

## ACUTE CARDIOVASCULAR CARE

# Percutaneous mechanical circulatory support: current concepts and future directions

Natalia Briceno,<sup>1</sup> Navin K Kapur,<sup>2</sup> Divaka Perera<sup>1</sup>

<sup>1</sup>Cardiovascular Division, British Heart Foundation Centre of Excellence and National Institute for Health Research Biomedical Research Centre, Rayne Institute, St Thomas' Hospital Campus, King's College London, London, UK  
<sup>2</sup>The Cardiovascular Center and Molecular Cardiology Research Institute, Tufts Medical Center, Boston, Massachusetts, USA

## Correspondence to

Dr Divaka Perera, Cardiovascular Division, British Heart Foundation Centre of Excellence and National Institute for Health Research Biomedical Research Centre, Rayne Institute, St Thomas' Hospital Campus, King's College London, London SE1 7EH, UK; [Divaka.Perera@kcl.ac.uk](mailto:Divaka.Perera@kcl.ac.uk)

## INTRODUCTION

Percutaneous mechanical circulatory support (MCS) strategies have been in the clinical arena for approximately half a century, with the main aim of providing adequate systemic tissue perfusion, while also favourably impacting myocardial oxygen supply and demand, to optimise myocardial recovery in the face of cardiogenic shock (CS). This can be in the context of acute haemodynamic instability following a myocardial insult such as an acute coronary syndrome or myocarditis, or acute decompensation in a patient with chronic heart failure due to varying aetiologies. Despite major advances in both pharmacological and interventional therapies, CS continues to have a very poor prognosis with mortality rates in the order of 40%–80%.<sup>1–3</sup> In addition to CS, MCS is more commonly being considered for patients with chronic heart failure undergoing high-risk percutaneous coronary intervention (PCI). This increasing population of ischaemic heart failure patients is due in part to improving survival after acute myocardial infarction (AMI), but with persistent myocardial damage despite timely reperfusion.<sup>4</sup> In the setting of haemodynamic collapse, inotropes and vasopressors are often started immediately, due to their rapid onset of action. Although they differ in terms of their effects on systemic vascular resistance, these agents increase myocardial oxygen demand through their impact on adrenergic pathways.<sup>5–6</sup> As a result, pharmacologic support can worsen mortality in CS and hence should only be used as a short-term means to achieve haemodynamic stability. In contrast to drug therapy, percutaneous MCS reduces myocardial oxygen demand, while providing systemic perfusion. Therefore, percutaneous MCS devices have an important role in the management of patients in CS or who are at risk of developing CS.

While several studies have established that left ventricular (LV) systolic dysfunction is a strong predictor of mortality following revascularisation,<sup>7–11</sup> recommendations for the use of percutaneous MCS in CS or those undergoing high-risk PCI were previously based on their proposed physiological mechanisms of action and registry data supporting their use. However, this position has not been definitively supported by large randomised clinical trials (RCTs) examining a variety of clinical indications from CS, AMI or high-risk PCI.<sup>12–15</sup> Despite neutral overall RCT results, there are subsets of patients (both within trials and real-world registries) who deteriorate either on inotropic therapy or during unsupported PCI, requiring bailout MCS therapy and subsequently suffer adverse clinical

## Learning objectives

- ▶ To obtain a greater understanding of the role of mechanical circulatory support (MCS) in the current clinical arena.
- ▶ To understand the physiology of cardiogenic shock and the varying physiological strategies employed by the current clinically available MCS devices and the existing evidence behind their use.
- ▶ To develop an algorithm of MCS therapy, which can be used to optimise patient management.

outcomes. There are also signals of benefit from long-term follow-up studies that underscore the difficulties in designing RCTs to evaluate MCS,<sup>16</sup> and indications that MCS benefit may be restricted to patient populations with altered pathophysiological states such as AMI, where coronary autoregulation may be dysregulated.<sup>17</sup> The aim of this article is to review the overall goals of MCS therapy, discuss their underlying physiological basis and review the clinical evidence for the main percutaneous MCS strategies currently being used (intra-aortic balloon pump (IABP), Impella, TandemHeart and veno-arterial extracorporeal membrane oxygenation (VA-ECMO)).

