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

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Acute Cardiac Unloading and Recovery
3rd Annual A-CURE Symposium
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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.

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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 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 ventricle (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. 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 captopril may curtail the process, as well as reducing filling pressures and improving exercise tolerance. 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. Since the publication of this study, a growing body of literature has established the benefits of mechanical myocardial unloading, 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 ECMQ, 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).

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.

Figure 1: Determinants of myocardial oxygen consumption

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

PE
SW
PVA
MVO2

Left ventricular volume

ESPVR

EDPVR

PVA=SW+PE

Left ventricular pressure

MV02 (ml O2/beat)

PVA (mmHg.ml)
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.crteach.com and www.pvloops.com).

> Figure 2: The ‘dose-dependence’ of myocardial support and unloading

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1. Pfeffer JM, Pfeffer MA, Braunwald E. Influence of chronic human hearts in 1996.9
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

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**Figure 1: The primary unloading hypothesis**

<table>
<thead>
<tr>
<th>1º Reperfusion</th>
<th>Infarct Size</th>
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<tbody>
<tr>
<td>90’ Occlusion</td>
<td>R=0.80, p=0.01</td>
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<tr>
<td>120’ Reperfusion</td>
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<table>
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<tr>
<th>1º Unloading</th>
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<tr>
<td>90’ Occlusion</td>
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<td>120’ Reperfusion</td>
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AAR = area at risk; LV = left ventricle; SDF-1α = stromal-derived factor 1 alpha

**Figure 2: Effect of delaying reperfusion**

- Primary Reperfusion
- PU-15
- PU-30
- PU-60
- Reperfusion then Unload

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

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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.
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. 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). It is known that ischaemic injury leads to an uncoupling of SDF-1-alpha and CXCR signalling. 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. An animal study found that, compared to primary reperfusion, primary unloading reduces LV scar and preserves cardiac output at 30 days after acute MI. 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.

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. In 2017, the US Food and Drug Administration approved a Phase I clinical trial examining the safety and feasibility of primary unloading.

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; pAkt = protein kinase B; pGSK3β = glycogen synthase kinase 3 beta; MMP = matrix metalloproteases; αSDF = stromal-derived factor 1 alpha. Source: Kapur et al, 2017
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.

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.

Figure 1: Coronary occlusion with and without left ventricular support

Source: Hajjar et al, 2017

<table>
<thead>
<tr>
<th>Without Impella</th>
<th>With Impella</th>
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<tr>
<td>Systolic arterial pressure (mmHg)</td>
<td></td>
</tr>
<tr>
<td>Time after occlusion (min)</td>
<td>0</td>
</tr>
<tr>
<td>Without Impella</td>
<td>60</td>
</tr>
<tr>
<td>With Impella</td>
<td>60</td>
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VF: Ventricular fibrillation

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
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.


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

Figure 1: Controlled cardiogenic shock in a porcine model

MAP = mean arterial pressure; SV02 = mixed venous oxygen saturation. Source: Møller et al, 2017 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.

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. 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.

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 recording. 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 catheterisation laboratory.

Prof Møller’s work has focused on porcine models for the various size advantages they have compared to 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). 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

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.


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, the rates of in-hospital mortality have remained unchanged for more than 20 years. 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.

One factor observed to be associated with early mortality in AMI/CS is increased inotrope exposure. 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. 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).

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).

These factors have been used to develop a protocol for use by the Detroit Cardiogenic Shock Initiative (CSI), a collaboration between four hospitals.
in Detroit, under the leadership of Dr William O’Neill, with the aim of increasing survival in Mi/CS (see Figure 3). 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 catheterization 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, 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. This patient populations is similar to that of the SHOCK trial (n=302). 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. 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.\(^6\) 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...
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 MVO2 (+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 MVO2 reductions (−13±4 %). Unsupported reductions in the preload (IVCX) decreased pressures. There was a decrease in MVO2 (−39±4 %), and PVA (−58±4 %). The Ea and Ees remained unchanged. Support with partial LVAD support (CTRL+PE) increased Ea and blunted the MVO2 reductions (−7±2 %). Of interest, the LVAD support altered the MVO2 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 MVO2 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/MVO2 relationship.

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. 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 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 its time-sensitive nature, enrolment decisions are based only on the time. A radial approach is used for access for the non-large bore site to reduce unnecessary vascular complications. Patient screening should allow us to understand the physiology and clinical correlates to DTU and how to use concomitant therapies to improve patient outcomes.

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.


