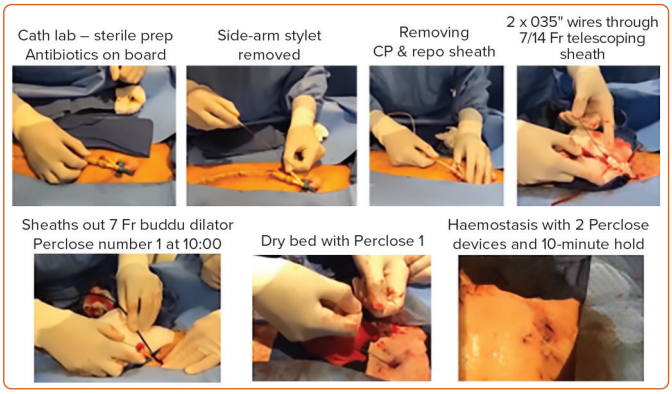
Dr George began his talk by introducing the ST-segment elevation MI (STEMI)-Door-to-Unload (DTU) pilot trial. The 3-year study investigated whether left ventricular (LV) mechanical unloading with an Impella CP transvalvular pump for 30 minutes prior to reperfusion in STEMI patients as a potential means to limit infarct scar size was safe and feasible.[1] Fifty anterior STEMI patients received an Impella CP device to assess safety and feasibility during a heart attack. The patients were randomised to receive ventricular unloading with immediate percutaneous coronary intervention (PCI) or ventricular unloading for 30 minutes prior to reperfusion. An MRI before and after the process was used to determine infarct size. The Impella device was removed after a minimum of 3 hours of support. Dr George commented that the use of the post-closure technique, shown in *Figure 1*, has been shown to improve clinical outcomes.[2]

The STEMI-DTU pilot trial results confirmed the safety and feasibility of STEMI trial randomisation, and demonstrated that unloading with delayed reperfusion by 30 minutes limits infarct size, irrespective of the MI area at risk. Mechanical unloading reduces myocardial ischaemia prior to PCI, with increased exposure time to unloading prior to PCI time decreasing infract size in STEMI-DTU pilot trial patients with large anterior MI.[3] These results enabled initiation of the currently enrolling STEMI-DTU pivotal randomised clinical trial to confirm whether LV unloading limits infarct size and reduces heart failure after STEMI in a larger patient sample.

Dr George summarised the case of one of the 10 patients enrolled in the STEMI-DTU pivotal trial. A 57-year-old man with previous tobacco use, hyperlipidaemia and blood pressure issues experienced stuttering chest pain for several days. He presented with an abrupt onset of chest pain 30 minutes prior to arrival in the emergency room. ECGs transmitted in the ambulance identified STEMI. The patient met enrolment criteria with willingness to obtain an MRI, non-shock status, blood pressure values in the 130s, heart rate at approximately 110, normal point of care lactate level and dramatic ST-elevation, as determined by ECG.

The patient was randomised to the Impella treatment arm. Upon arrival in the catheterisation lab, fluoroscopic identification of the femoral head using ultrasound and a micropuncture kit enabled meticulous large bore access of the femoral artery. A left ventriculogram enabled placement of the Impella CP. Dr George noted that the additional 20–30 seconds taken to identify appropriate anatomic landmarks during vascular access can minimise complications in trial patients. Immediate unloading with the Impella CP resolved ST-segment elevation in the patient, as detected by ECG, and the patient stated he was pain free upon initiation of the device prior to reperfusion. These observations correlate with prior anecdotal evidence of chest pain resolution and decreased ST-segment with mechanical unloading alone. After unloading, Dr George placed an angioplasty balloon in the patient using the same femoral artery access point. This single-access approach involved micropuncture adjacent to the Impella catheter, inserting an 0.035" wire through the micropuncture, inserting a 6 Fr sheath through the Impella repositioning sheath and then inserting the balloon. Optical coherence tomography (OCT) to identify distal and proximal reference vessel size was performed. Use of the single-access technique instead of two access points by radial technique can decrease vascular complications. After 30 minutes of unloading, Dr George performed PCI, followed by OCT. Placement of an Xience 3.5 × 23.0 mm drug-eluting stent appeared to be angiographically adequate, but OCT imaging indicated poor opposition in the proximal segment of the blood vessel. Such a configuration could produce acute stent thrombosis. Dr George resolved the issue by consecutive post-dilatation using a 4.0 × 8.0 mm balloon and a 5.0 × 8.0 mm balloon.

Figure 1: Impella CP Post-closure after 5 Days of Support



The final post-PCI angiogram revealed excellent results for the patient with normal distal flow, no residual stenosis and no additional complications. Removal of the catheter sheath produced no bleeding. Post-PCI ECG indicated that ST-segments continued to be resolved. An echocardiogram on days 1 and 30 post-MI revealed resolution of a pronounced wall motion abnormality and LV function restoration. An MRI on days 3 and 30 post-Impella also revealed resolution of the wall motion abnormality, as well as resolution of anterior oedema and hypokinesis.

Dr George concluded that the patient provided an excellent example of trial enrolment, MI resolution immediately after unloading, single-access technique and post-closure technique. Meticulous care of vascular access should be performed from the arteriotomy to post-closure to enable clinical detection of the effect of unloading on infarct size. ❑

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Abstract: Left Ventricular Unloading Protects Against Both Ischaemic and Reperfusion Injury

Presented by Lija Swain, PhD

Tufts Medical Center, Boston, MA, US

Dr Lija Swain is a postdoctoral fellow in the Kapur Laboratory at Tufts Medical Center.

The Kapur Laboratory previously demonstrated that left ventricular (LV) transvalvular unloading limits damage due to ischaemic injury during MI.[1] LV unloading reduced infarct size, despite 210 minutes of occlusion without reperfusion or opening the blocked artery. Reperfusion injury still occurred with and without unloading. However, the magnitude of injury was lower in the unloaded treatment arm. These data suggest that ischaemia and reperfusion injury are distinct phenomena.

Dr Swain's research hypothesis is that LV unloading reduces infarct size and promotes myocardial recovery by first reducing ischaemic injury, then further limiting reperfusion injury. Hypoxia characterises the ischaemic phase of a heart attack before reperfusion. Subsequent metabolic changes in myocardial cells result in increased glycolysis, lactate production, impaired calcium handling during reperfusion, mitochondrial disruption and, ultimately, apoptosis or necrosis.[2]

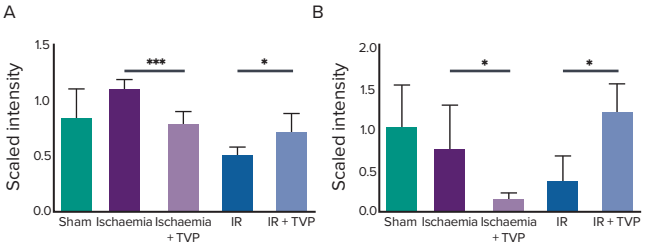
LV unloading with Impella CP improves oxygen delivery in a preclinical ischaemic model of coronary artery occlusion, as is evidenced by decreased levels of hypoxia-inducible factor-1 α and its downstream target proteins in the unloaded ventricle.1 Global metabolic analysis and the reduction of lactate and glucose levels suggest that LV unloading during ischaemia decreases glycolysis compared with ischaemia alone, reducing tissue hypoxia within the infarct zone (*Figure 1*).

LV unloading reduces oxidative stress before and after reperfusion, as indicated by decreased hydrogen peroxide levels (*Figure 2*), and also stabilises calcium handling after reperfusion (*Figure 3*). Taken together, these unpublished data demonstrate that LV unloading reduces ischaemic injury by mitigating tissue hypoxia.

Future studies include optimising the kinetics of ischaemic and post-ischaemic conditioning with Impella, as well as further investigation into the molecular mechanisms of ischaemic unloading and unloading post-reperfusion.

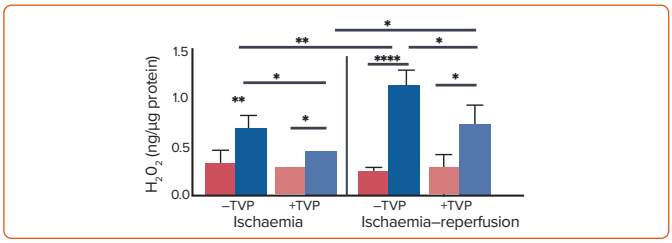
Dr Swain's abstract presentation was awarded an Acute Cardiac Unloading and REcovery Research Grant. ❑

Figure 1: Left Ventricular Unloading Reduces Anaerobic Glycolysis Before Reperfusion, Indicating Reduced Ischaemic Injury



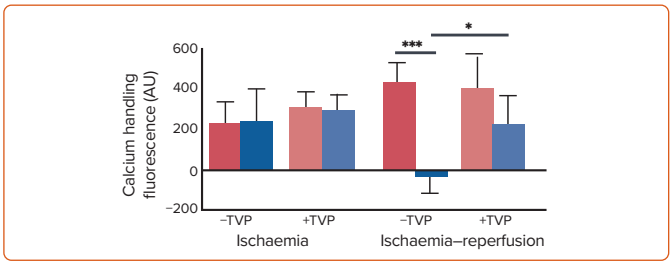
*A: Lactate; B: Glucose. *p<0.05; ***p<0.001. IR = ischaemia–reperfusion; TVP = transvalvular pump.*

Figure 2: Left Ventricular Unloading Reduces Oxidative Stress Before and After Reperfusion



**p<0.05; **p<0.01; ***p<0.001; ****p<0.0001. TVP = transvalvular pump.*

Figure 3: Left Ventricular Unloading Preserves Calcium Handling After Reperfusion



**p<0.05; ***p<0.001. TVP = transvalvular pump.*

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Abstract: Acute Haemodynamic Effects of Pre-emptive Impella Unloading Before Venoarterial Extracorporeal Membrane Oxygenation in a Preclinical Model of Acute MI

Presented by Kay Everett, MD, PhD

Tufts Medical Center, Boston, MA, US

Dr Kay Everett is a Cardiology Fellow at the Beth Israel Deaconess Medical Center and Research Fellow in the Kapur Laboratory at Tufts Medical Center.

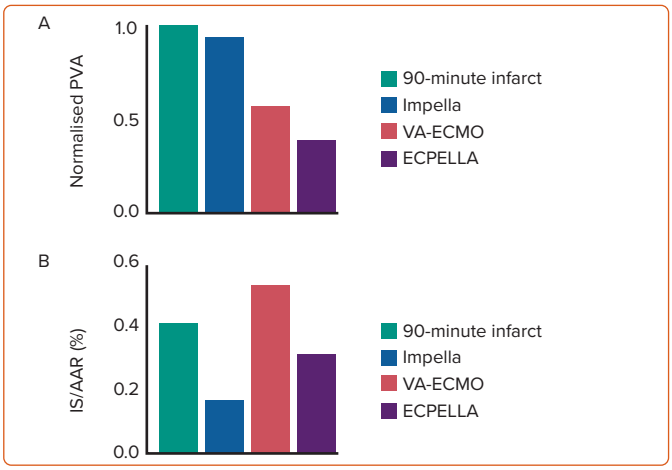
Venoarterial extracorporeal membrane oxygenation (VA-ECMO) causes an increase in left ventricular (LV) afterload, reducing forward blood flow, increasing end-diastolic pressure, increasing pressure–volume work and potentiating LV distention.[1] Increased LV afterload is associated with poor clinical outcomes. ECPELLA, or the combined use of ECMO with Impella, a percutaneous microaxial pump, can limit this deleterious effect. However, the optimal method, timing and potential reduction of myocardial injury remains to be defined.

Dr Everett's research hypothesis is that pre-emptive ECPELLA, or Impella activation before VA-ECMO initiation, significantly limits the ECMO-mediated increase in LV pressure–volume area (PVA) and reduces infarct size compared to bailout ECPELLA, or Impella activation after VA-ECMO initiation. LV pressure–volume loops, pressure areas, arterial pressures and infarct size were assessed in adult swine with 90 minutes of coronary artery occlusion, followed by 30 minutes of pre-emptive ECPELLA.

Results from four animals demonstrated that pre-emptive ECPELLA reduces PVA compared with either Impella or VA-ECMO alone (*Figure 1*). Impella vents the LV, so subsequent VA-ECMO activation increased LV pressure, but not volume, and ECPELLA ultimately reduced overall PVA (*Figure 2*). Aortic and LV pressure uncoupled after 5 minutes of ECPELLA with maximal PVA reduction observed at 15 minutes. Pre-emptive ECPELLA also significantly reduced LV loading and distension as a function of LV end-diastolic pressure and LV end-systolic pressure (*Figure 2*). Infarct size was also decreased, but less than with Impella alone, suggesting that VA-ECMO introduces a unique insult that combination therapy with ECPELLA cannot overcome.

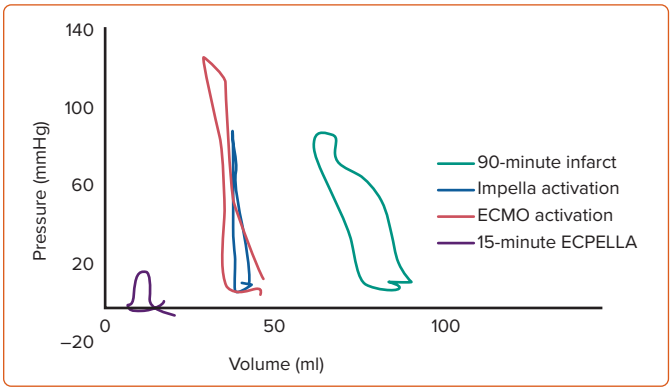
Taken together, these data indicate that pre-emptive Impella activation before VA-ECMO significantly limits the increase in LV PVA induced by VA-ECMO compared with VA-ECMO alone. Future directions include the pre-emptive Impella Unloading is Superior to Bailout Impella after VA-ECMO for ECPELLA (PRIMUS) preclinical study to compare pre-emptive ECPELLA to bailout ECPELLA, as well as active versus passive venting in VA-ECMO. LV pressure–volume loops, pressure areas, arterial pressures, infarct size and molecular mechanisms of myocardial injury will be assessed. A clinical trial comparing the effectiveness of pre-emptive ECPELLA to

Figure 1: Pre-emptive ECPELLA Reduces PVA, but not Infarct Size, Compared with Impella or VA-ECMO Alone



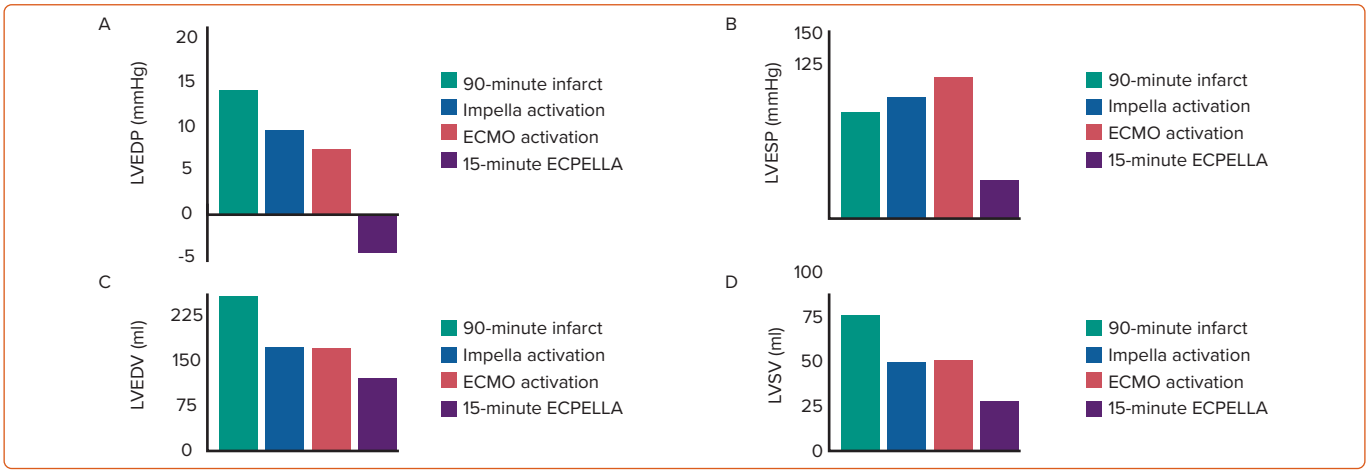
ECPELLA = combined use of ECMO with Impella; IS/AAR = infarct size divided by area at risk; PVA = pressure–volume area; VA-ECMO = venoarterial extracorporeal membrane oxygenation. Error bars represent standard error; n=3–5 per group.

Figure 2: Pre-emptive ECPELLA Reduces Pressure–Volume Area Compared with Impella or VA-ECMO Alone



TVP = transvalvular pump.

Figure 3: Pre-emptive ECPELLA Reduces Left Ventricular Loading and Distension



ECMO = venoarterial extracorporeal membrane oxygenation; ECPELLA = combined use of ECMO with Impella; LVEDP = left ventricular end diastolic pressure; LVEDV = left ventricular end diastolic volume; LVESP = left ventricular end systolic pressure; LVSV = left ventricular systolic volume.

bailout ECPELLA in improving myocardial recovery in shock and acute MI is the ultimate goal of this project.

Dr Everett's abstract presentation was awarded an Acute Cardiac Unloading and REcovery Research Grant. ❑

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Abstract: Negative Impacts of Acute Reloading Following Use of Mechanical Left Ventricular Unloading

Presented by Renata Mazurek, PhD

Icahn School of Medicine at Mount Sinai, New York, NY, US

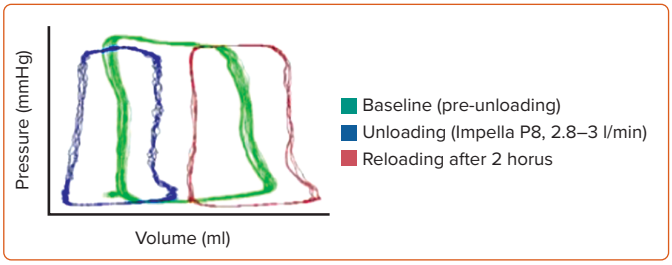
Dr Renata Mazurek is a Postdoctoral Fellow in the Ishikawa Laboratory at the Icahn School of Medicine at Mount Sinai.

Left ventricular (LV) unloading of the heart after acute MI and prior to reperfusion reduces infarct size by decreasing LV wall stress and improving coronary perfusion, thereby reducing the magnitude of ischaemia–reperfusion injury.[1] There is an unmet clinical need to understand the effects of reloading after unloading occurs.

Dr Mazurek's hypothesis is that acute reloading is detrimental to the heart. Haemodynamic measurements and tissue samples were collected from six Yorkshire pigs that underwent unloading with Impella CP for 2 hours, followed by device removal and reloading for 2 hours. Preliminary results indicated a 45% increase in end-diastolic wall stress (EDWS) after 5 minutes of reloading and increased pressure–volume area with decreased systolic function after 2 hours. A significant increase in apoptotic markers, including DNA fragmentation, Puma and caspase-3 was also observed in the reloading-alone group. These data indicate that acute reloading has a negative impact on the normal heart.

Dr Mazurek's hypothesis is that gradual reloading can mitigate deleterious apoptotic and EDWS effects induced by rapid reloading of the ventricle.

Figure 1: Reloading After 2 Hours Increases Pressure Volume (n=5)



Future studies will include investigating the effects of acute reloading and gradual reloading in animal models of acute MI (AMI). Measurements of haemodynamics, apoptosis and infarct size 1 week after AMI will be

collected from six Yorkshire pigs with coronary artery occlusion. These animals underwent unloading with Impella CP for 2 hours, followed by either consecutive acute reloading and reperfusion or consecutive gradual reloading using Impella-mediated pressure adjustments and reperfusion. Acute study endpoints will assess apoptosis and no-reflow area, whereas chronic study endpoints will include infarct size, LV function and ventricular remodelling.

Dr Mazurek's abstract presentation was awarded an Acute Cardiac Unloading and REcovery Research Grant. ❑

1. Esposito ML, Zhang Y, Qiao X, et al. Left ventricular unloading before reperfusion promotes functional recovery after acute myocardial infarction. *J Am Coll Cardiol* 2018;72:501–14. https://doi.org/10.1016/j.jacc.2018.05.034 PMID: 30049311; PMID: 30049311.

Abstract: Acute Haemodynamic Effects of Venoarterial Extracorporeal Membrane Oxygenation on Left Ventricular Mechano-energetics: The Ramp and Clamp Study

Presented by Pankaj Jain, PhD

CardioVascular Center for Research and Innovation, Tufts Medical Center, Boston, MA, US

Dr Pankaj Jain is an Interventional Cardiology Fellow and Research Fellow at the CardioVascular Center for Research and Innovation in the Kapur Laboratory at Tufts Medical Center.

Venoarterial extracorporeal membrane oxygenation (VA-ECMO) is associated with poor short- and long-term outcomes in acute cardiogenic shock (CS) patients, including a low incidence of myocardial recovery.[1–3] VA-ECMO causes an acute increase in left ventricular (LV) afterload, reducing forward blood flow, increasing end-diastolic pressure, increasing pressure–volume work and potentiating LV distention.[4] Preclinical studies and in silico modelling have provided conflicting findings as to the acute effects of VA-ECMO initiation on ventricular load.[5,6] LV unloading prior to VA-ECMO may improve outcomes, but the precise mechanism is unclear.

Dr Jain's hypothesis is that VA-ECMO impairs native LV myocardial contractility. LV pressure–volume loop measurements were conducted on CS patients undergoing VA-ECMO with or without prior LV unloading. Systemic pulmonary haemodynamics, including LV pressure and volume, were continuously recorded during VA-ECMO initiation, or ramp conditions. Consecutive clamping of the ECMO circuit (clamp conditions) simulated off-pump conditions, and was followed by quantification of end-systolic and end-diastolic pressure–volume relationships.

VA-ECMO induced an acute increase in LV afterload in two patients who experienced ramp and clamp conditions with or without prior Impella LV unloading. VA-ECMO induced an increase in pressure–volume area (PVA) while decreasing LV stroke work, contractility and LV end-diastolic pressure (LVEDP). CLAMP conditions enabled reloading of the right ventricle, but did not restore LV function, as measured by stroke work, indicating LV impairment or a stunning effect. Decreased area of LV pressure–volume loops compared to baseline further suggests that reloading after ECMO reduces LV contractility and causes immediate haemodynamic collapse. As expected, decreased LVEDP, despite increased LV volumes and PVA, indicates that ECMO induced venting, but not unloading, in the patient without Impella, while the patient who received unloading with Impella prior to ECMO displayed decreased LVEDP with marked pressure–volume decoupling, indicative of venting and unloading. Decreased LV elastance and decreased end-diastolic pressure–volume relationship were also observed 12 minutes after ECMO initiation in the patient without unloading, a condition not previously described in humans.

These preliminary data provide the first pressure–volume loop assessment of VA-ECMO activation in humans. VA-ECMO increases ventricular afterload, while altering diastolic ventricular compliance and reducing contractility in CS patients. Transvalvular unloading with Impella prior to VA-ECMO initiation vents or reduces LVEDP, while also unloading or reducing myocardial energy requirements. Future studies include the ECMO ramp and clamp study, a prospective assessment of the acute haemodynamic impact of VA-ECMO with or without LV unloading on LV contractility using pulmonary artery catheters, pressure–volume loops and the Impella SmartAssist console. The acute load imposed by VA-ECMO is anticipated to have an immediate and deleterious effect on LV contractility.

Dr Jain's abstract presentation was a runner-up for an Acute Cardiac Unloading and REcovery Research Grant. ❑

1. Garan AR, Eckhardt C, Takeda K, et al. Predictors of survival and ability to wean from short-term mechanical circulatory support device following acute myocardial infarction complicated by cardiogenic shock. *Eur Heart J Acute Cardiovasc Care* 2018;7:755–65. https://doi.org/10.1177/2048872617740834; PMID: 29094607.
2. Vallabhajosyula S, Patlolla SH, Dunlay SM, et al. Regional variation in the management and outcomes of acute myocardial infarction with cardiogenic shock in the United States. *Circ Heart Fail* 2020;13:e006661. https://doi.org/10.1161/CIRCHEARTFAILURE.119.006661; PMID: 32059628.
3. Schrage B, Becher PM, Bernhardt A, et al. Left ventricular unloading is associated with lower mortality in patients with cardiogenic shock treated with venoarterial extracorporeal membrane oxygenation circulation: results from an international, multicenter cohort study. *Circulation* 2020;142:2095–106. https://doi.org/10.1161/CIRCULATIONAHA.120.048792; PMID: 33032450.
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Abstract: Impella RP Versus Pharmacological Vasoactive Treatment in Profound Cardiogenic Shock due to Acute Ischemic Occlusion of the Right Coronary Artery

Presented by Jakob Josiassen, PhD

Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark

Dr Jakob Josiassen is a researcher at Rigshospitalet, Copenhagen University Hospital.

Cardiogenic shock (CS) due to acute right ventricular (RV) failure represents 7% of all shock cases and has a high 30-day mortality rate.[1] The standard of care for acute RV failure includes fluids, vasoactive treatment and pacing. However, there are limited data identifying the best approach to managing these patients.

Dr Josiassen's research compares the effects of a pharmacological vasoactive strategy to the Impella RP transvalvular RV mechanical support pump on end-organ perfusion and unloading of the heart in a porcine model of CS shock due to acute RV failure. RV CS induced by stepwise injection of polyvinyl alcohol microspheres into the right coronary artery presented as sustained reduction in cardiac output ≥50% with or without a >50% reduction in mixed venous oxygen saturation (SvO_2) compared with baseline or an absolute SvO_2 <30%. Echocardiogram confirmed dilation and dysfunction of the RV compared with baseline.

Pharmacological vasoactive treatment consisted of 0.1 µg/kg/min norepinephrine for 30 minutes, followed by 0.4 µg/kg/min milrinone for 150 minutes. Impella treatment consisted of implantation and activation of Impella RP at the highest performance level for 180 minutes. Impella treatment was supplemented with norepinephrine treatment if mean arterial pressure declined >50 mmHg in order to maintain coronary perfusion pressure. Pressure–volume area (PVA), cardiac workload and end-organ perfusion were monitored throughout the experiment. CS shock was successfully induced in 14 animals.

Impella RP treatment efficiently unloaded the failing RV, as measured by a reduced PVA (reflecting potential energy and stroke work) compared with vasoactive treatment. Compared with Impella RP, vasoactive treatment caused a greater increase in cerebral venous oxygen saturation. Both interventions increased renal perfusion to a similar degree. Limitations of the study include the use of healthy animals and the irreversible ischaemia and microcirculatory obstruction caused by microsphere use. Future directions include further analysis of echocardiography and biomarkers from this study, as well as future studies comparing extracorporeal membrane oxygenation (ECMO) alone versus Impella activation before vasoarterial-ECMO.

Dr Josiassen's abstract presentation was a runner-up for an Acute Cardiac Unloading and REcovery Research Grant. ❑

1. Josiassen J, Helgestad OKL, Møller JE, et al. Cardiogenic shock due to predominantly right ventricular failure complicating acute myocardial infarction. *Eur Heart J Acute Cardiovasc Care* 2021;10:33–9. https://doi.org/10.1093/ehjacc/zuaa010; PMID: 33620420.

Abstract: Right Ventricular Energetic Efficiency Improvement During Left Ventricular Unloading in Post-MI Pigs

Presented by Taro Kariya, MD

University of Tokyo, Tokyo, Japan

Dr Taro Kariya is a researcher at the University of Tokyo Japan. His research project was conducted in collaboration with the Ishikawa lab at the Icahn School of Medicine at Mount Sinai.

Thirty per cent of heart failure patients experience right ventricular (RV) overloading, dilation and subsequent RV failure after left ventricular (LV) unloading by a mechanical support device, such as Impella. The Ishikawa lab presented data at the 2019 Acute Cardiac Unloading and REcovery (A-CURE) symposium demonstrating flow-dependent RV dilatation after LV Impella support in pigs with MI.

The impact of acute LV unloading with Impella on RV energetic efficiency remains unclear.

Dr Kariya's hypothesis is that myocardial oxygen consumption (MVO_2) efficiency improves in the loaded RV during Impella LV support in post-MI pigs. Female Yorkshire pigs (n=3) received LV Impella CP support 1 week after induction of MI. The impact of LV Impella support on RV energetics was studied using a Millar pressure–volume catheter in the right ventricle. The RV MVO_2 rate was studied by measuring the blood oxygen content difference between the right coronary artery and coronary vein on the RV free wall surface (by surgical approach). Regional myocardial perfusion was assessed using fluorescently labelled microspheres.

Impella support reduced LV pressure and volume while increasing RV stroke work, stroke work (SW) over 1 minute (SW × heart rate), pressure–volume area (PVA), and PVA over 1 minute (PVA × heart rate). MVO_2 as a function of stroke work over 1 minute also significantly decreased in all pigs, indicating improved energy efficiency in loaded RV during LV Impella support. Future directions include repeating the study with additional animals and *in silico* mechanistic investigations into how Impella LV support affects the behaviour of sarcomeric proteins in the RV wall.

Dr Kariya's abstract presentation was a runner-up for an A-CURE Research Grant. ❑

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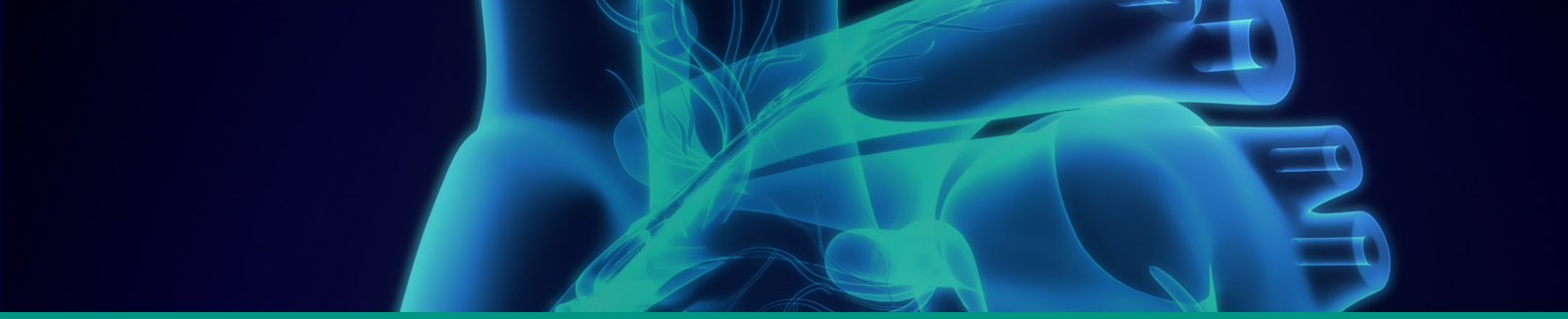

Foreword

Welcome to this special supplement devoted to the proceedings of the 6th Annual Acute Cardiac Unloading and Recovery (A-CURE) Working Group meeting, which was held virtually on 28 January 2022 (https://a-cure.org/a-cure-symposium/). The A-CURE Working Group is comprised of leading academic experts in clinical and basic cardiac research who are dedicated to advancing the science and clinical application of acute cardiac unloading. This meeting brought together experts from various disciplines, including interventional cardiologists, heart failure specialists, cardiac surgeons, molecular biologists and biomedical engineers.

The A-CURE symposium is a platform to promote discussion of the latest discoveries in the field of ventricular unloading and heart recovery. The 2022 symposium featured invited talks and abstract presentations that highlighted cutting-edge advances in the field of acute cardiac unloading with a special focus on topics of heart recovery and novel surgical applications of mechanical circulatory support (MCS).

This supplement features 21 presentations covering a broad range of subjects related to cardiac unloading. Dr Dan Burkhoff opened the symposium with his state-of-the-field address highlighting the achievements of two recent Nobel Laureates, Dr Gregg Semenza from 2019 and Dr Ardem Patapoutian from 2021, whose work had immediate relevance to mechanisms of unloading. The first session focused on advances in basic and preclinical science of acute unloading and myocardial salvage, featuring six abstract winners with state-of-the-art preclinical works in acute MI (AMI), cardiac arrest, right ventricular failure, extracorporeal membrane oxygenation and concomitant Impella support (ECPELLA) and novel percutaneous ventricular assist devices. Dr Renata Mazurek, the 2022 Young Investigator Award recipient, closed the session with her talk on the importance of a weaning protocol with MCS use in revascularisation.

This supplement contains summaries from three invited lectures. For the Innovation Lecture, Dr Navin Kapur discussed the past, present and future of the field's understanding of the molecular mechanisms of unloading. He emphasised the growing body of knowledge supporting the understanding that molecular changes in the myocardium directly inform a patient's ability to recover. There are several research arenas, such as mitochondrial integrity and calcium cycling, that Dr Kapur believes will provide new insight into optimising cardiac unloading and recovery. This dovetailed with the Keynote Lecture by Dr Clyde Yancy, who highlighted the benefits of a holistic approach to treating advanced heart failure. Dr Yancy's wide-ranging discussion underscored the growing consensus in the field of unloading that there must be a robust understanding of both the physical and molecular changes to the myocardium in heart failure (HF). He posited this will lead to better therapeutic avenues and options, which will likely include varying combinations of unloading devices and drug therapy, tailored to the patient's biology. This year's Distinguished Lecture was given by Dr Emma Birks, an internationally recognised expert in HF recovery. Dr Birks provided an in-depth review of her discoveries in the Remission from Stage D Heart Failure (RESTAGE-HF) trial, which revealed that unloading combined with customised pump support and aggressive drug therapy can result in durable, long-term recovery in HF patients.

The second session featured real-world applications of acute ventricular unloading. Dr Tharusan Thevathasan, the Best in Research Award recipient, opened the session with a presentation on ECPELLA outcomes in the cardiac arrest patient population. Top physician scientists from Europe and the US presented findings from recently completed and ongoing clinical trials testing innovative clinical applications of ventricular unloading in myocarditis, high-risk percutaneous coronary intervention, AMI cardiogenic shock and ST-elevation MI. This was followed by the third session, which highlighted the new frontiers in surgical and clinical applications of unloading. Upcoming clinical studies of MCS in cardiac and non-cardiac surgery were presented by four renowned cardiac surgeons. The last session addressed the topic of clinical science and evidence of cardiac recovery. Led by leading experts in heart recovery and advanced HF programs, the symposium closed with discussions on the fundamentals of heart recovery versus remission, a real-world heart recovery program and a new percutaneous MCS device designed for bridge-to-recovery applications in the HF space.

In addition to the live talks, 38 scientific posters were accepted for A-CURE 2022 from top-class researchers around the world. The posters can be viewed at the A-CURE website (https://www.posterpresentations.com/research/groups/acure/acure.html). The presentations this year highlighted exciting new developments and represented substantial advances in the field of acute myocardial unloading and heart recovery over the past year. The A-CURE Working Group meeting is unique in including a diverse group of experts from various disciplines within an open, constructive and intimate public setting.

We hope that you find this supplement informative and interesting. ❑

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Annual Update: The State of the Field in Cardiac Unloading

Presented by Daniel Burkhoff, MD, PhD

Cardiovascular Research Foundation, New York, NY, US; Columbia University, New York, NY, US

Dr Burkhoff is the Director of Heart Failure, Hemodynamics and Mechanical Circulatory Support Research at the Cardiovascular Research Foundation. He has authored more than 380 peer-reviewed publications and is a world expert in heart failure, haemodynamics and heart muscle mechanics. Dr Burkhoff is a founding member of the Acute Cardiac Unloading and REcovery (A-CURE) Working Group.

Dr Burkhoff opened the 6th A-CURE symposium by defining ventricular unloading. The 2018 A-CURE consortium defined unloading as "the reduction of total mechanical power expenditure of the ventricle which correlates with reductions in myocardial oxygen consumption and hemodynamic forces that lead to ventricular remodeling".[1]

Dr Burkhoff demonstrated this concept using Impella as the means of primary unloading. As the left ventricle is unloaded under Impella support, the pressure–volume loop shifts leftwards, reducing the pressure–volume area and thus the work of the heart. Overall, unloading the ventricle with the Impella device results in decreased total work, with a concomitant reduction in myocardial oxygen consumption. Dr Burkhoff described additional benefits of unloading in hearts under stress conditions, such as in cardiogenic shock. Unloading the heart provides the opportunity to potentially withdraw medications such as inotropes and vasopressors, reducing heart rate and inotropic stimulation while maintaining cardiac output, blood pressure and normal wedge pressure. Weaning of inotropes can further reduce the pressure–volume area and myocardial oxygen consumption. Thus, unloading offers both primary and secondary benefits to the myocardium under stress.

Dr Burkhoff shared a recent review covering the myriad cardioprotective effects of ventricular unloading during myocardial infarction.[2] These cardioprotective effects include decreased oxygen consumption, activation of cardioprotective signalling pathways, increased cardiac microvascular perfusion into the infarct zone, haemodynamic stabilisation through reperfusion-dependent arrhythmia, the ability to bridge through reperfusion-induced myocardial stunning and reduced acute infarct size and subsequent scar size.

Dr Burkhoff emphasised a number of milestones reached as a result of the A-CURE initiative and research. These include several ongoing clinical trials, including the seminal pilot study for Door-to-Unload (DTU), the currently enrolling DTU pivotal study, the recent publication of the early feasibility data of the preCardia device, the PROTECT Kidney study, which is examining the effect of mechanical unloading on end organ perfusion (kidney), and the IMPACT trial for the use of unloading in the context of cardiac surgeries.[3,4] In addition, he highlighted new uses for mechanical circulatory support as an enabler for other procedures, such as bridging patients with advanced heart failure through non-cardiac surgeries and other high-risk cardiac procedures such as MitraClip. Dr Burkhoff pointed out a number of novel research initiatives also scheduled to begin this year, such as investigating the impact of Impella on microvascular obstruction in ST-elevation MI.

Dr Burkhoff highlighted two recent Nobel Prize-winning scientific investigations and their immediate relevance to the field of unloading. He emphasised the work of Dr Gregg Semenza, who received the 2019 Nobel Prize in Medicine or Physiology for his discovery of hypoxia-inducible factor-1 (HIF-1),[5] and pointed out a recent research article demonstrating how unloading prior to revascularisation led to a significant reduction in infarct size, where the HIF-1 pathway was clearly implicated.[6] He next highlighted Dr Ardem Patapoutian, who received the 2021 Nobel Prize in Medicine or Physiology for his discovery of PIEZO1/2.[7] PIEZO1 is a channel protein on the membrane that changes the entry of calcium into the cell when force is applied, and is another molecular mechanism by which unloading can impact myocardial contractility.

Dr Burkhoff concluded that these fundamental research discoveries are critical to better understanding the biology and physiology of cardiac unloading. ❑

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3. Kapur NK, Kiernan MS, Gorgoshvili I, et al. Intermittent occlusion of the superior vena cava to improve hemodynamics in patients with acutely decompensated heart failure: the VENUS-HF Early Feasibility study. *Circ Heart Fail* 2022;15:e008934. https://doi.org/10.1161/CIRCHEARTFAILURE.121.008934; PMID: 35000420.
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7. Coste B, Mathur J, Schmidt M, et al. Piezo1 and Piezo2 are essential components of distinct mechanically activated cation channels. *Science* 2010;330:55–60. https://doi.org/10.1126/science.1193270; PMID: 20813920.