Ventricular Unloading and Inflammation – The Role of Impella in Myocarditis

Presented by Carsten Tschope
Charité, CVK, Berlin, Germany

Acute fulminant myocarditis and giant cell myocarditis have a poor prognosis. At present, short-term mechanical circulatory support (MCS) for myocarditis patients with refractory cardiogenic shock (ICS) has predominantly used extracorporeal membrane oxygenation (ECMO). Despite this, MCS is associated with significant short- and long-term complications. The IMPPELLA device has been used in both acute myocardial infarction (AMI) and non-AMI settings for circulatory support. The IMPPELLA CP device is a percutaneous ventricular assist device that can be used for short-term circulatory support for up to 144 hours. The device is inserted percutaneously via a radial or femoral approach, and the pump is placed in the LV. The pump provides continuous unloading of the LV, reducing LV wall stress and decreasing myocardial oxygen consumption. The device also provides hemodynamic stability and minimizes the need for pharmacotherapy, allowing for the possibility of anticoagulation and reperfusion therapy. The device is explanted after 3–4 hours of support. The primary endpoints are the composite of major adverse cardiac and cerebrovascular event (MACCE) at 30 days, cardiovascular mortality, re-infarction, stroke/TIA, major vascular complication, and major vascular complication at 30 days. The exploratory efficacy endpoint is the infarct size as percentage of LV mass, evaluated by cardiac magnetic resonance (CMR) at 30 days post-PPCI. The device is explanted after 3–4 hours of support. 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.
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 auxiliary 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.

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.

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.\(^2\) 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 findings from 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 cardiectomy 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\(^\text{®}\) 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.

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.
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 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. 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. In addition, early progression of pulmonary oedema (within 24 hours) has been found to predict mortality in patients with extracorporeal membrane oxygenation (ECMO). 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 pulmonary congestion in CS develops differently according to the type of MCS (Impella versus intra-aortic balloon pump [IABP]), and 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 Westenfeld 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. 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).

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.

Table 1: Patient characteristic on admission

<table>
<thead>
<tr>
<th></th>
<th>IABP (n=30)</th>
<th>Impella (n=30)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>69±12</td>
<td>65±14</td>
<td>0.12</td>
</tr>
<tr>
<td>Gender (f/m)</td>
<td>7/23</td>
<td>12/18</td>
<td>0.17</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>2 ± 5</td>
<td>27 ± 5</td>
<td>0.59</td>
</tr>
<tr>
<td>CPR (%)</td>
<td>47</td>
<td>50</td>
<td>0.8</td>
</tr>
<tr>
<td>STEMI (%)</td>
<td>47</td>
<td>37</td>
<td>0.44</td>
</tr>
<tr>
<td>Revascularisation (%)</td>
<td>80</td>
<td>60</td>
<td>0.09</td>
</tr>
<tr>
<td>SOFA score</td>
<td>9 ± 2.9</td>
<td>9 ± 2.8</td>
<td>0.72</td>
</tr>
<tr>
<td>APACHE score</td>
<td>23 ± 8.8</td>
<td>22 ± 6.2</td>
<td>0.55</td>
</tr>
</tbody>
</table>


Figure 1: Ventricular unloading is associated with pulmonary decongestion in cardiogenic shock
The evolution of CVD therapy worldwide is moving towards identifying risk at early stages of life. 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. While recent work has highlighted the rapid advances that have been made in understanding diluted cardiomyopathy, a precursor to HF, and assist devices have proven effective in end-stage disease, 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. These include screening assays based on levels of pro-brain natriuretic peptide and troponin, leading to high-sensitivity cardiac troponin (hs-cTn) assays. Six-year increases in the levels of hs-cTn, suggestive of progressive myocardial damage, are independently associated with HF. 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.

Other aspects of changing approaches to CVD include a greater focus on the atherosclerotic disease burden rather than on features of individual plaques, and the evolving paradigm of CVD as a systemic disease that is dependent on macrophage activity. 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. Evolving non-invasive technologies are also evaluating ischaemia at the microcirculation level. In the future, Dr Fuster predicts that ischaemia of each artery will be assessed by non-invasive techniques.

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.

Dr Ishikawa’s talk focused on his investigations into how left ventricular mechanical support affects left atrial hemodynamics. 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 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 hemodynamics. In the same porcine model of MI, he observed a flow-dependent unloading of the left ventricle would affect left atrium (LA) physiology. In this demonstration, he showed that as the unloading pressure decreased, the LA pressure also decreased, indicating a reduction in LA volume. He further demonstrated that the LA-PV pressure gradient increased, indicating an increase in LA-PV flow. This finding is consistent with the previous studies that showed a decrease in LA volume and an increase in LA-PV flow following LV unloading. Therefore, the findings of this study support the hypothesis that LV unloading can result in LA volume reduction and increase in LA-PV flow, which can be potentially beneficial in managing HF patients with preserved ejection fraction (HFrEF).

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, 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

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.
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 environment. 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. 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. 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. 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 estimate 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
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.

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.
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).

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.
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 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. 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. 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. However, prolonged use of ECMO (>2 days) is associated with greatly increased mortality. 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.

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 significantly more rapid weaning of ECMO = extracorporeal membrane oxygenation. Source: Westermann et al

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.

5. Westermann D. Unpublished data.

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 Burkoff 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.