Functional Role of Hypoxia-inducible Factor-1α in Cardioprotection with Left Ventricular Unloading During Acute MI

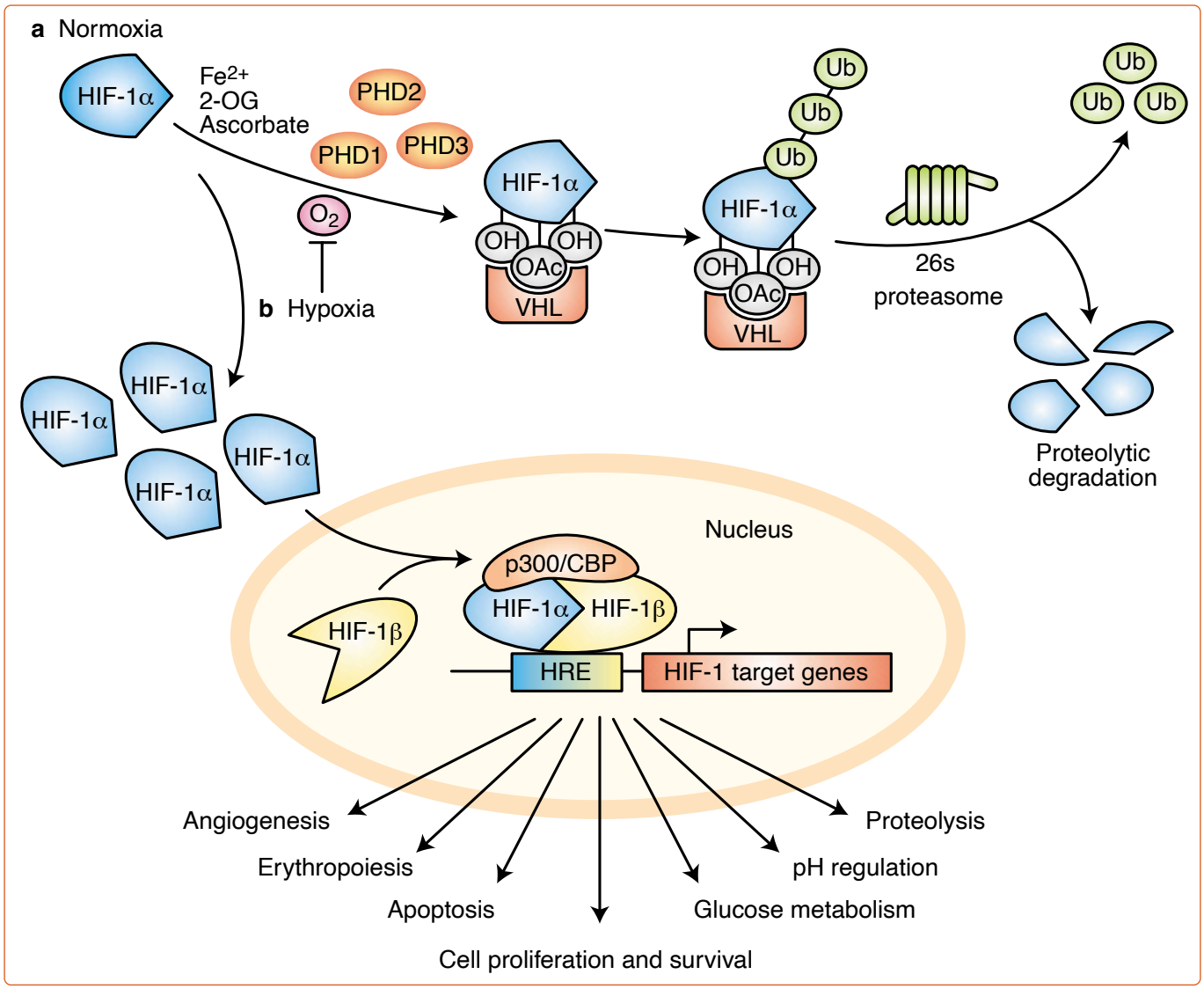
Presented by Lija Swain, PhD

Tufts University School of Medicine, Boston, MA, US

Dr Swain is a postdoctoral researcher in the Navin Kapur Laboratory at Tufts University School of Medicine. Dr Swain's abstract was selected for oral presentation at the 6th A-CURE symposium.

Previous preclinical work demonstrated left ventricular (LV) unloading initiated at least 30 minutes prior to reperfusion reduces LV wall stress and infarct size, despite delaying reperfusion by 60 minutes in acute MI (AMI). Dr Swain's recent publication showed that transvalvular unloading by Impella and delayed reperfusion preserve myocardial energy substrate utilisation, ultimately protecting mitochondrial function in AMI.[1] In a comparison of Impella and venoarterial extracorporeal membrane oxygenation, only unloading by Impella was able to reduce infarct size by protecting mitochondrial function.[1] To understand the underlying mechanism behind the benefits of initiating unloading during the ischaemic phase, Dr Swain and her team set out to differentiate the molecular changes in ischaemia from those during reperfusion.

Figure 1: Hypoxia-Inducible Factor-1α Regulation by Proline Hydroxylation



2-OG = 2-oxoglutarate; CBP = CREB binding protein; HIF = hypoxia-inducible factor; HRE = hypoxia-response elements; OAc = acetylation of HIF-1α; PHD = proline hydroxylase; Ub = ubiquitin; VHL = von Hippel–Lindau tumour-suppressor gene. Source: Carroll and Ashcroft.[3] Used with permission from Cambridge University Press.

Dr Swain provided a brief overview of the major molecular mechanisms in ischaemia versus reperfusion, emphasising that in ischaemia cells switch to anaerobic glycolysis by upregulating the expression of genes involved in anaerobic metabolism.[2] A key consideration in ischaemia versus reperfusion is the molecular mechanism for switching to anaerobic glycolysis when oxygen is absent. Hypoxia-inducible factor-1α (HIF-1α) is critically involved in the molecular sensing of oxygen. In the presence of oxygen, prolyl hydroxylase domain (PHD) enzymes hydroxylate HIF-1α, facilitating recognition of HIF-1α by von Hippel–Lindau tumour-suppressor protein, leading to ubiquitination and proteolytic degradation. Under hypoxic conditions, HIF-1α accumulates in the cytoplasm, translocates to the nucleus and forms complexes that trigger upregulation of target genes involved in glycolysis (*Figure 1*).[3]

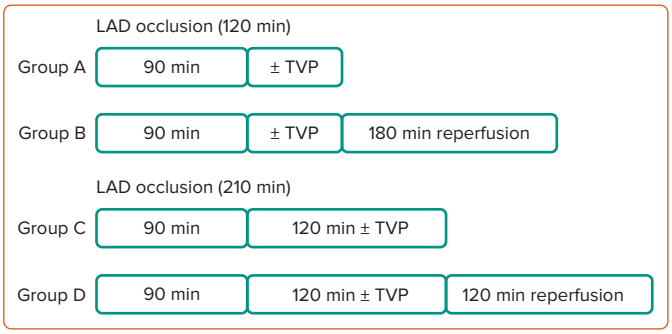
Dr Swain and her team designed a model to uncouple ischaemia and reperfusion (*Figure 2*). Four experimental groups were tested. Groups A and B were exposed to shorter ischaemia of 120 minutes; after 90 minutes ischaemia, Group A received unloading with a transvalvular pump for 30 minutes and was terminated without reperfusion, whereas Group B was reperfused for an additional 3 hours after the 30-minute unloading. Groups C and D were exposed to a prolonged ischaemic time of 210 minutes to mimic the real-life delay between patient symptoms and balloon time: after 90 minutes ischaemia, Group C remained in ischaemia for 120 minutes with unloading, whereas Group D subsequently received 2 hours reperfusion. The control groups for each of the four scenarios did not receive unloading treatments.

In the groups with a shorter duration of ischaemia, ischaemia alone did not generate any significant infarct scar; only under ischaemia followed by reperfusion (I/R) was a significant infarct scar produced, and this was significantly reduced by LV unloading. For the groups subjected to prolonged ischaemia, a small infarct zone was observed with ischaemia alone, whereas I/R presented a much larger infarct zone. In both cases, infarct size was significantly reduced by Impella unloading compared with control. Taken together, LV unloading initiated prior to reperfusion greatly limited infarct size in both short and prolonged I/R scenarios.

Dr Swain measured the activity of mitochondrial complex I, a critical enzyme in the respiratory chain, in hearts collected from all four groups ± unloading. Complex I activity was preserved in all four scenarios with transvalvular unloading. HIF-1α protein expression was also assessed; interestingly, HIF-1α expression declined with unloading under ischaemia-only conditions (Groups A and C), regardless of ischaemia duration. This suggests reduced ischaemic burden in the infarct zone of unloaded hearts and consequently destabilised HIF-1α proteins. Under I/R conditions (Groups B and D), HIF-1α protein levels increased with unloading in both groups. To understand whether the observed changes in HIF-1α protein levels are functionally relevant, Dr Swain measured the expression of HIF downstream targets prolyl-4-hydroxylase domain 3 (*PHD3*) and glucose transporter 1 (*Glut1*). The expression patterns of both proteins similarly matched that of HIF-1α. To demonstrate HIF-1α is driving the cardioprotective effect of unloading in I/R, Dr Swain infused 2-methoxyestradiol, a chemical inhibitor of HIF-1α, during transvalvular unloading in the prolonged I/R model (Group D). She confirmed that inhibitor infusion led to significant downregulation of HIF-1α protein in the heart. Inhibition of HIF-1α significantly attenuated the cardioprotective effects of unloading, as evidenced by increased infarct size and reduced complex I activity. This study suggested that HIF-1 is critical to the protective effects of unloading in I/R.

Dr Swain concluded that this work introduces HIF-1α as a major molecular player involved in cardioprotective effects of LV unloading in I/R. ❑

Figure 2: A Model to Uncouple Ischaemia and Reperfusion



Groups A and B: unloading plus 30 min delay before reperfusion; Groups C and D: unloading for the duration of the 120-minute delay before reperfusion. LAD = left anterior descending artery; TVP = transvalvular pump.

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Effect of Impella RP Versus Vasoactive Treatment on Left Ventricular Strain in Cardiogenic Shock

Presented by Peter Frederiksen, MD

Department of Cardiology, Odense University Hospital, Odense, Denmark

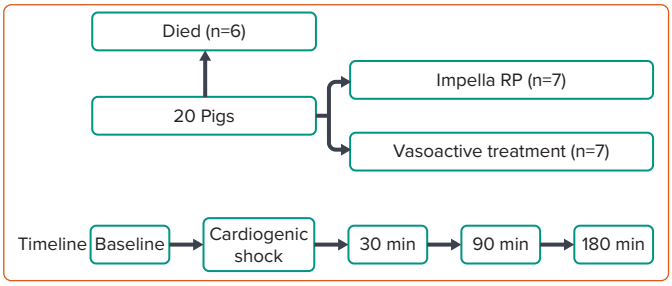
Dr Peter Frederiksen is a PhD student from the Department of Cardiology at Odense University Hospital in Southern Denmark. Dr Frederiksen's abstract was selected for oral presentation at the 6th A-CURE symposium.

Dr Frederiksen's research examined the effect of the Impella RP and vasoactive treatment on left ventricular (LV) longitudinal strain during cardiogenic shock.

Dr Frederiksen used a porcine model of cardiogenic shock with right coronary artery embolisation, where shock was defined as a ≥50% reduction of cardiac output and/or a ≥50% reduction of venous oxygen saturation (SvO_2) compared with baseline or an absolute SvO_2 of <30%. The interventions used in the study included Impella RP or vasoactive treatment with milrinone and norepinephrine. The Impella RP was kept at the highest performance level throughout the entire study period, and the vasoactive treatment was initiated with norepinephrine for 30 minutes, and then an initial dose of milrinone followed by continuous infusion. For each intervention, seven animals were examined with echocardiograms obtained at five time points: baseline, cardiogenic shock and after 30, 90 and 180 minutes of treatment (*Figure 1*). Obtaining high-quality echocardiogram images required making a subxiphoid incision to allow the probe to be directly placed at the diaphragm. Haemodynamic data were also collected with conductance catheters (to measure ventricular volume based on blood electrical conductance) in both the LV and right ventricle, and Swan-Ganz catheters in the pulmonary artery. Blood gas analysis was performed on samples collected from the jugular vein, renal vein, arterial line and pulmonary artery.

Comparisons of echocardiograms revealed that cardiogenic shock severely reduced longitudinal function of the right ventricle. The septum lost nearly all function, and paradoxical movement was observed when the hyperdynamic lateral wall was contracting. Previous work focusing on the right ventricle showed a large reduction in SvO_2 when in shock.[1] However, implementation of the Impella resulted in increased SvO_2 and reduced myocardial work, whereas vasoactive treatment increased SvO_2 but at the cost of increased myocardial work. Dr Frederiksen and colleagues focused their analysis on the LV, which was divided into septal and lateral walls.

Figure 1: Experimental Scheme



Animals were assessed with echo at 30, 90, and 180 minutes post cardiogenic shock.

Dr Frederiksen presented LV strain results from speckle-tracking echocardiography, which produces a negative percentage as a readout; more negative strain values indicate a higher hyperdynamic state, whereas less negative strain values indicate reduced cardiac function. Dr Frederiksen noted how shock induction led to a decline in LV function from baseline, with less negative strain. Both treatments resulted in an improvement in overall strain values. Examination of the septal wall showed no changes from either treatment once in cardiogenic shock; conversely, the lateral wall was greatly affected by both treatments, with vasoactive treatment resulting in more negative strain than baseline over time and the Impella RP treatment resulting in normalisation to baseline values. The lower overall strain with vasoactive treatment suggests greater improvement in LV contractile function; however, it also suggests a higher energy consumption, undesirable in stress conditions. Therefore, in the context of MI shock, the lower-than-baseline strain under vasoactive treatment is not ideal for the heart.

Dr Frederiksen concluded that under profound cardiogenic shock due to occlusion of the right coronary artery, LV strain is immediately impacted. Both Impella RP and vasoactive treatment improved lateral wall strain, whereas vasoactive treatment produced greater negative strain, signalling increased energy consumption. ❑

1. Josiassen J, Helgestad OKL, Udesen NLJ, et al. Impella RP versus pharmacologic vasoactive treatment in profound cardiogenic shock due to right ventricular failure. *J Cardiovasc Transl Res* 2021;14:1021–9. https://doi.org/10.1007/s12265-021-10131-x; PMID: 33977379.

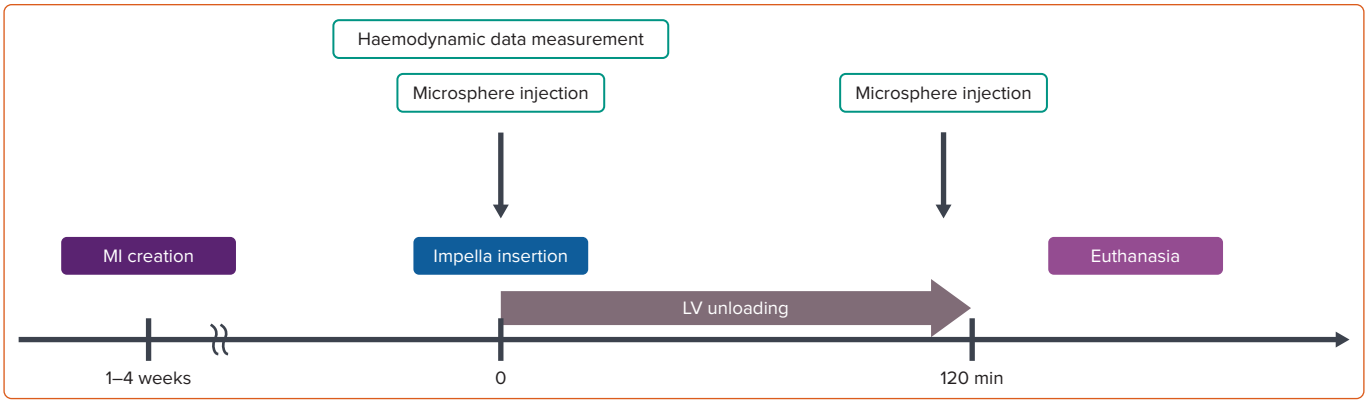
Impaired Diastolic Function Predicts Improved Ischaemic Myocardial Flow Improvement with Mechanical Left Ventricular Unloading

Presented by Tomoki Sakata, MD

Cardiovascular Research Institute, Icahn School of Medicine at Mount Sinai, New York, NY, US

Dr Sakata is a cardiothoracic surgeon and a postdoctoral fellow in the Kiyotake Ishikawa laboratory at the Cardiovascular Research Institute, Icahn School of Medicine at Mount Sinai. Dr Sakata was awarded the 2021 A-CURE Research Fellowship Grant. His abstract was selected for oral presentation at the 6th A-CURE Symposium.

Figure 1: Experimental Scheme to Monitor Coronary Blood Flow in a Pig Model of MI

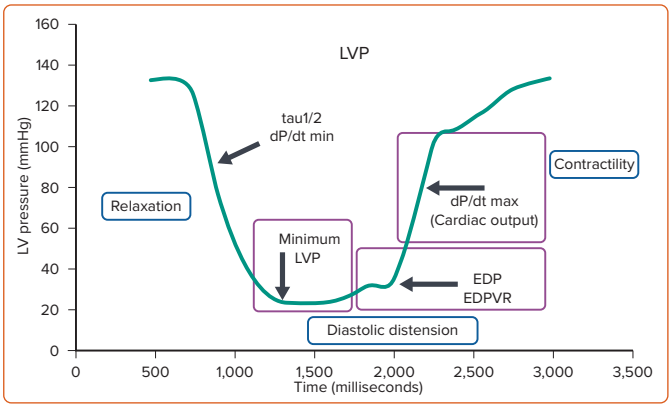


The goal of Dr Sakata's work was to understand the effects of unloading on coronary blood flow. Previous work has shown that coronary flow is increased in the infarct zone with initiation of Impella, and this was correlated with end-diastolic wall stress.[1] However, because increased coronary flow in the infarct area is highly variable, Dr Sakata and his team aimed to determine the factors that predict coronary flow improvement in the infarcted heart before and after Impella insertion using a porcine model. Briefly, 15 pigs underwent left ventricular (LV) unloading with Impella CP 1–4 weeks after MI (*Figure 1*). Fluorescent microspheres were injected prior to and after LV unloading to measure radial basis function (RBF), and linear regression analysis was conducted with baseline haemodynamic measurements to identify predictors of RBF improvement.

Coronary flow was measured before and after Impella support in the infarct, border and remote zones. Only coronary flow in the infarct zone showed a trend towards improvement under Impella support; however, statistical significance was not reached due to non-responders. Dr Sakata hypothesised that these non-responders were haemodynamically different from the animals with coronary flow improvements. Using univariate analysis, Dr Sakata showed that improvements in coronary flow were related to cardiac output, pulmonary arterial wedge pressure, left atrial pressure, minimum LV pressure (LVP), end-diastolic LV pressure, maximum dP/dt and the end-diastolic pressure–volume relationship (EDPVR). Multivariate analysis determined that maximum dP/dt and EDPVR were independent predictive factors of coronary flow improvement.

Ultimately, this study showed high EDVPR and low maximum dP/dt were associated with improved coronary flow under Impella support. High

Figure 2: Representative Left Ventricular Pressure Over One Cardiac Cycle



Parameter associated with improved coronary flow are highlighted with purple boxes. EDP = end-diastolic left ventricular pressure; EDPVR = end-diastolic pressure–volume relationship; LVP = left ventricular pressure; tau = left ventricular relaxation time constant.

EDPVR was correlated with cardiac stiffness and low maximum dP/dt was correlated with decreased contractility, both commonly seen in patients after MI. This suggests that Impella may be more effective in improving coronary flow in ischaemic heart failure.

According to the present univariate analysis, factors that influence coronary flow span broadly over the cardiac cycle, from the beginning of LV filling to the isovolumic contraction phase (*Figure 2*). Dr Sakata's next goal is to more precisely determine how coronary flow is increased.

Ongoing studies aim to directly measure coronary flow simultaneously with LVP under unloading. Interestingly, preliminary results have shown that coronary flow is increased throughout all of diastole, consistent with the regression analysis results. Future work will focus on identifying the specific factors that cause these changes in each cardiac phase. Dr Sakata concluded that a higher EDPVR slope and lower maximum dP/dt are associated with better improvement in coronary blood flow in the infarct area during mechanical LV unloading. ❑

1. Watanabe S, Fish K, Kovacic JC, *et al.* Left ventricular unloading using an impella CP improves coronary flow and infarct zone perfusion in ischemic heart failure. *J Am Heart Assoc* 2018;7:e006462. https://doi.org/10.1161/jaha.117.006462; PMID:29514806.

Promising First Results of a Newly Developed Percutaneous Left Ventricular Assist Device in a Large Animal Model of Cardiac Arrest

Presented by Sebastian Billig, MD

Department of Anesthesiology at University Hospital RWTH Aachen, Aachen, Germany

Dr Sebastian Billig is a Graduate Student at the Department of Anesthesiology at University Hospital RWTH Aachen. Dr Billig's abstract was selected for oral presentation at the 6th A-CURE symposium.

Dr Billig's research focuses on investigating the efficacy of the use of percutaneous left ventricular assist devices (pLVADs) in cardiac arrest. Dr Billig emphasised that previous work has shown that survival after cardiac arrest improves with use of a pLVAD over chest compressions, but the uptake of this strategy has been limited because of the complex nature of insertion techniques requiring a guidewire. Dr Billig's current research aims were to evaluate the placement of the new expandable pLVAD, the Impella ECP, without a guidewire and to test its efficacy for resuscitation in cardiac arrest using a porcine model. The group tested two versions of the Impella ECP, one without a modified catheter and one with a modified catheter to better fit the swine anatomy. Cardiac arrest was induced in six pigs (75 kg) with electrical fibrillation for 5 minutes; the pigs were then resuscitated with either a non-modified or modified Impella ECP inserted through a 10 Fr sheath and norepinephrine added prior to defibrillation. After return of spontaneous circulation was observed, the pigs were followed up for 5 hours before the devices were explanted and cardiac function was evaluated. The guidewire-less pLVAD insertion was monitored under transoesophageal echocardiography (TOE). Dr Billig showed a representative TOE to demonstrate the ease and speed of aortic value crossing and positioning of the device without a guidewire.

Dr Billig described the initial results of this study comparing the use of a non-modified versus modified Impella ECP. Insertion was successful in all six animals without the guidewire, with a mean (± SD) time of 58 ± 21 seconds from the start of insertion to pump activation. Although the non-modified version successfully resuscitated one of three pigs, the modified Impella ECP successfully resuscitated all three pigs. Dr Billig reported that a mean (± SD) of 2.25 ± 1.50 defibrillations and 1.5 ± 0.6 mg norepinephrine were required for resuscitation. There were no adverse events due to the new Impella device, including aortic regurgitation after explant. In animals with the Impella ECP, blood pressure increased markedly 10 minutes after the return of spontaneous circulation compared with baseline, which was followed by a drop and return to stable haemodynamics that was maintained throughout the 5 hours of support and at 1 hour after device explant. Similarly, sufficient lactate clearing was observed, with levels returning to baseline even after device explant.

Dr Billig concluded that guidewire-free device placement is feasible and simple to perform with the new Impella device, and therefore likely to result in fewer complications and better patient outcomes in cardiac arrest. ❑

Combining Venoarterial Extracorporeal Membrane Oxygenation and Impella (ECPELLA) Before Reperfusion Mitigates Left Ventricular Loading and Injury Due to VA-ECMO in Acute MI

Presented by Kay Everett, MD, PhD

Beth Israel Deaconess Medical Center, Boston, MA, US

Dr Everett is a Clinical and Research Fellow in Cardiovascular Disease at Beth Israel Deaconess Medical Center and a Postdoctoral Fellow at Tufts Medical Center. Dr Everett's abstract was selected for oral presentation at the 6th A-CURE symposium.

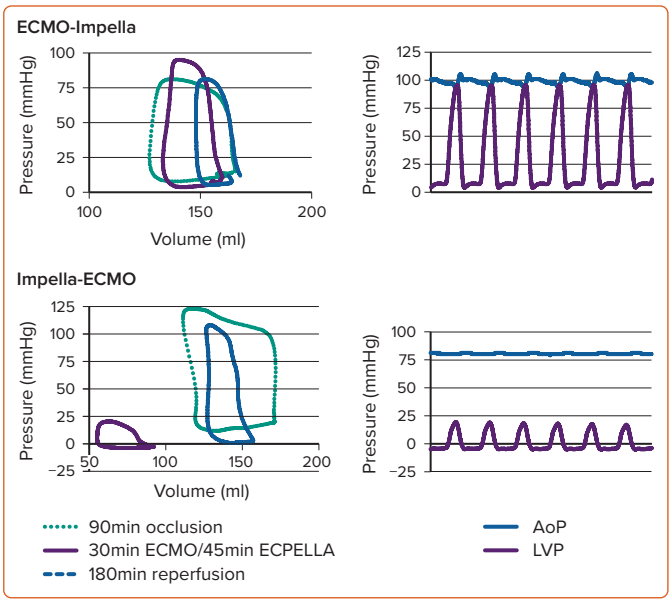
Dr Everett's research aims to understand the ventricular haemodynamics of mechanical circulatory support in acute MI (AMI). She shared her ongoing work examining how extracorporeal membrane oxygenation (ECMO) with concomitant Impella support (ECPELLA), can mitigate left ventricular (LV) injury and loading due to veno-arterial (VA) ECMO.

Dr Everett opened by reviewing the current mechanical circulatory support tools used in AMI cardiogenic shock (CS). VA-ECMO is widely used in CS. The impact of VA-ECMO on LV physiology depends on a number of factors, including ECMO speed, the degree of LV systolic dysfunction, mean arterial pressure and afterload. It has been shown that higher VA-ECMO flow generates higher afterload, which can worsen LV injury and lead to LV distension. Using pressure–volume (PV) loops, Dr Everett highlighted the differences in effects on LV pressure between ECMO, Impella and ECPELLA. VA-ECMO activation results in elevated LV pressures and volumes; the addition of unloading to ECMO, ECPELLA, mitigates these increases in pressures and volumes, although it is thought this configuration cannot achieve the same degree of unloading as isolated Impella. Dr Everett summarised that haemodynamics data support combining transvalvular unloading, known to offer myocardial protection in AMI, with VA-ECMO, which offers systemic perfusion in CS. It remains to be determined whether the combined unloading and VA-ECMO strategy indeed offers myocardial protection, and the best timing to implement unloading with VA-ECMO in AMI-CS. For her study, Dr Everett hypothesised that compared to ECMO alone, ECPELLA mitigates LV loading and injury when Impella is activated prior to ECMO and reperfusion in AMI.

Dr Everett's work was performed in a porcine model of ischaemia–reperfusion injury (IRI) with mid-left anterior descending artery occlusion followed by reperfusion. Dr Everett compared IRI animals with three groups of mechanical circulatory support: VA-ECMO alone and two ECPELLA groups, one with Impella implanted before ECMO (Impella-ECMO) and one with Impella after ECMO implantation (ECMO-Impella). All three groups had VA-ECMO implantation prior to reperfusion.

Dr Everett's results showed that infarct size was increased with VA-ECMO alone, and this was comparatively reduced in both ECPELLA groups. Samples with the lowest infarct size had the lowest PV area (PVA), which was particularly true for the Impella-ECMO ECPELLA group. A comparison of PV loops revealed that Impella-ECMO also markedly reduced PVA and end-diastolic pressure (*Figure 1*), whereas ECMO-Impella did not. Furthermore, a subset of the Impella-ECMO group achieved large (≥50 mmHg) reductions in ventriculo-arterial (VA) uncoupling, an effect not observed in the other treatment groups (*Figure 1*). Dr Everett observed that these effects correlate with molecular signatures of cardioprotective pathways. Markers for the reperfusion injury salvage kinase (RISK) pathway, which is a known cardioprotective pathway, were evaluated. RISK pathway members Akt, extracellular signal-regulated kinase, and glycogen synthase kinase 3β were significantly upregulated in both ECPELLA groups.

Figure 1: ECPELLA Can Dramatically Reduce Pressure–Volume Area



Panels on the left are pressure–volume loops; panels on the right are pressure versus time tracings at 30 min ECMO/45 min ECPELLA timepoint. AoP = aortic pressure; LVP= left ventricular pressure.

Dr Everett concluded that ECPELLA with Impella initiated prior to VA-ECMO reduces infarct size and LV PVA and increases VA uncoupling and cardioprotective signalling in IRI. Together, these results suggest that early LV unloading coupled with VA-ECMO may mitigate LV injury in AMI-CS. ❑

Negative Effects of Acute Reloading after Mechanical Left Ventricular Unloading for Acute MI in a Pig Model

Presented by Renata Mazurek, PhD

Icahn School of Medicine at Mount Sinai, New York, NY, US

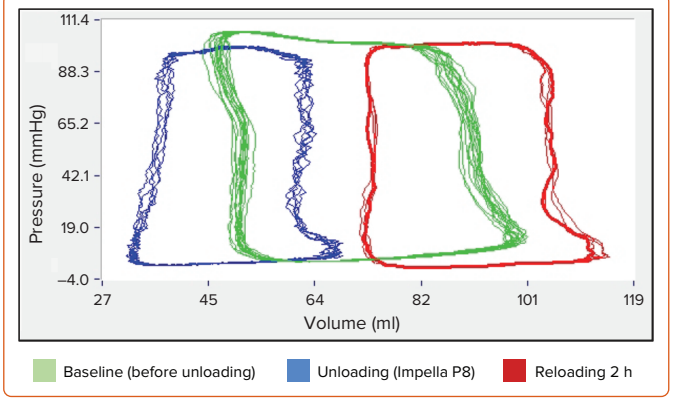
Dr Mazurek is a postdoctoral fellow at the Icahn School of Medicine at Mount Sinai. Dr Mazurek is the recipient of the 6th A-CURE Young Investigator Award.

Ventricular unloading in the setting of MI has demonstrated promising results in preclinical settings, with improved perfusion and reduced infarct size. However, as studies progress towards clinical applications, there is a lack of data on the effects of device removal on outcomes. Maximising the therapeutic benefits of unloading requires evaluation of the effects of device explant and reloading. Using a porcine large animal model of ischaemia–reperfusion injury (IRI), Dr Mazurek hypothesised that acute support removal, or 'acute reloading', is detrimental to the heart, but gradually reducing support prior to device removal ameliorates the negative effects of reloading.

First, Dr Mazurek tested whether 'acute reloading' causes any damage in healthy hearts. In healthy adult pigs, pressure–volume (PV) loops were recorded at baseline and after acute reloading: that is, 2 hours of unloading with the Impella device at the maximum possible support level, then weaning off the device by stopping support in a single step. PV loops after acute reloading showed a rightward shift rather than a return to baseline, possibly suggesting decreased contractility with acute reloading in normal hearts (*Figure 1*). In support of this finding, key parameters of systolic function, such as cardiac output and maximum dP/dt, were decreased 2 hours after acute reloading. End-diastolic wall stress was also affected, demonstrating a significant increase 5 minutes after reloading. In addition, increases in the apoptotic markers caspase-3, p53 upregulated modulator of apoptosis (PUMA) and terminal deoxyribonucleotidyl transferase-mediated dUTP–digoxigenin nick end-labelling (TUNEL) staining demonstrated that cardiomyocyte apoptosis occurred with acute reloading.

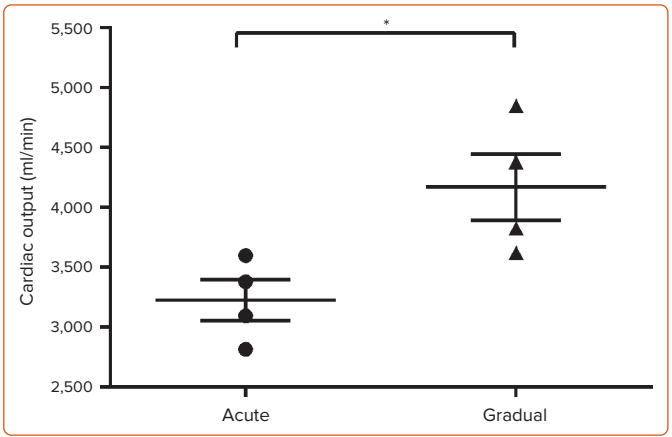
With the potential harm of acute reloading established, Dr Mazurek tested the effect of reloading in the porcine IRI model. Following 90 minutes of left anterior descending artery occlusion, Impella support was initiated 30 minutes prior to reperfusion. Acute reloading involved simply stopping and explanting the Impella device after 90 minutes of support, whereas gradual reloading involved stepwise reloading where the Impella device settings were reduced by one P-level every 15 minutes prior to device explantation. All animals were allowed to recover for 1 week after explant and were then assessed for haemodynamics and tissue remodelling. In a heart with IRI, gradual reloading resulted in significantly higher cardiac output than in the acute group (*Figure 2*); ejection fraction, as well as circumferential and longitudinal strain, showed trends towards improvement. Both infarct size and no-reflow areas were reduced in the gradual reloading group compared with the acute group.

Figure 1: Acute Reloading in Healthy Swine Heart Results in a Rightward Shift in Pressure–Volume Loops



Representative pressure–volume loop from healthy pigs (n=5).

Figure 2: Cardiac Output in the Gradual and Acute Reloading Groups After 1 Week of Recovery



*Cardiac function was assessed 1 week post MI and reperfusion with Impella support. Cardiac output was significantly higher with gradual reloading during Impella weaning (n=4, *p<0.05).*

Dr Mazurek concluded that a strategy of gradually reducing mechanical support prior to device explantation ameliorates the negative effects of reloading, making the exit strategy an important consideration in the clinical setting. ❑

Innovation Lecture: Current Understanding of the Molecular Mechanisms of Unloading and Recovery – Past, Present and Future

Presented by Navin Kapur, MD

Tufts University School of Medicine, Boston, MA, US

Dr Kapur is a faculty of the A-CURE Working Group and an associate professor at Tufts University School of Medicine. He serves as the executive director of the Cardiovascular Center for Research and Innovation and director of the Acute Mechanical Circulatory Support Program, the Interventional Research Laboratories and the Cardiac Biology Research Center, Molecular Cardiology Research Institute at Tufts Medical Center.

Dr Kapur's talk covered the new and rising areas of research interest in the field of ventricular unloading.

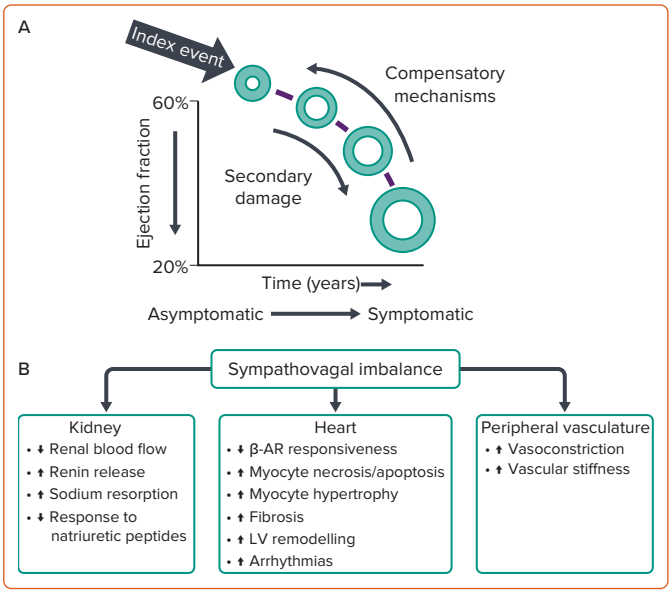
In the field of cardiac unloading, emerging research topics include heart failure and heart recovery. Despite advances in drug and device therapies, the prognosis for heart failure is poor and the disease burden is increasing in the US. This continued clinical need provides the rationale for gaining a better understanding of the physiology and biology of heart failure and remodelling. Research efforts have uncovered many molecular players in the myocardial response to damage and compensatory mechanisms.[1] Dr Kapur noted that the big question is whether the damaged heart reverse remodel back in the current era (*Figure 1*).

Another topic in the field is the question of elective coronary revascularisation. In patients with acute MI (AMI) presenting with or without shock, revascularisation is a must to rescue the myocardium from ischaemia. However, recent surgical and percutaneous coronary intervention (PCI) literature has reported that patients with ischaemic cardiomyopathy (ICM), early or late stage, may also benefit from revascularisation. From a metabolic perspective, the normal myocardium prefers fatty acid oxidation and oxidative phosphorylation to generate ATP, whereas myocardium under ischaemia has to shift to inefficient glycolysis (*Figure 2*), limiting its recovery potential. The other key factor in this setting is that adverse cardiac remodelling is load dependent: analysis of large randomised control trials showed that reduced left ventricular (LV) end systolic volume is indicative of favourable clinical outcomes in revascularisation, suggesting that load reduction is beneficial in ischaemia.[2] Studies are underway to evaluate whether unloading during revascularisation in AMI or ICM additionally promotes myocardial recovery.

Bringing these concepts together, the ultimate question for the cardiac unloading community is whether acute cardiac unloading can be harnessed as a therapeutic approach to improve myocardial recovery. It will be important to test unloading as a therapeutic strategy beyond its current role as an enabler of adjustive procedures, in particular in reversible damage settings such as AMI.

The concept of unloading as a therapy is supported by historical haemodynamic science, going back to Drs Frank and Starling in the 1800s. Fundamental studies in haemodynamics demonstrated that myocardial oxygen consumption is proportional to mechanical work, and calcium cycling and basal metabolism constitute basal oxygen consumption.[3,4] The advent of LV assist devices in the 2000s presented a major paradigm shift in the field of cardiac replacement and recovery. This

Figure 1: Pathogenesis of Heart Failure with Reduced Ejection Fraction



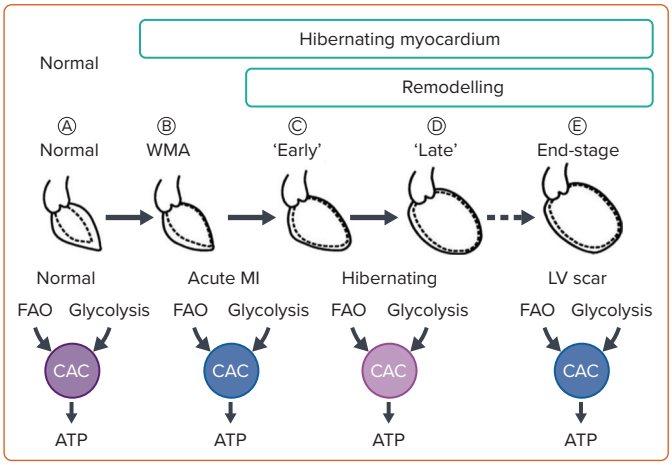
CAC = citric acid cycle; FAO = fatty acid oxidation; LV, left ventricle; WMA = wall motion abnormality. Source: Mann and Felker 2021.[1] Reproduced with permission from Wolters Kluwer Health.

was the beginning of a shift to understanding how reduced pressure–volume area and work aid in heart recovery. As a result, there are now a range of opportunities to intervene with unloading in the clinical setting, including AMI with or without cardiogenic shock (CS), high-risk PCI, acute decompensated heart failure (ADHF), ADHF with or without CS and advanced HF.

The concept of reducing myocardial oxygen demands in AMI was first introduced in 1971.[5] That seminal study demonstrated that, in addition to restoring the blood flow, reducing myocardial oxygen demand further reduced the infarct scar and damage. Ventricular load in ischaemia refers to any variable that increases myocardial oxygen demand, such as heart rate, LV wall stress, LV systolic and diastolic pressures and stroke work. These variables are now being considered through the lens of unloading, and many interesting studies are underway.

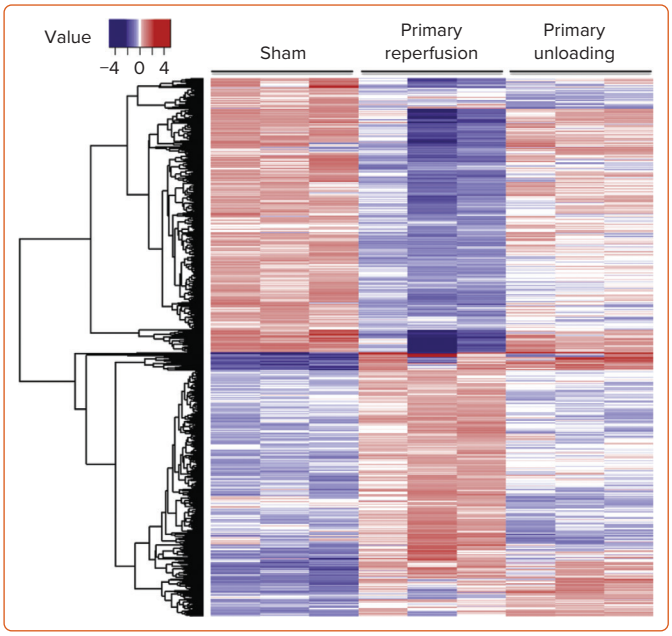
Most cardioprotective approaches in MI have historically focused on reducing reperfusion injury, but new approaches are investigating how reducing ischaemic burden can change the trajectory of myocardial damage. The concept that 'time is muscle' is extremely important;

Figure 2: Coronary Revascularisation: A Metabolic Perspective



β-AR = β-adrenoceptor; CAC= citric acid cycle; FAO= fatty acid oxidation; LV = left ventricle. WMA = wall motion abnormality. Adapted from: Rahimtoola et al. 2006.[13] *Used with permission from Elsevier.*

Figure 3: Microarray Analysis and Preservation of Mitochondrial Integrity with Left Ventricular Unloading



Source: Esposito et al. 2018.[10] *Reproduced with permission from Elsevier.*

however, it is also important to recognise that unloading may now create a window in the time trajectory to allow other strategies of intervention.

The development of transvalvular pumps, such as Impella, has expanded the field of ventricular unloading. One of the earliest mechanistic studies with Impella showed that the mechanism of myocardial salvage involved not only increased myocardial perfusion, but also a reduction in metabolic requirements.[6] In that study, Meyns et al. showed that reduced myocardial oxygen consumption under unloading was correlated with reduced infarct scar. This occurred not only during the reperfusion phase, but also during the ischaemic phase, uncoupling ischaemia from reperfusion.[6]

The timing of unloading is another important research topic. A number of ongoing studies are investigating the timing of unloading with regard to reperfusion, as well as the impact of unloading on coronary blood flow. For example, recent work showed that Impella unloading prior to reperfusion increases coronary collateral flow, which continues to increase over 30 minutes and optimises flow prior to opening a blocked artery.[7] Dr Kapur and colleagues demonstrated that mechanical unloading for 30 minutes prior to reperfusion not only reduced infarct size, but also produced measurable changes in the cardioprotective signalling pathways;[8] this was further improved by lengthening the unloading prior to reperfusion to 60 minutes.[9] Dr Kapur's group also performed transcriptomic profiling of the hearts after primary reperfusion versus primary unloading, identifying an array of differentially altered genes and pathways (*Figure 3*),[10] which warrants continued investigation and therapeutic development. One of the major pathways altered was mitochondrial metabolism; genes related to mitochondrial integrity, as well as the physical structure, were protected in the primary unloaded hearts.[10]

This has highlighted the need to study the role of dysfunctional mitochondria in myocardial recovery. Hypoxia, and particularly the gene hypoxia inducible factor 1 (*HIF-1*), is a marker of the level of ischaemia in a tissue. Dr. Kapur noted the possibility that HIF1 may be a therapeutic target in ischaemia, as well as in unloading and myocardial recovery. Dr Kapur's recent work showed that unloading promotes increases in myocardial HIF-1 expression; using molecular tools, his group showed that increased HIF-1 was necessary for reductions in infarct size with unloading.[11] Furthermore, unloading increased HIF-1 expression even after reperfusion, suggesting that pharmacological manipulation of HIF-1, in tandem with unloading, could be a novel strategy in further reducing infarct size.

Finally, calcium cycling is another exciting new target for unloading research. Recent work has revealed that there are changes in calcium handling that occur days and weeks after a period of unloading, which is beginning to unravel the long-term implications of calcium cycling on myocardial recovery.[12] A deeper dive into extracorporeal membrane oxygenation (ECMO) is also ongoing, because how ECMO affects right ventricular or LV biology, vascular biology or the kidney is currently poorly understood.

Dr Kapur closed by highlighting the great scientific achievements the A-CURE research community has brought forth over the years: many more exciting findings are to come. ❑

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Keynote Lecture: Treatment of Stage D Heart Failure – Devices, Drugs, Biology and Genes: Evidence and Guidelines

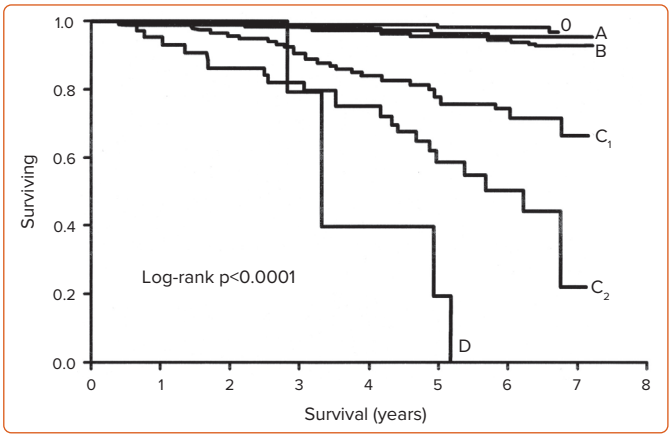
Presented by Clyde Yancy, MD, MSc

Northwestern University Feinberg School of Medicine, Chicago, IL, US

Dr Yancy is the Chief of Cardiology and the Associate Director and Professor of Medicine and Medical Social Sciences at the Bluhm Cardiovascular Institute at Northwestern Memorial Hospital. He is also the Vice Dean for Diversity and Inclusion at Northwestern University and the Deputy Editor of *JAMA Cardiology*.

Dr Yancy opened his lecture by reviewing the American College of Cardiology (ACC)/American Heart Association (AHA) guideline for Stage D heart failure (HF) management.[1] By the modern definition, HF is partitioned into various stages by the level of left ventricular ejection fraction (LVEF) exhibited.[2] In particular, Dr Yancy aimed to illustrate how unloading the left ventricle (LV) can improve LVEF in HF with mid-range ejection fraction and HF with improved ejection fraction (HFimpEF). By definition, HFimpEF patients must have received guideline-directed medical therapy (GDMT) and subsequently improved LVEF at least 10 percentage points to ≥40% from a previously reduced baseline.[3] This improvement is not thought to be a measurement phenomenon, but rather represents a distinct biological phenotype with corresponding clinical outcomes. As such, the new definition of HF accounts for the specific symptoms and signs of HF, and these symptoms and signs must be corroborated by either elevated natriuretic peptide levels, objective evidence of cardiogenic, pulmonary or systemic congestion or both.[2] This altered definition, which provides quantifiable metrics for determining the stage of HF, changes the algorithm for the use of GDMT to include the concept of HF in remission.

Figure 1: Prevalence and Prognostic Significance of Heart Failure Stages

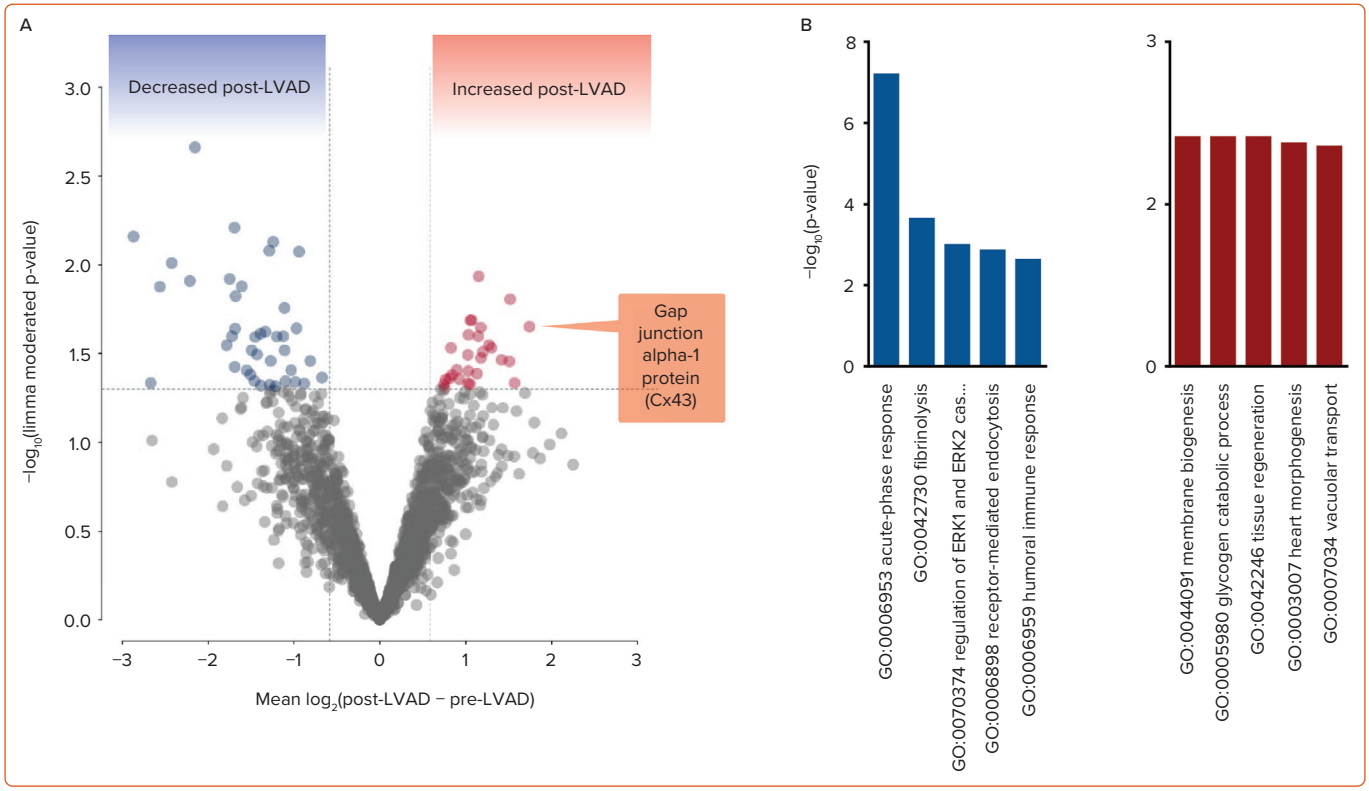


Source: Ammar et al. 2007.[4] Used with permission from Wolters Kluwer Health.

Dr Yancy emphasised that patients with Stage D HF are a population with a number of unmet needs, including effective treatments to improve long-term survival (*Figure 1*).[4] Current therapeutic options for select patients with advanced HF include heart transplant, mechanical circulatory support (MCS) as a bridge to transplant or bridge to candidacy and long-term MCS as destination therapy (DT). Dr Yancy highlighted that current ACC/AHA guidelines do not contain any Class I recommendations for the use of MCS in HF; however, there are several Class IIa recommendations in place. He noted the current evidence level in support of MCS is rated 'B'; more robust data are needed to move that recommendation to Class I.

In order to achieve recovery in these patients, clinicians must focus not only on the macro effects of LV unloading, such as flow rate, or the incidence of complications, like thrombosis, but also study the micro effects of unloading. In particular, consideration must be given to the biological changes in myocytes, changes to the myocardial tissue and changes in circulating systemic markers.[5] In a recent study, five HF patients with an LV assist device (LVAD) were analysed with pairwise tissue sampling at the time of LVAD implementation and LVAD removal at autopsy to compare proteomic and metabolomic alterations.[6] The researchers found significantly decreased expression of genes associated with fibrosis, extracellular signal-regulated kinase 1/2 regulation and immune response at LVAD implantation, whereas the expression of genes associated with tissue regeneration, heart morphogenesis, vacuolar transplant and myocyte metabolism was significantly increased after ≥1 year of LVAD support (*Figure 2*). Of note, connexin-43, a gene involved in the development of gap junctions between cells, was among those significantly increased with LVAD support, and may be a marker of recovery. This was further supported by improved transverse tubule (t-tubule) histology, t-tubules being invaginations of the cell membrane critical to the process of excitation–contraction in cardiomyocytes. After LVAD, the t-tubules were observed to have structurally recovered, indicating the patient experienced restored biological function in the myocardium.[6] Dr Yancy emphasised how using these types of analyses is more sophisticated and informative than a simplified list of clinical symptoms, and that examining these types of datasets can help more precisely refine study populations in future studies.

Figure 2: Impact of Left Ventricular Assist Device on Cardiac Proteome



Proteomic analysis of myocardial tissue collected from patients pre- and post-LVAD (n=5). A: Volcano plot, proteins with >50% increase or decrease with significance are noted in red and blue, respectively. B: Gene ontology of proteins found to be decreased (blue) or increased (red) post-LVAD. Cx43 = connexin 43; ERK = extracellular signal-regulated kinase; GO = gene ontology; LVAD = left ventricular assist device. Source: Shahinian et al. 2020.[6] Reproduced from Wiley under a Creative Commons CC BY licence

Although there is a paucity of large-scale randomised control trials (RCTs) on Impella and LVAD, Dr Yancy highlighted two ongoing trials that are addressing this issue. The Danish Cardiogenic Shock Trial (DanShock) aims to determine whether Impella provides a benefit in the context of acute myocardial infarction with cardiogenic shock (AMICS). Meanwhile, the Impella-supported PCI in High-Risk Patients with Complex Coronary Artery Disease and Reduced Left Ventricular Function (PROTECT IV) trial is of an adaptive design, investigating Impella use during high-risk percutaneous coronary intervention (PCI) in patients with reduced left-sided heart function. Dr Yancy also highlighted another trial that examined intramyocardial injection of mesenchymal precursor cells and subsequent temporary weaning from LVAD support in patients with advanced HF.[7] Although no benefit was observed in that study, it still functioned as a proof of concept for combining device and biological interventions in clinical trials. Furthermore, data presented as supplementary material for that publication showed a signal that patients with ischaemic cardiomyopathy had better success rate than those with non-ischaemic disease, suggesting that recalibration of the patient population to target specific patients, such as that performed by Shahinian et al.,[6] could reveal more information on this form of potential therapy.

The recent first pig-to-human heart transplant has also opened up further discussion on the subject of xenotransplantation. This concept comes with numerous crucial targets, including the prevention of hyperacute rejection, delayed xenograft rejection and the prevention of injection transmission.[8] However, the long-term function of these xenotransplantations poses new questions, including whether the heart will adapt to cardiometabolic stress demands, whether sufficient graft tolerance will allow for reduced immunosuppression, how this transplant will compare to outcomes of human cardiac transplants and other support methods and whether there will be novel ethical considerations. A recent successful kidney xenotransplant into a brain-dead patient revealed the kidney could function normally, and was a successful proof of concept for future investigations and applications.[9]

Dr Yancy next discussed the hurdles to receiving endorsement for novel devices and tools from the ACC, AHA, Heart Failure Society of America and, ultimately, the Food and Drug Administration (FDA). The level of RCT evidence required for the highest class of recommendation (A) has decreased, whereas that for the second (B) class of evidence has increased and that for the third class (C) has markedly decreased.[10] Thus, the bar for Class A is deliberately very high, and achieving these recommendations requires careful calibration of studies. Meanwhile, there are several paths to FDA approval, including: 510(k), which is the most common and involves an iterative process demonstrating that new devices are as safe and effective as prior approved devices; *de novo*, which is for innovative, lower-risk devices that are not comparable to pre-existing devices; and pre-market approval (PMA), which has the most stringent data requirements, is reserved for high-risk devices or when controls cannot be written and that usually uses performance to demonstrate safety and efficacy. To help researchers navigate these considerations, Dr Yancy provided insight from his 10 years at the FDA (*Box 1*). Dr Yancy stated that there must truly be an unmet need, and not simply a market opportunity, and there must be at least some historical or observation comparator data. In addition, although placebo-controlled data are the preferred standard, an alternative could be 'objective performance criteria' (OPC), which can be derived from previous case reports or data. The mode of analysis is also important, and a Bayesian analysis is the preference, as is an intention-to-treat population analysis rather than per-protocol analysis. Finally, as always, the therapy must be

Box 1: Lessons learned from 20 Years on the Food and Drug Administration Cardiovascular Device Panel

- What problem are you trying to solve? Is there an unmet need?
- De minimis: historical or observational comparator data
- Preference: placebo-controlled
- Alternative: 'objective performance criteria
- Analysis: Bayesian with an informed prior
- Intention to treat versus per protocol
- 'Safe and reasonably effective' remains the bar
- NO ventricular assist devices are both guideline-based COR I/LOE A and FDA approved via PMA

COR I = class of recommendation I; FDA = Food and Drug Administration; LOE A = level of evidence A; PMA = pre-market approval.

safe and reasonably effective. It is worth noting that currently there is no ventricular assist device that is both Class I recommended and FDA-approved via PMA.

Dr Yancy proposed that as biological targets evolve and devices improve, the type, quality and precision of evidence should also evolve. Traditional forms of evidence, such as case reports/series, observation studies and phased trials, are slow and expensive, often with small numbers, hidden safety signals and bias. More contemporary forms of evidence, such as single-arm trials with OPC, Bayesian analyses and quality-of-life endpoints, are promising but unproven. The preference remains with RCT design, and the default endpoints remain morbidity and mortality. Dr Yancy anticipates that the future will include more genomic analyses, such as identification of at-risk phenotypes, treatment with induced pluripotent stem cells, gene therapy and genetic engineering. He foresees that data science, Mendelian randomisation, network meta-analyses, 'n of 1' trials, and bioengineering will be at the forefront. These tools may help better collate patient cohorts and speed the process of clinical trials. However, the costs, evidence requirements and implementations of these new frontiers and tools remain to be determined.

Dr Yancy concluded that although the need in the arena of unloading and improving LV performance is great, the science is actively evolving. Breakthroughs should come not just from MCS, but also from biology and genomics, and this will require new surrogate endpoints, including those related to quality of life, proteomics, metabolomics and genomics. Dr Yancy encouraged the exploration of radically new designs, noting that guideline endorsement and FDA approval are possible for new technology, but evidence is paramount. ❑

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Treatment with Impella and Venoarterial Extracorporeal Membrane Oxygenation During Cardiac Arrest Improves Survival: A Multicentre Cohort Study

Presented by Tharusan Thevathasan, MD

Department of Cardiology, Charité – University Hospital Berlin (CBF), Berlin, Germany

Dr Thevathasan is a cardiology resident at Charité – University Hospital Berlin in Berlin, Germany. Dr Thevathasan is the recipient of the 6th A-CURE Best in Research Award.

Dr Thevathasan's work focuses on comparing outcomes of venoarterial extracorporeal membrane oxygenation (VA-ECMO) with VA-ECMO combined with Impella (ECMELLA or ECpella) in patients with cardiac arrest. Past studies in this field have demonstrated that extracorporeal cardiopulmonary resuscitation (ECPR) offers a survival benefit over traditional cardiopulmonary resuscitation (CPR).[1] Despite a 10-fold increase in ECPR usage from 2003 to 2014, overall survival has remained unchanged at approximately 29%.[2] Although studies such as the ARREST trial showed significant survival increases with ECPR,[3] a prospective registry study from the same year revealed virtually identical survival rates between ECPR and conventional CPR,[4] suggesting there are unknown factors involved with the effect of ECPR on survival after a cardiac arrest. Dr Thevathasan aimed to answer these questions by conducting a cohort study of cardiac arrest patients in three tertiary care centres in Berlin over the past 5 years.

Dr Thevathasan and his team hypothesised that the type of ECPR may affect survival outcome. Adult patients with cardiac arrest due to acute MI who were treated with either VA-ECMO or ECMELLA were propensity matched for age, location of cardiac arrest, ECG rhythm and the IABP-SHOCK II score. The primary outcome was 30-day mortality, and secondary outcomes were the lengths of hospital and intensive care unit (ICU) stay. Overall, the cohort of 95 patients had a mean age of 64, with 60% of patients having an in-hospital cardiac arrest; patients had a SAVE score of −9 and relatively few comorbidities, with a Charlson comorbidity index (CCI) of 3. After propensity matching, the ECMELLA group had a 50% lower 30-day mortality risk than patients treated with VA-ECMO alone. Both the hospital and ICU lengths of stay were 50% longer in the ECMELLA group, which can be attributed to the increased survival of this patient group. Multivariate analysis revealed that ECMELLA therapy improved survival in patients who were male, aged ≤75 years, experienced in-hospital cardiac arrest, scored <3 on the CCI or had a greater than Class IV SAVE score. Interestingly, physician experience also played a role, because patients treated by an experienced cardiologist (defined as having treated three or more ECPR cases) also had lower mortality.

Together, these findings suggest that ECPR offers significant survival improvements, and that certain patient characteristics are associated with the best outcomes of ECMELLA therapy.

Similar to previous reports in cardiogenic shock, one of the most frequent complications observed with both therapies in this study was critical bleeding, defined as a drop in haemoglobin of ≥5 g/dL. This complication is likely attributed to the large cannula used for devices, as well as anticoagulation and antiplatelet therapies used after percutaneous coronary intervention. Haemolysis trended higher in the ECMELLA group, likely due to the inlet–outlet interactions and continuous blood flow through the Impella device. These effects have been reported in studies of cardiogenic shock, but not previously in cardiac arrest.[5]

Dr Thevathasan summarised that LV unloading with Impella in patients treated with VA-ECMO was associated with lower mortality rates during ECPR, and that a randomised controlled clinical trial is vital to further evaluate the benefits of left ventricular unloading in patients with therapy-refractory cardiac arrest. ❑

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Complete Revascularisation and Acute Unloading Prior to Percutaneous Coronary Intervention Increases Survival in Acute MI Cardiogenic Shock

Presented by Andreas Schäfer, MD

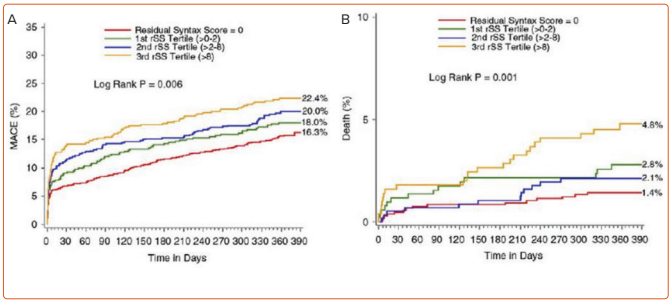
Hanover Medical School, Hanover, Germany

Dr Schäfer is the Deputy Director of Hanover Medical School, in Hanover, Germany, and specialises in interventional cardiology. Dr Schafer is a member of the A-CURE Working Group.

The focus of Dr Schäfer's talk was the impact of complete revascularisation in acute MI cardiogenic shock (AMICS). When considering revascularisation in this context, two methods of percutaneous coronary intervention (PCI) are used: culprit-lesion-only PCI, which involves revascularisation of the lesion involved in the index acute MI; and complete revascularisation, which targets all significant lesions in the coronary tree, not just the culprit lesion.

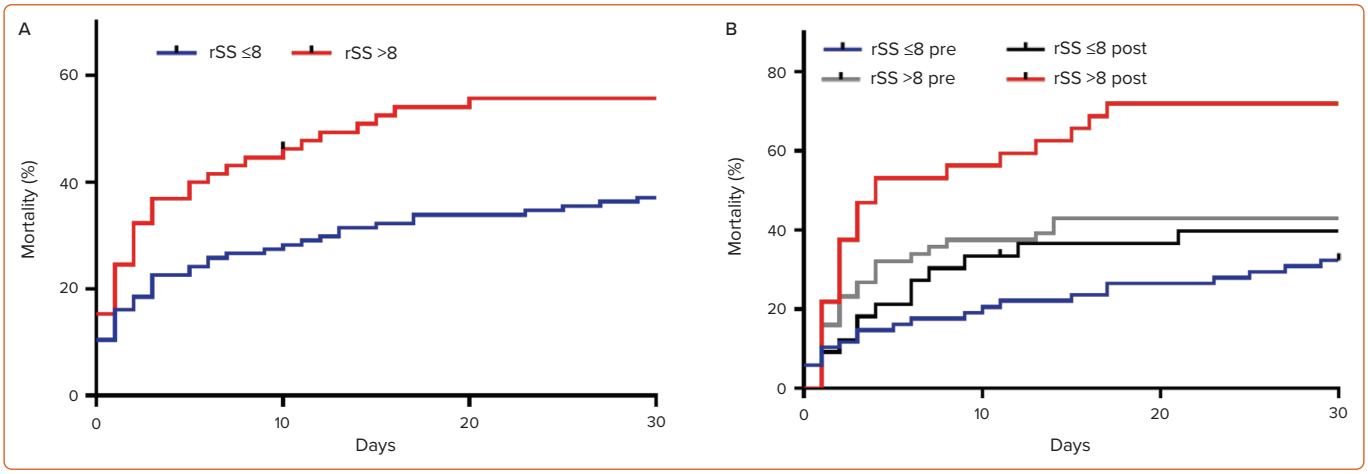
Recent work from the CULPRIT-SHOCK trial has suggested that outcomes with multivessel PCI are inferior to culprit-lesion-only PCI in terms of 30-day mortality.[1] Closer analysis of the results showed that the difference in all-cause mortality between these two PCI methods was 8.2% and that most of this difference can likely be attributed to anoxic brain injury, which was 6.8% higher in multivessel PCI. Brain injury is common in patients who experience cardiac arrest. It has been reported that 50–60% of

Figure 1: Kaplan-Meier Curves Showing Cumulative Event Rates for 1 Year



A: MACE. B: Death. MACE = major adverse cardiovascular events; rSS = Residual Syntax Score. Source: Généreux et al. 2012.[2] Used with permission from Elsevier..

Figure 2: 30-day Mortality in Acute MI Cardiogenic Shock Depending on Timing of Impella and Completeness of Revascularisation



A: Mortality in acute MI cardiogenic shock treated with Impella was lower if complete revascularisation defined by rSS ≤8 was achieved by percutaneous coronary intervention (PCI). B: Lowest mortality was observed in patients receiving Impella pre-PCI and achieving complete revascularisation. Source: Schäfer at al. 2021.[3] Reproduced from Frontiers under a Creative Commons CC BY licence.

AMICS patients in clinical studies have experienced cardiac arrest prior to randomisation.[1] Dr Schäfer believes that the disproportionate representation of brain injury may be related to the high proportion of resuscitated patients in the trial rather than the cardiogenic shock itself. In fact, in the CULPRIT-SHOCK population, the 30-day mortality due to refractory cardiogenic shock was 8.4% lower for multivessel than culprit-lesion-only PCI.[1] In addition, the increased amount of contrast agent and longer procedure duration could have contributed to the adverse outcomes in the multivessel PCI group. Dr Schäfer asserted that outcomes in the multivessel PCI group could be improved by using mechanical circulatory support (MCS).

Specifically, Dr Schäfer presented data from 10 publications showing that installation of MCS and unloading prior to the PCI procedure were consistently associated with improved 30-day mortality outcomes in AMICS patients. Based on the analysis Dr Schäfer's group performed on 166 real-world AMICS patients from four EU centres, the use of Impella as an unloading strategy during multivessel PCI in AMICS patients significantly reduced mortality in the highest-risk group stratified by the SHOCK-II score.

Although assessing complete revascularisation is difficult, the Residual Syntax Score (rSS), which measures the burden of residual coronary artery disease after PCI, is an independent predictor of cardiac death and MI in acute cardiogenic shock PCI patients.[2] An rSS <8 indicates complete revascularisation and is associated with significantly reduced rates of major adverse cardiac and cerebrovascular events, as well as improved survival rates (*Figure 1*). Dr Schäfer and his team used the rSS to investigate the effect of complete revascularisation while on Impella CP support before PCI in AMICS. Mortality rates were significantly reduced among patients who achieved an rSS ≤8 than among patients with an rSS >8 ($p<0.0001$; *Figure 2A*). Furthermore, mortality was significantly reduced among patients who received Impella support before versus after PCI for both rSS groups. Together, the data indicate that patients with an rSS ≤8 who received Impella support before PCI had the lowest mortality rates, whereas mortality rates in patients with an rSS >8 who received Impella support after PCI were the highest (*Figure 2B*).

Dr Schäfer concluded that implanting the Impella CP prior to PCI, with the goal of complete revascularisation while on Impella support, resulted in decreased mortality rates in patients with AMICS. ❑

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Effect of Ventricular Unloading on Heart Recovery

Presented by Carsten Tschöpe, MD

Berlin Institute of Health at Charité, Berlin, Germany

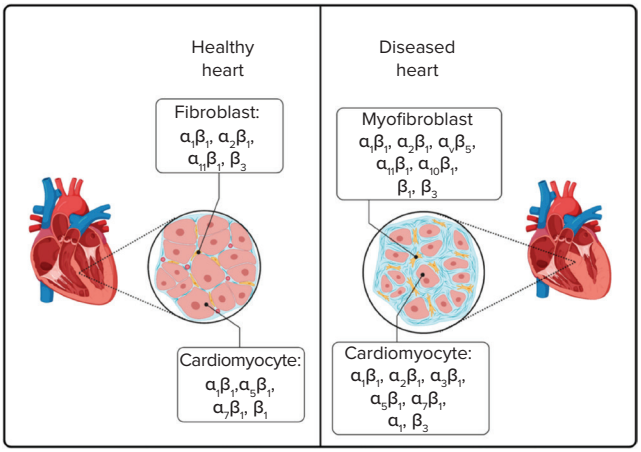
Dr Tschöpe is a Professor of Medicine and Cardiology and the Vice Director of the Department of Cardiology at the Cardiology Department at the Berlin Institute of Health at Charité (BIH) in Berlin, Germany. His main research interests are the potential of cell therapies to cure heart failure and the role of the immune system in heart failure.

In cardiac disease resulting in severe heart failure, there are numerous molecular effectors translating the change in wall stress to cardiac remodelling. Various molecules act as sensors, reacting to mechanical stress and altering the mechanical properties of the heart by means such as cardiac fibrosis, and ultimately affecting cardiac contractility. Such sensors include integrins and their downstream products, with differential expression between healthy and diseased hearts (*Figure 1*). Cardiomyocytes express several integrin transmembrane receptors, including $\alpha_1\beta_1$-, $\alpha_5\beta_1$-, $\alpha_7\beta_1$- and β_1-integrin. These receptors are critical components of the pathway affecting Titin regulation, controlling the force and stiffness of myocytes. In cardiac fibroblasts, $\alpha_1\beta_1$-, $\alpha_2\beta_1$-, $\alpha_{11}\beta_1$- and β_3-integrin are involved in the response to mechanical stress, stimulating the production of collagen and extracellular matrix remodelling. In diseased myocardium, as in dilated cardiomyopathy (DCM), there is a change in integrin expression patterns in myocytes and fibroblasts.[1]

Dr Tschöpe hypothesised that effective prolonged unloading with Impella (termed 'PROPELLA') targets integrin-related cardiac remodelling pathways in patients with severe heart failure in non-classical cardiogenic shock (Society for Cardiovascular Angiography and Interventions [SCAI] A/B) and set out to test whether PROPELLA can be a bridge-to-recovery strategy for these patients, potentially avoiding the use of permanent mechanical circulatory supports such as durable left ventricular assist devices.

Using mass spectrometry, Dr Tschöpe's team analysed cardiac biopsies from severe myocarditis patients with DCM bridged with PROPELLA. Samples were collected at baseline, during Impella support and 5–6 months after device explant. Principal component analysis demonstrated a marked shift in protein expression patterns across these time points. Quantitative polymerase chain reaction analysis of gene expression revealed that the expression of the integrin receptors, specifically α_1-, α_5-, α_6- and α_{10}-integrin, decreased significantly during unloading with Impella and returned to baseline levels after explanting the device. Similar to integrin receptor expression, immunohistochemical staining for four different inflammatory cell populations showed that immune cell presence decreased during active unloading time points. Interestingly, during unloading, collagen and matrix protein (e.g. vimentin) expression was reduced and remained reduced after Impella weaning. Phosphorylation of Titin, a critical component of myocardial stiffness, was increased during

Figure 1: Integrin Expression in Healthy and Diseased Heart



Diseased heart has a higher proportion of myofibroblasts than a heart in healthy condition. Both myofibroblasts and cardiomyocytes show modified expression of integrins in the diseased state. Source: Meagher et al. 2021.[1] Reproduced from MDPI under a Creative Commons CC BY-NC licence.

Impella therapy, along with protein kinase A and G activity, both of which are important for Titin phosphorylation; these changes were maintained after removal of the device. Together, the data indicate that unloading modifies integrin-related systems, including improving Titin phosphorylation, energy metabolism, collagen expression, inflammation and the immune system response.[2]

Dr Tschöpe noted that a mismatch can occur between mechanical and molecular unloading in a subset of patients, in whom mechanical improvements in conductance measurements are observed but integrin and immune signalling fail to respond to Impella unloading. Consequently, these patients exhibited no benefit after Impella weaning.

Dr Tschöpe concluded that PROPELLA may favourably alter cardiac remodelling in patients at risk of severe heart failure. Identifying non-invasive markers will help determine which patients may benefit from a bridge-to-recovery strategy with PROPELLA and which patients will not recover with prolonged unloading. ❑

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Wall Motion Score Index in Revascularisation and Ventricular Recovery

Presented by Enrico Romagnoli, MD, PhD

Department of Cardiovascular Sciences, Gemelli University Hospital, Rome, Italy

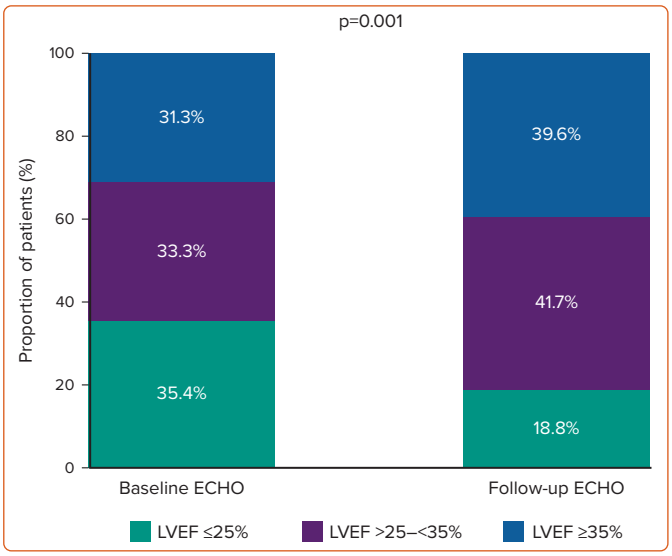
Dr Romagnoli is the Medical Director of the Department of Cardiovascular Sciences at Gemelli University Hospital, Rome, Italy.

Dr Romagnoli's work examined the correlation between the extent of myocardial revascularisation and the functional recovery of the left ventricle (LV) in Impella-protected percutaneous coronary intervention (PCI) patients. LV support is often used in complex and high risk indicated procedures/patients (CHIP). These patients generally present with both LV dysfunction and severe coronary artery disease (CAD), as indicated by a high British Cardiovascular Intervention Society myocardial jeopardy score (BCIS-JS). (The BCIS-JS is a simplified scoring system that classifies the extent of CAD by estimating the amount of myocardium at risk based on the location of coronary artery stenoses. The BCIS-JS is similar to the SYNTAX score, which also uses the number of coronary lesions and their complexity, location and functional impact on the vasculature to qualify the myocardium's condition.[1])

In patients with LV dysfunction and severe CAD, the risk of intraprocedural heart failure is the key factor driving the choice of Impella support in both acute and stable patients. Dr Romagnoli emphasised that the goals of using an Impella device are to reduce periprocedural complications and in-hospital mortality, as well as to achieve a more complete revascularisation regardless of anatomical complexity. Although there is clear clinical evidence to support these intraprocedural or in-hospital benefits,[2–6] Dr Romagnoli noted the evidence for long-term benefit is still debated. Therefore, his group sought to determine whether the beneficial effects on procedural outcomes in protected PCI are consistent with functional LV ejection fraction (LVEF) improvement and recovery.

Dr Romagnoli and colleagues designed the ImpEco study, a prospective single-centre registry investigation. The primary goal of the study was to determine whether the acute procedural outcome of Impella-protected PCI in patients with LV dysfunction is associated with substantial LV recovery at follow-up. The study included 48 patients who required mechanical circulatory support during elective or urgent revascularisation. BCIS-JS was collected at the time of angiography, whereas the Wall Motion Index Score (WMSI) and LVEF were collected from transthoracic echocardiography at baseline and within 1 year after the procedure (mean follow-up time: 146 days [42–381]). Dr Romagnoli and colleagues combined the WMSI and BCIS-JS by analysing the changes in WMSI in each ventricular segment according to the segment's revascularisation status according to the BCIS-JS.Almost all patients (97.9%) had multivessel disease. Both the BCIS-JS and SYNTAX scores were markedly reduced from preprocedural levels, with an overall revascularisation index of 76%. After a median follow-up of 4 months, echocardiographic results revealed no changes in LV end-diastolic and end-systolic diameters, indicating that the patients had not experienced negative remodelling. Conversely, LV end-systolic volume was significantly reduced and LVEF was significantly increased (*Figure 1*), indicating increased contractility and function. Diastolic function, represented by the E/A ratio, improved as well. The WMSI showed the most significant improvement at follow-up. Interestingly, the improvement was driven by the changes in the revascularised segments, with no change in the non-revascularised segments. The improvement in WMSI was proportional to the dysfunction at baseline and was correlated with the extent of revascularisation.

Figure 1: Left Ventricular Function Improvement After Revascularisation



At follow-up echo assessment, LVEF was significantly improved in patients compared to baseline with a greater proportion of patients in the higher LVEF groups. ECHO = echocardiography; LVEF = left ventricular ejection fraction.

Dr Romagnoli concluded that in patients with severe CAD and LV dysfunction, Impella support allowed for more extensive revascularisation. More complete revascularisation was associated with mid-term LV contractile recovery, in terms of both systolic and diastolic function. In addition, regional wall motion recovery was more evident in revascularised segments and was correlated with preprocedural dysfunction, which suggests the possibility of a multimodal imaging approach to optimise and personalise revascularisation strategies in patients with such complex presentations. ❑

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The 'Hack Attack' Program: Enabling 24/7 Enrolment in the STEMI-DTU Pivotal Trial

Presented by Haroon Faraz, MD

Hackensack University Medical Center, Hackensack, NJ, US

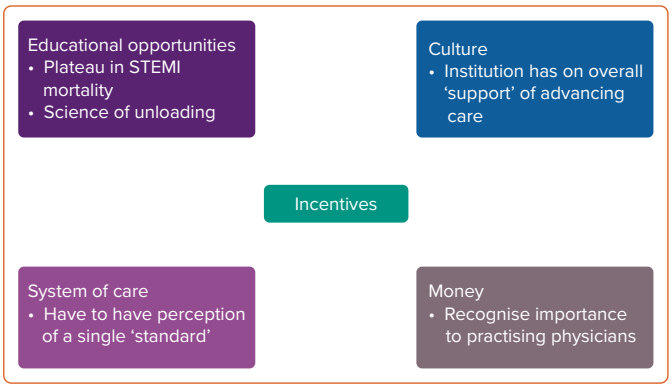
Dr Faraz is the Director of Interventional Cardiology Research at the Hackensack University Medical Center in Hackensack, NJ, US. Dr Faraz is an A-CURE Working Group faculty member.

Dr Faraz discussed the 'Hack Attack' program for the ST-Segment Elevation MI Door-to-Unloading (STEMI-DTU) pivotal trial, covering the process of identifying and enrolling eligible patients at any time of day, any day of the week (24/7). The STEMI-DTU pivotal trial is a prospective multicentre double-arm randomised control trial evaluating patients undergoing Impella or standard of care treatment for a STEMI heart attack.[1] Despite Hackensack University Medical Center being a large-volume tertiary centre with an annual STEMI volume of >100, the initial enrolment for the STEMI-DTU pivotal trial was low, with only 8 of 107 STEMI patients (7.5%) screened for the trial, resulting in one enrolment in 2020. Similarly, in 2021, 22 of 110 STEMI patients (20%) were screened, with only six being enrolled in the trial. Dr Faraz recognised that in order to successfully translate scientific findings to clinical application through a clinical trial, maximising the screening of potential study candidates is crucial because a significant portion of candidates get filtered out by the eligibility criteria.

In order for the clinical trial to enrol enough patients to be successful, the principal investigator (PI) at each site must actively mobilise system resources to maximise possible enrolment. The PI is the primary person responsible for evaluating patients for enrolment in the STEMI-DTU trial; at Hackensack University Medical Center, the PI has a team working together to manage 24/7 enrolment. This team includes four interventionalist faculty members, who can serve in place of the PI in case of multiple simultaneous STEMI presentations, and provide consultations to non-faculty staff for trial screening and enrolment. In addition, eight practicing interventionalists provide 24/7 primary percutaneous coronary intervention (PCI) coverage for STEMI, and these interventionalists are educated and encouraged to notify faculty about potential STEMI-DTU trial candidates.

Dr Faraz noted that due to the 24/7 nature of the enrolment process, the success of the STEMI-DTU trial relies on everyone in the team playing their part. First, the emergency department (ED) physicians have to recognise and activate STEMI in a timely fashion; the on-call cardiologists follow by properly recognising the anterior STEMI without prior cardiac arrest or shock as a potential DTU patient and consult the faculty involved in the trial. The faculty then screens and subsequently qualifies the patient for enrolment after discussion with the national committee via TigerConnect. Research nurses and administrative staff are responsible for data collection and submission. As an example, Dr Faraz provided a case review of a DTU randomised patient, sharing the timeline from STEMI activation through to 6-month follow-up. The patient was activated on a Sunday afternoon in the ED; within 20 minutes, the patient was qualified by the faculty and the national committee, and consented in the ED. Ten minutes after consenting, the patient was on the cath lab table; once femoral access and imaging had been obtained, the patient was randomised. By 1 hour after STEMI activation, the Impella was implanted, with a total DTU time of 81 minutes. Strong communication and teamwork were vital to the successful identification and enrolment of patients in the STEMI-DTU study, as events unfold quickly and require rapid assessment and decisions.

Figure 1: A Key to 24/7 Enrolment is Active Engagement of the Emergency Department and Cath Lab Staff



24/7 enrolment requires team effort. Incentives for individuals involved can be different. Educational opportunity is a universal incentive that can be related to all. Creating a culture of support and perception of single care standard at the institute is another important incentive for different groups involved. Lastly, financial incentive should also be considered.
STEMI = ST-elevation MI.

To achieve the highest success, there must be active engagement and incentives for all levels of the team (*Figure 1*). Dr Faraz concluded by noting that COVID-19 continues to be a significant obstacle to the STEMI-DTU study. He also emphasised that individual clinicians can be unaccepting of paradigm-shifting changes, uninvested in research and possess an intrinsic belief that they already know how to best treat patients presenting with STEMI. These intrinsic biases are significant obstacles to this type of trial and should be kept in mind when enrolling patients in the STEMI-DTU or other similar trials. ❑

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Mechanical Circulatory Support in High-risk Coronary Artery Bypass Graft Surgery

Presented by Ed Soltesz, MD

Department of Thoracic and Cardiovascular Surgery, Cleveland Clinic, Cleveland, OH, US

Dr Soltesz is the Surgical Director of the Kaufman Center for Heart Failure and Recovery and the Program Director for the Department of Thoracic and Cardiovascular Surgery of the Cleveland Clinic in Cleveland, OH, US.

Dr Soltesz discussed how he and his team at the Cleveland Clinic are using Impella 5.5 to support patients who are at high risk for heart surgery. Many high-risk cases are denied surgery due to significant risk of postoperative mortality. Furthermore, many patients who do undergo surgery still require salvage support due to post-cardiotomy cardiogenic shock (PCCS); however, these therapies come with their own significant drawbacks and risks. For example, the intra-aortic balloon pump (IABP) offers minimal support while requiring the patient to be bed-bound and intubated for a prolonged period, and extracorporeal membrane oxygenation (ECMO) also renders the patient bed-bound and intubated while providing poor unloading and a risk of bleeding. As such, some patients are being directly referred to advanced therapies, such as durable left ventricular assist devices.

The Coronary Artery Surgery Study (CASS) trial, which compared the medical and surgical treatment of patients with chronic, stable coronary artery disease, revealed that coronary artery bypass graft (CABG) surgery is demonstrably effective for patients with left ventricular failure.[1] Similarly, the Surgical Treatment for Ischemic Heart Failure (STITCH) trial, which investigated the effect of combining CABG with medical therapy in heart failure patients, demonstrated that, in patients with ischaemic cardiomyopathy, CABG results in a 21% reduction of death from cardiovascular causes at the 10-year follow-up.[2] Dr Soltesz noted that although long-term survival was significantly increased, the risk of death is higher in the first 30 days, suggesting that therapies need to be focused on getting patients through that early hazardous period to reap the long-term benefits. Most early mortalities are due to PCCS, which occurs in 0.2–9% of cardiac surgeries, is difficult to predict and carries a high mortality rate, ranging from 10% to 75%.[3,4] Of note, low ejection fraction, high-dose inotropes and long cardiopulmonary bypass (CPB) times are associated with increased risk.

The primary goal of pericardiotomy assist is to unload the injured ventricle, followed by weaning toxic levels of pressors while maintaining end-organ perfusion and function. At the molecular level, this enables cytokine metabolism and ATP store replenishment, allowing the myocardium to recover. Conventional therapies include vasopressors, inotropes, IABP and venoarterial (VA-) ECMO. Vasopressors and inotropes may not be ideal, because they increase myocardial oxygen consumption and stress the myocardium. IABP offers only a slight reduction in pressure–volume area and increased coronary perfusion, whereas VA-ECMO supports systemic perfusion but is costly in terms of myocardial energetics. Dr Soltesz emphasised that unloading is the key to decreasing the chances of poor outcomes for patients at high risk for CABG. Comparisons of different temporary mechanical circulatory supports (MCS), VA-ECMO, TandemHeart and Impella, clearly reveal that Impella provides the best unloading while setting the stage for end-organ recovery (*Table 1*).

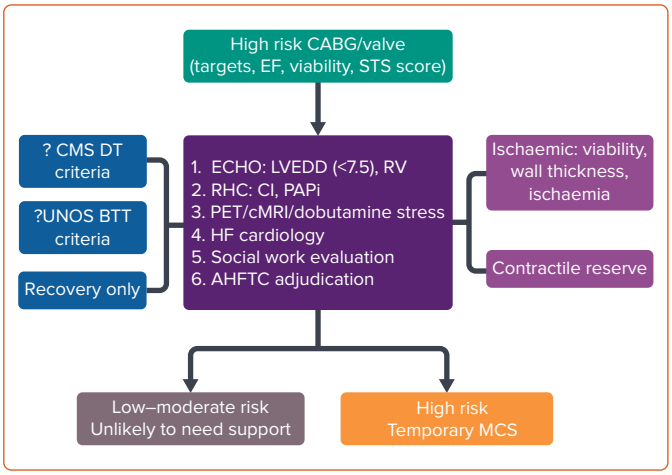
The key to avoiding PCCS is to anticipate it, by performing risk stratification, prehabilitation, planning a temporary MCS and identifying an exit strategy. Defining surgical risk requires consideration of numerous patient factors, as well the quality of the coronary target and the viability of the myocardium. Prehabilitation may include Swan-guided therapy, hepatic decongestion, inotropes and/or vasodilator therapy, and possibly preoperative IABP or temporary MCS. At the Cleveland Clinic, risk evaluation is conducted in a stepwise fashion (*Figure 1*).

Table 1: Energetics of Temporary Mechanical Circulatory Support

VA-ECMO	TandemHeart	Impella
Increases CO	Increases CO	Increases CO
Increases afterload	Mild decrease MVO_2	Decrease MVO_2
Increase MVO_2	No direct LV unloading	Decrease PVA
Increase PVA	Moderate decrease in PVA	Reduces EDP and EDV

CO = cardiac output; EDP = end diastolic pressure; EDV = end diastolic volume; LV = left ventricle; MVO_2 = myocardial volume oxygen; PVA = pressure–volume area; VA-ECMO = venoarterial extracorporeal membrane oxygenation.

Figure 1: Algorithm for High-Risk Cardiac Surgery Evaluation



AHFTC = Advanced Heart Failure Transplant Cardiology; BTT = bridge to transplant; CABG = coronary artery bypass grafting; CCF = congestive cardiac failure; CI = cardiac index; cMRI = cardiac MRI; CMS = Centers for Medicare and Medicaid Services; DT = destination therapy; ECHO = echocardiography; EF = ejection fraction; HF = heart failure; LVEDD = left ventricular end-diastolic diameter; MCS = mechanical circulatory support; PAPi = pulsatility index; STS = Society of Thoracic Surgeons; RHC = right heart catheterisation; RV = right ventricle; UNOS = United Network for Organ Sharing.

Dr Soltesz walked the audience through a case to demonstrate the evaluation system, where a high-risk patient was identified and subsequently treated with CABG and Impella with successful outcomes. Ultimately, the key to success in treating these high-risk patients is both the pre- and intra-operative treatment considerations, which requires assessing the patient thoroughly and providing the best support to reduce mortality risks.

Dr Soltesz concluded that PCCS can be mitigated by minimising CPB time and rapidly escalating the preplanned temporary MCS; pre-emptive use of a pump such as Impella allows left ventricular unloading and improved postoperative recovery. With their algorithm, Dr Soltesz and his team at the Cleveland Clinic have seen improved outcomes with cardiac surgery in properly identified high-risk patients. Defining risk and an exit strategy are key to success. ❑

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Mechanical Circulatory Support in Off-pump Coronary Artery Bypass Graft Surgery

Presented by David Joyce, MD

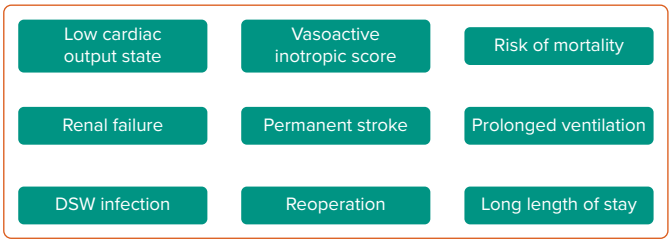
Department of Surgery, Medical College of Wisconsin, Milwaukee, WI, US

Dr Joyce is an Associate Professor in the Department of Surgery at the Medical College of Wisconsin in Milwaukee, WI, US.

Coronary artery bypass graft (CABG) patients are often elderly and have complex disease that requires either surgery or medical therapy. Typically, these patients have high Society of Thoracic Surgeons (STS) risk scores (a calculation that assess a patient's risk of mortality and morbidities for cardiac surgeries), with moderate mitral regurgitation and borderline renal function. Viability studies do not necessarily provide clarification on the best treatment option, leaving clinicians to navigate through multiple options, including CABG, transplant, left ventricular assist devices (LVAD) or a combination of these. It is known that CABG reduces long-term mortality compared with medical therapy over 10 years, but that the first 30 days come with a 4% mortality rate.[1] Thus, therapies should focus on getting through that high-risk, 30-day period.

Dr Joyce and his team have initiated a single-centre prospective observational study examining Impella-supported off-pump CABG in high-risk revascularisations. Enrolment has started with candidate patients who are ≥18 years old, with an ejection fraction of ≤35%, with three-vessel coronary artery disease and with candidate vessel targets evaluated and approved by a surgeon. Enrolled patients will receive an Impella 5.5 prior to undergoing off-pump CAB. The strategy was designed to leverage the benefits of the Impella device for perioperative haemodynamic stability. This prepares the patient for surgery, stabilises them during beating-heart, off-pump revascularisation and prevents the common low output state that presents frequently during the postoperative period. The primary endpoint is intraoperative haemodynamic stability, as determined by a mean arterial pressure >60 mmHg, cardiac index >2 l/min/m^2, central venous pressure <15 mmHg and cerebral near-infrared spectroscopy-measured oxygen at >60%. Secondary endpoints encompass factors included in STS risk analysis (*Figure 1*). Dr Joyce's trial is currently enrolling, and his team looks forward to sharing the outcomes. ❑

Figure 1: Key Secondary Endpoints for the OPCAB Trial



DSW = deep sternal wound.

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Bariatric Surgery Supported With Transvalvular Pumps: New Strategy for Morbidly Obese Patients to Get to Heart Transplantation

Presented by Nicolas Brozzi, MD

Department of Thoracic and Cardiovascular Surgery, Cleveland Clinic, Miami, FL, US

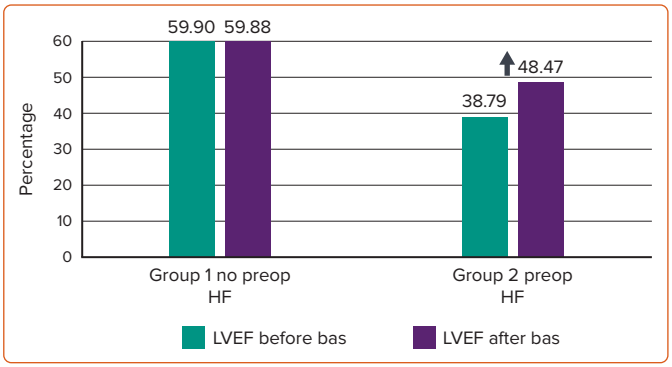
Dr Brozzi is a cardiothoracic surgeon and researcher in the Department of Thoracic and Cardiovascular Surgery at the Cleveland Clinic in Miami, FL, US.

Heart failure is an epidemic in the US, affecting over 6 million people annually, and expected to surpass 10 million within a decade.[1] Of patients with heart failure, approximately 10% progress to advanced heart failure, and patients with disease refractory to medication have high mortality rates of 30–50% within 1 year. The most effective treatment for advanced heart failure patients is a heart transplant, which has survival rates of >50% over 10 years.

One of the factors that can influence heart health and failure is excess body weight. Research on obesity indicates that it can influence metabolic, hormonal and inflammatory systems, which, in turn, can influence cardiac health.[2] Indeed, obesity correlates with increased risk of heart failure and has been rising steadily in the US, creating a need for better understanding and tools to treat obese heart failure patients.[3,4] Bariatric surgery offers benefits for obese patients such as improved cardiovascular risk factors, lipid and inflammatory profiles and left ventricular (LV) function. However, bariatric surgery in heart failure patients results in a marked increase in in-hospital mortality and in-hospital complications, including MI, sepsis and kidney failure.[5] Furthermore, heart transplant outcomes are bleak in obese patients, with increasing BMI correlating with increased 1-year mortality rates.[6]

More recently, the use of LV assist devices (LVAD) has shifted to a destination therapy, particularly in obese patients. As such, these patients represent an underserved population that requires innovative techniques to provide better treatment and outcomes. Dr Brozzi presented two clinical cases of morbidly obese patients with heart failure who were treated with off-label Impella use. The first patient progressed from repeated ventricular arrhythmia to cardiac shock, and was initially stabilised with intra-aortic balloon pumping (IABP), diuretics and IV milrinone. Implantation of an LVAD was not an option due to the risk of complications and patient lifestyle, and therefore an Impella CP was implanted instead, followed by a laparoscopic sleeve gastrectomy 24 hours later. The patient was stable throughout the surgery, with an unremarkable postoperative recovery. Within 2 months the patient had lost ~49 kg (108 lb), and was listed for heart transplant.

Figure 1: Left Ventricular Ejection Fraction Changes After Bariatric Surgery



Source: Sarmiento-Cobos et al. 2021.[6] Used with permission from Elsevier.

The second patient presented with acute heart failure due to non-ischaemic cardiomyopathy. This patient was also stabilised with IABP, diuretics and IV milrinone, and was also declined LVAD support due to potential complications. Instead, an Impella 5.5 was implanted before the patient underwent a laparoscopic sleeve gastrectomy. The patient was stable throughout the surgery with robust haemodynamics; again, patient recovery was unremarkable. The patient lost ~39 kg (85 lb) within 6 weeks and was listed on the heart transplant list. The patient was readmitted 75 days later with cardiogenic shock and was supported with venoarterial extracorporeal membrane oxygenation, but received a heart transplant 8 days later. Ultimately, the patient survived and was stable 3 months after transplant with a BMI of 35.5 kg/m^2.

Dr Brozzi concludes that these cases demonstrate that bariatric surgery supported with transvalvular axial flow pumps is a feasible alternative to expedite weight loss and the heart transplant listing of severely obese patients with advanced heart failure. ❑

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Impella-supported MitraClip in Cardiogenic Shock Patients Complicated With High-grade Mitral Regurgitation

Presented by Divya Ratan Verma, MD

SSM Health Saint Louis University Hospital, St Louis, MO, US

Dr Verma is a structural cardiologist from the SSM Health Saint Louis University Hospital in St Louis, MO, US.

High-grade or acute mitral regurgitation (AMR) is difficult to treat and the medical management of these cases has very poor outcomes with regard to survival. Ruptures are more common in the posterior medial than anterior lateral papillary muscle due to the single blood supply coming from the posterior descending artery. This can often be corrected by transcatheter edge-to-edge repair (TEER) surgery, which repairs the rupture to correct mitral valve function, but this is not always an option due to the severity of presentation and low surgical survival odds. AMR results in increased left ventricular (LV) and atrial volumes and pressures, decreased ejection fraction and pulmonary congestion, and the decreased systemic flow can result in cardiogenic shock (CS). The SHOCK trial, which examined direct invasive emergency revascularisation in patients with CS complicating acute MI, showed in-hospital mortality of 71% for AMR shock patients and 40% for surgical candidates.[1] These mortality rates have remained steady since the publication of that study in 2000, demonstrating a clear unmet need for this population.[2] Dr Verma and his team therefore asked whether mechanical circulatory support (MCS) with Impella, followed by repair of the mitral valve with MitraClip and TEER, can improve the survival of these patients.

Recent published case reports have revealed desirable haemodynamics (increased blood pressure and reduced left atrial pressure) for AMR patients who received MitraClip therapy, as well as improved forward systemic flow.[3,4] In addition, these case reports revealed no evidence of patients with a low cardiac output state after Mitral clipping, which has been reported historically in patients who undergo surgery for AMR.[5–7] These improvements observed with percutaneous repair by MitraClip have also resulted in reduced mortality risks at 1 year.[8] Dr Verma and his team hypothesised that Impella can stabilise the patient, which, in turn, can improve the MitraClip surgical process and outcomes. In their study, there was a 100% technical success rate with implementation of the Impella and MitraClip, and all patients were successfully weaned from MCS support after implantation of MitraClip. Patients demonstrated continually improving haemodynamics over 30 days, with greatly reduced mitral regurgitation and steadily increasing LV ejection fraction.[9] The haemodynamic improvements resulted in functional improvements, and Dr Verma and his team observed a survival rate of 86% at 30 days.

Dr Verma reviewed the work-up algorithm that his consortium uses for patient evaluation to determine whether this combined approach is appropriate for each patient's presentation. Patients are initially treated with medication, maximum revascularisation and percutaneous MCS as appropriate, but, if severe mitral regurgitation is still suspected, patients are considered as candidates for TEER, and a heart team consult is obtained. Dr Verma concluded that although AMR is typically associated with significant haemodynamic compromise and poor outcomes, treating patients with Impella and MitraClip plus TEER can provide a survival advantage, and this approach therefore merits further study. ❑

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Distinguished Lecture: Heart Recovery – Insights from RESTAGE-HF

Presented by Emma Birks, MD, PhD

Department of Cardiovascular Medicine, University of Kentucky, Lexington, KY, US

Dr Birks is a Professor of Medicine and Section Chief of Heart Failure, Heart Transplant, and Mechanical Circulatory Support in the Department of Cardiovascular Medicine at the University of Kentucky in Lexington, KY, US. Dr Birks serves as an A-CURE faculty member.

The Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) tracks the outcomes of all implantable devices in the US. According to this registry, the rates of device explantation, a measure of native heart recovery, is extremely low in patients with a left ventricular assist device (LVAD). Dr Birks noted that this is due, in part, to the fact that long-term devices are typically inserted as a bridge-to-transplant strategy. Furthermore, treating centres often lack testing for underlying myocardial function, pump speed optimisation to maximise unloading and drug therapy to promote recovery.

Conversely, when clinicians are using LVADs to attempt to reverse chronic heart failure and induce myocardial recovery, there are numerous crucial steps to take, including: regular, safe, and reliable testing; pump speed increases and drug additions to shrink the heart; medications and techniques designed to maximise recovery durability; and novel explant techniques engineered to minimise trauma to the heart.

In particular, targeted adjuvant therapies that enhance LVAD reverse remodelling are crucial for recovery. The aims of these therapies are to shrink the heart and induce reverse remodelling, enhance contractility, enhance recovery durability and counteract fibrosis. Dr Birks emphasised that she has found aggressive drug therapy in tandem with LVAD support to be critical for recovery, along with regular testing both before and after device removal.[1] Over the years and across studies, device explantation rates have been low (3–24%), but most of these studies included very little or no HF medication therapy and none were optimised as part of the protocol.[2–6]

Conversely, studies such as Dr Birks' that have included aggressive medical therapy in addition to LVAD reveal vastly increased rates of explanted devices of between 50% and 73%.[7,8] More recent studies have provided further evidence that aggressive medical therapy improves survival and quality of life, regardless of patient or pump, suggesting that medical therapy is important in the population regardless of therapeutic aims.[9]

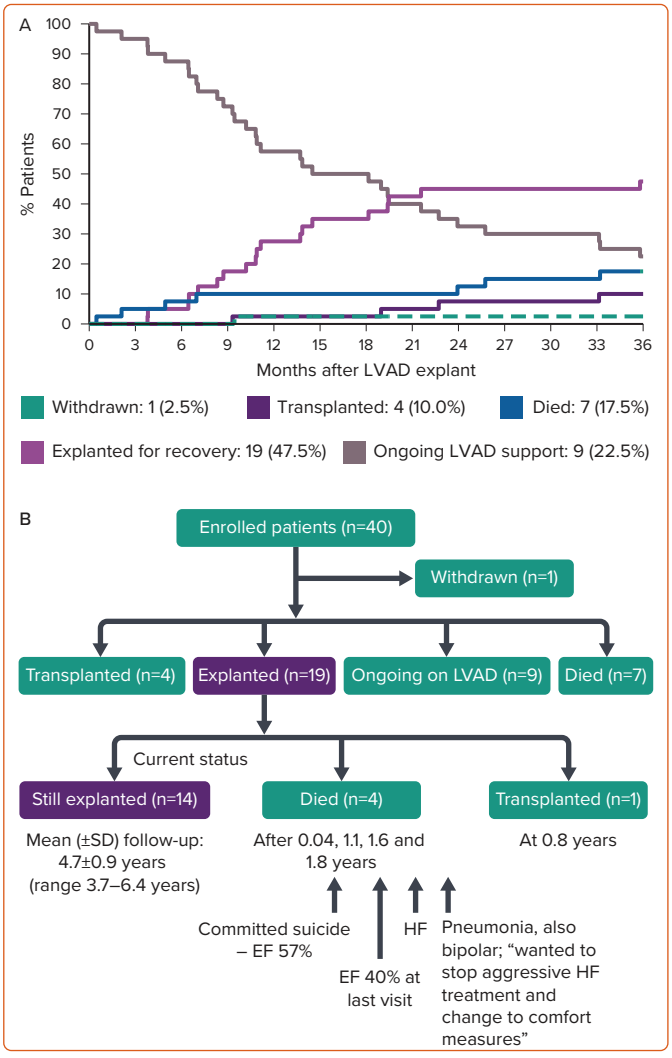
The Remission from Stage D Heart Failure (RESTAGE-HF) study sought to determine whether the aggressive attempts to maximise reverse remodelling and recovery with optimised LVAD and drug therapy are

Table 1: Post-implant Pharmacological Therapy

Drug Name	Maximum Dose	Frequency
Lisinopril (ACEi)	40 mg	Daily
Carvedilol (BB)	25 mg	Three times daily
Sprionolactone (MRA)	25 mg	Daily
Digoxin	125 µg	Daily
Losartan (ARB)	150 mg	Daily

ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; BB = β-blocker; MRA = mineralocorticoid receptor antagonist.

Figure 1: Competing Outcomes Post-LVAD All Enrolled (n= 40)



A: 3-year clinical outcomes post-LVAD implantation for the RESTAGE-HF trial patients (n=40); B: Patient outcomes flowchart for the RESTAGE-HF trial. EF = ejection fraction; HF = heart failure; LVAD = left ventricular assist device.

consistently reproducible. This uniform, prospective analysis was performed across six centres with existing experience of recovering patients, and with specific interest in recovery. The primary objective was to determine the proportion of patients who had sufficient improvement in ventricular function after standardised LVAD and pharmacological therapy and testing to allow removal of the LVAD within 18 months. Furthermore, patients were followed for up to 3 years to determine the durability of sustained remission, ultimately to identify predictors of recovery.[10]

Dr Birks noted that the 18-month window was not necessary, because most recruited patients were on destination therapy, and it is likely that future studies would not include this limit. The device explant criteria at zero flow (6,000 RPM) were: left ventricular (LV) end-diastolic diameter (LVEDD) <60 mm, LV end-systolic diameter <50 mm, LV ejection fraction >45%; LV end-diastolic pressure or pulmonary capillary wedge pressure ≤15 mmHg; resting cardiac index >2.4 l/min/m^2; and with or without myocardial volume oxygen >16 ml/kg/min. Dr Birks and her team hypothesised that >10% of patients would achieve the primary endpoint of being free from mechanical circulatory support or heart transplant by 1 year after LVAD removal.

Dr Birks described how she and her team used echocardiography early and often in the patient care timeline to optimise the LVAD pump speed for each patient and to monitor LV function. Pump speed was increased in increments of 200 RPM while maintaining blood pressure <100 mmHg. This was continued until LVEDD was <60 mm and mitral regurgitation was Grade 2 or less.

In addition, a combination of drugs was used at varying frequencies, but notably not clenbuterol (*Table 1*). Once the echocardiography explant criteria were met, patients underwent right heart catheterisation to test how well the heart was pumping, on normal and low flow, for 15 minutes.

Of 40 patients, 19 were ultimately explanted for recovery (47.5%; *Figure 1A*). Furthermore, of the 19 explanted patients, 17 were still in remission after >1 year, one had died from unrelated causes and one was transplanted. Overall, 16 of 40 patients (40%) achieved the primary endpoint, far and above the 10% needed to reject the null hypothesis, and long-term follow-up revealed that 14 of 40 patients were still explanted at a mean (± SD) of 4.7 ± 0.9 years, demonstrating robust long-term recovery (*Figure 1B*).

Dr Birks expanded on the study outcomes, with univariate and multivariate analyses revealing that a predischarge LVEDD of <60 mm and a reduction in LVEDD of >7.5 mm between pump implantation and early after explantation were associated with a higher likelihood of having the device explanted and achieving recovery. Together, these findings suggest that those patients who respond early after device implantation with shrinking heart size have the best chance of ultimately recovering.

Dr Birks summarised that it is possible for patients in late-stage chronic heart failure to progress to recovery and eventual LVAD removal with aggressive medical and LVAD therapy. She concluded by emphasising that there is more to be done to optimise pumps and their use, and to identify novel medical approaches to enhance reverse remodelling and improve long-term patient outcomes and quality of life. ❑

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Fundamentals of Heart Recovery Versus Remission

Presented by Jane Wilcox, MD

Northwestern University Feinberg School of Medicine, Chicago, IL, US

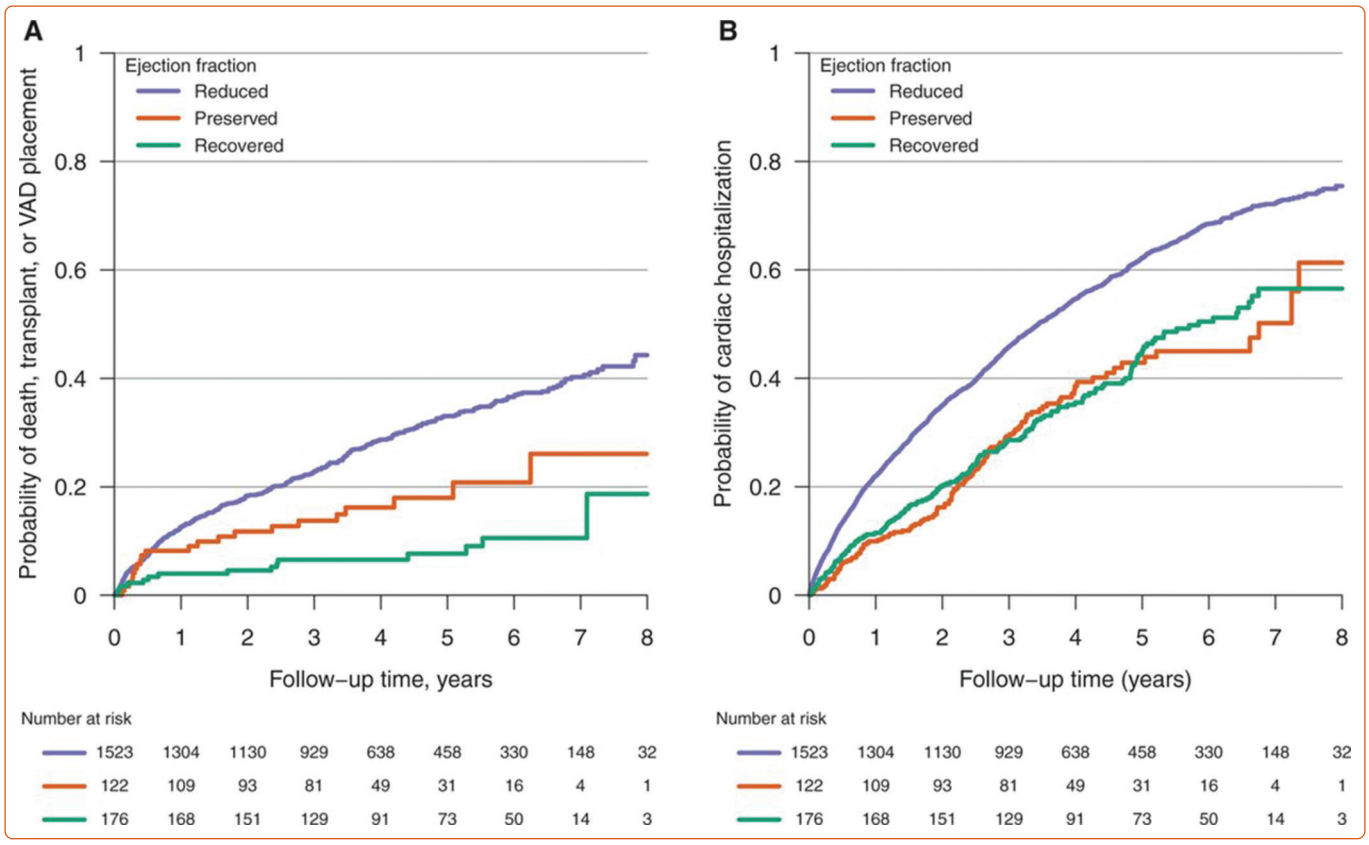
Dr Wilcox is the Chief of the Section of Heart Failure Treatment and Recovery and an Assistant Professor of Medicine at Northwestern University Feinberg School of Medicine. She is also the Associate Director of the T1 Center for Cardiovascular Therapeutics in the Bluhm Cardiovascular Institute at Northwestern Memorial Hospital. Dr Wilcox serves as an A-CURE faculty member.

Dr Wilcox's talk focused on the differences between myocardial recovery and remission, and how to differentiate and target patient treatment between the two. Historically, heart failure (HF) has been considered as a steady track towards mortality, but the evidence from the field clearly demonstrates that HF is not a death sentence, and that recovery and remission are possible. HF is a syndrome of repeated hospital admissions, with failure to handle salt and water normally and accompanying neurohormonal abnormality. Given these components, the goal for treating HF patients should be to improve ejection fraction and to aid recovery from cardiomyopathy.

Traditionally, guideline-directed medical therapy (GDMT) for HF includes neurohormonal therapy, which reduces HF symptoms, reverses cardiac remodelling and improves survival. However, because the definition of cardiomyopathy recovery is constantly changing, it can be easier to define what HF with recovered ejection fraction (HFrecEF) is not, which is constantly evolving with better information and understanding of the HF recovery process. For example, HF with a midrange ejection fraction (45%) is not considered recovery, but rather is a biology that is associated with reverse remodelling and a reduction in left ventricular volume.[1]

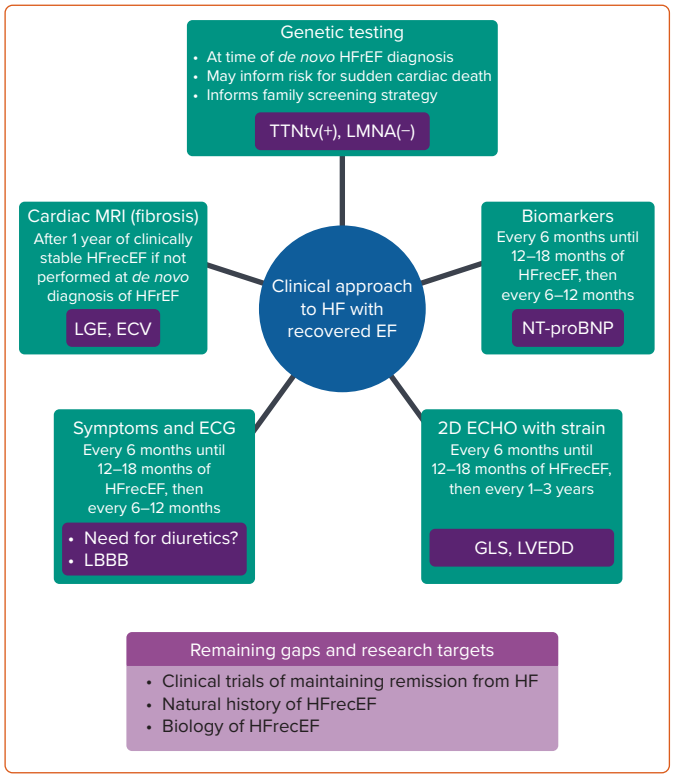
Dr Wilcox presented a working definition of HFrecEF, where recovery is an improvement in left ventricular ejection fraction (LVEF) to an absolute value >40%, with at least a >10% improvement from the patient's baseline, accompanied by reductions in ventricular volumes. The primary difference between remission and recovery is in the myocardial substrate, with persistent abnormalities in remission but 'normal' structure and function in recovery.[2] Essentially, until the myocardium has become completely non-viable (i.e. late gadolinium scar, dead muscle), that myocardium should be a target for therapy and recovery.[3]

Figure 1: Improved Survival with Recovered-Cardiomyopathy



Patients with recovered cardiomyopathy had an improved survival compared to their HFrEF and HFpEF counterparts but has persistent risk of hospitalisation. Probability of all-cause death, cardiac transplantation, or ventricular assist device for all participants (A) and probability of cardiac hospitalisation for all participants (B) from time of referral to an outpatient heart failure specialty care centre. VAD = ventricular assist device. Source: Basuray et al. 2014.[3] Used with permission from Wolters Kluwer Health.

Figure 2: Clinical Assessment of Patients with Recovered Left Ventricular Ejection Fraction



ECHO = echocardiography; ECV = elevated extracellular volume; EF = ejection fraction; GLS = global longitudinal strain; HF = heart failure; HFrecEF = heart failure with recovered ejection fraction; HFrEF = heart failure with reduced ejection fraction; LBBB = left bundle branch block; LGE = late gadolinium enhancement; LMNA(–) = lamin A/C mutation negative; LVEDD = left ventricular end-diastolic diameter; NT-proBNP = N-terminal pro B-type natriuretic peptide; TTNtv(+) = truncating variants of the titin gene. Source: Wilcox et al. 2020.[5] Used with permission from Elsevier.

Dr Wilcox noted that hearts that have recovered from HF are still vulnerable to relapse; this is largely due to the fact that during recovery gene transcription becomes normalised, but the networks that had been persistently dysregulated will assume a novel biological set-point. As such, although recovery is associated with improved survival (*Figure 1A*), a persistent risk of hospitalisation still exists (*Figure 1B*).[4] Dr Wilcox also noted that there are a number of factors to predict whether a patient is likely to recover from HF, including clinical parameters, genetic factors, echocardiographic/cardiac MRI and biomarker profile.[5] In particular, non-ischaemic aetiology, shorter duration of HF and no left bundle branch block are indicators of reverse left ventricular (LV) remodelling with GDMT. In addition, well-preserved global longitudinal strain, a measure of LV systolic function that has been shown to be more reproducible than LVEF, can indicate that even a dilated patient may be able to achieve recovery, whereas abnormal global longitudinal strain can indicate future deterioration. Even among patients who achieve the traditional >40% LVEF, more normal global longitudinal strains are still indicative of long-term success, and even small incremental improvements can have long-term effects.[5]

Patients who have recovered from HF still require maintenance in the form of medical therapies. The TRED-HF study examined withdrawal of pharmacological treatment for HF in patients with recovered dilated cardiomyopathy and revealed that cessation of medication resulted in a 44% rate of recrudescent HF within 8 weeks, requiring the resumption of medications. Thus, there are numerous angles from which to clinically approach HFrecEF, to understand personalised risks and improve long-term survival (*Figure 3*).[5]

Dr Wilcox proposed that recovery can, and should, be a medical target for HF patients. Impella 5.5 can be a helpful tool in achieving this, and is effective across many relevant indications, including cardiomyopathy cardiogenic shock, acute MI with cardiogenic shock and post-cardiotomy cardiogenic shock. Improvements with Impella 5.5 are robust and most patients can achieve improvement to allow for device removal. Future goals include novel devices that are specifically targeted to recovery, such as the developing Impella BTR (bridge-to-recovery), which received conditional investigational device exemption approval in January 2022 for a first-in-human early feasibility study.

Dr Wilcox concluded that although the goal should be to achieve recovery, achieving remission is an excellent result, and using temporary unloading devices as a platform for neurohormonal therapy may be the future for HF recovery and remission. ❑

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Clinical Experience of a Real-world Heart Recovery Programme

Presented by Manreet Kanwar, MD

Allegheny General Hospital, Pittsburgh, PA, US

Dr Kanwar is the Medical Director of the Mechanical Circulatory Support and Cardiac Transplant Program and the Co-Director of the Division of Heart Failure and Pulmonary Hypertension at Allegheny General Hospital in Pittsburgh, PA, US. Dr Kanwar serves as an A-CURE faculty member.

Dr Kanwar's talk was focused on sharing a real-world clinical experience in heart failure recovery with temporary and durable left ventricular assist devices (LVAD). Dr Kanwar noted that until recently, discussions and terminology on LVAD, heart failure and cardiogenic shock were siloed and considered separately, rather than noting and exploring the connections between these conditions and therapies.

Dr Kanwar explained the notion of 'recovery disconnect', where carefully curated patient selections can result in 50% survival in studies such as RESTAGE-HF,[1] but in large-scale databases, such as INTERMACS, survival to explant may be as low as 1–2%.[2]

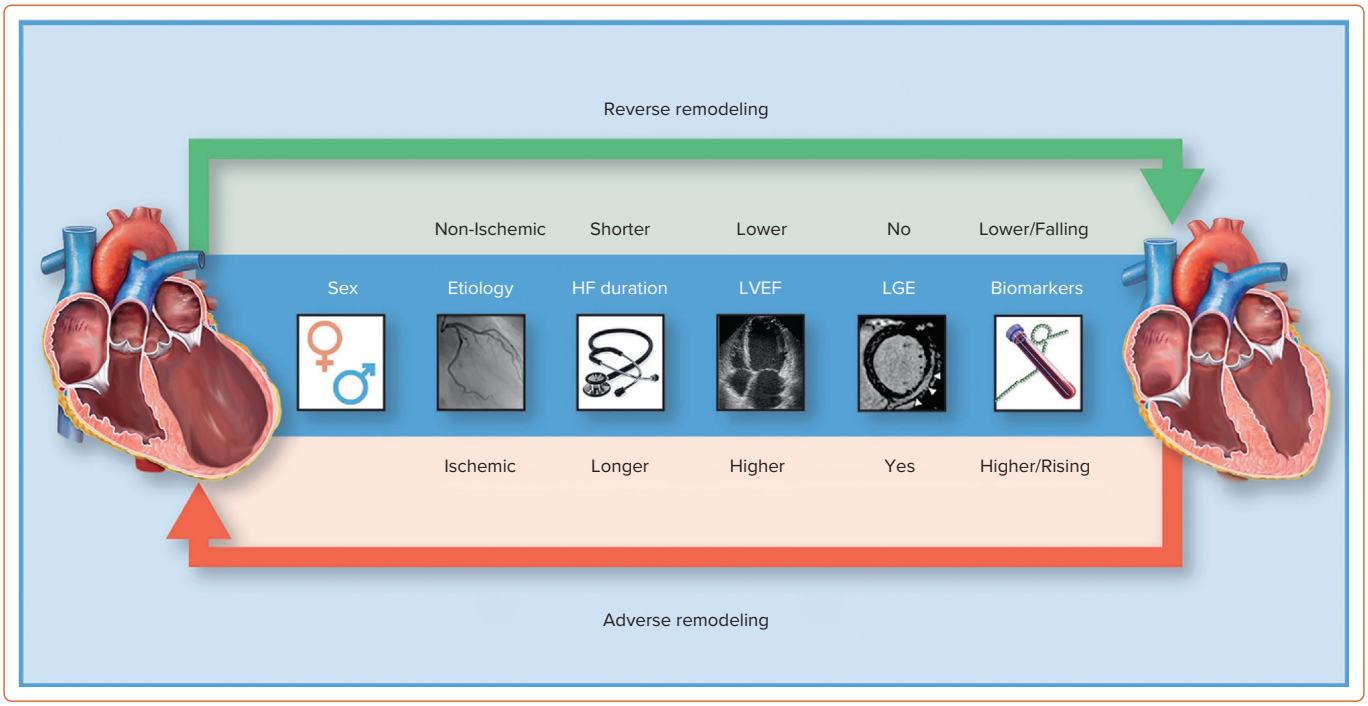
Furthermore, although there are more patients recommended for and receiving heart transplants, there are fewer patients being removed from the transplant list or reported as on a path to recovery. This suggests that patients may be 'rushed' to transplant without enough time with an LVAD to determine the likelihood of recovery, especially since the United Network for Organ Sharing allocation policy change.[3]

As an example, Dr Kanwar described a case of a patient who, upon review, most clinicians recommended for urgent transplant; however, Dr Kanwar and her team instead proceeded with a durable LVAD as a bridge to transplant and began guideline-directed medical therapy (GDMT). The device was explanted 11 months later, and the patient's left ventricular ejection fraction remains at 55% 3 years later.

This concept for providing ample time and support for recovery is not new. The use of mechanical circulatory support (MCS) as a bridge to recovery may promote myocardial recovery, resulting in higher rates of clinically successful device explants. As such, LVAD optimisation must be personalised, with the goal of recovery rather than transplant. Patients should be evaluated on a case-by-case basis to determine the haemodynamic needs and reversibility of the condition, and then therapies, particularly unloading devices, must be tailored to the specific needs of the patient. LVAD can be used as a durable support and bridge to recovery, as well as a bridge to transplant.

For the various types of MCS, there are different considerations depending on the goals of the therapy. Patients must be carefully phenotyped with regard to their likelihood of recovery (*Figure 1*); their long-term outcome goals need to be considered to determine the therapeutic aims. Temporary MCS provides early and upfront unloading, rhythm control,

Figure 1: Main Predictors of Reverse and Forward Remodelling in Heart Failure



Source: Aimo et al. 2019.[4] Used with permission from Elsevier.

non-cardiac end-organ management, patient mobility and improved quality of life. Furthermore, it allows for time to monitor the patient's metrics and determine an exit strategy.

Durable LVAD provides a long timeline, where appropriate patients are optimised and prepared carefully before, during and after device implantation. The patients should receive appropriate GDMT with careful monitoring, and device explantation should be considered upon long-term improvement.

Dr Kanwar concluded that biology is not binary and recovery is not just about device explantation. Important consideration must be given to the specifics of each patient in order to determine the best path for their specific medical needs and goals, with transplant as a last option rather than a primary goal. ❑

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