## THE THERAPEUTIC GOALS OF PERCUTANEOUS MCS

The therapeutic goals of percutaneous MCS are to maintain distal organ perfusion, increase cardiac output, improve coronary perfusion and reduce myocardial oxygen demand.<sup>18</sup> Each MCS device achieves these goals to differing degrees and the actual goals differ in the setting of high-risk PCI versus CS. The ideal MCS device should also be safe to use, particularly with respect to vascular and bleeding complications.

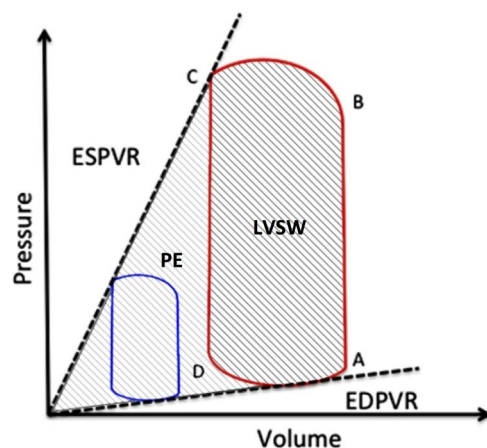
Uncorrected CS can lead to a vicious downward spiral, which includes haemodynamic embarrassment, a systemic inflammatory response, activation of systemic neurohormones and worsening myocardial ischaemia.<sup>1</sup> Ventricular pressure volume (PV) loops can be used to illustrate many of the physiological effects of each MCS device. Plotting simultaneous changes in ventricular pressure and volume during each cardiac cycle yields loops that characterise a patient's pathophysiological state as well as the effect of MCS on ventricular performance and



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work, the latter being determined by a complex interaction between the intrinsic heart rate, preload, afterload, myocardial muscle mass and contractile function<sup>19</sup> (figure 1). During uncorrected CS, LV volumes and end-diastolic pressures increase, while contractility and stroke volume are reduced. The area within the PV loop equates to stroke work and the area bounded by the PV loop, the end-systolic PV relationship and the end-diastolic PV relationship represent potential energy, while the sum of these areas (PV area (PVA)) is a surrogate of myocardial oxygen demand<sup>20</sup> (figure 1). One of the main goals of MCS in CS is maintenance of organ perfusion by augmenting or replacing native cardiac output. In AMI with or without CS, it is critically important to optimise the myocardial supply-demand balance to maximise the prospects of myocardial recovery. MCS strategies that reduce myocardial oxygen demand will reduce PVA, usually due to a downward and left shift of the PV loop reflecting reduced LV volumes, stroke work and end-diastolic pressure (figure 1). The decrease in myocardial oxygen demand should ideally be accompanied by augmentation (or, at the very least, maintenance) of myocardial perfusion. In contrast, during high-risk PCI, the main goal of MCS is to prevent the deleterious effects of ischaemia in patients predisposed to CS, particularly during procedures likely to involve repetitive or prolonged ischaemia, when myocardial contractility can become acutely reduced. Table 1 summarises the various MCS devices that are currently used with their proposed physiological effects and potential complications and disadvantages to their use.



**Figure 1** Pressure volume (PV) loops in a normal heart (red) and the PV loop of an 'ideal' mechanical circulatory support device (blue). This demonstrates the changes in pressure and volume during one cardiac cycle in the left ventricle. (A) Mitral valve closing. (B) Aortic valve opening. (C) Aortic valve closing. (D) Mitral valve opening. Between B and C is systolic ejection and between D and A is diastolic filling. ESPVR, end-systolic pressure volume relationship. EDPVR, end-diastolic pressure volume relationship. The area within the red PV loop is the left ventricular stroke work (LVSW). The area bounded by the ESPVR, EDPVR and PV loop is the potential energy (PE). LVSW plus PE is known as the pressure volume area (PVA).

## BALLOON COUNTERPULSATION-IABP

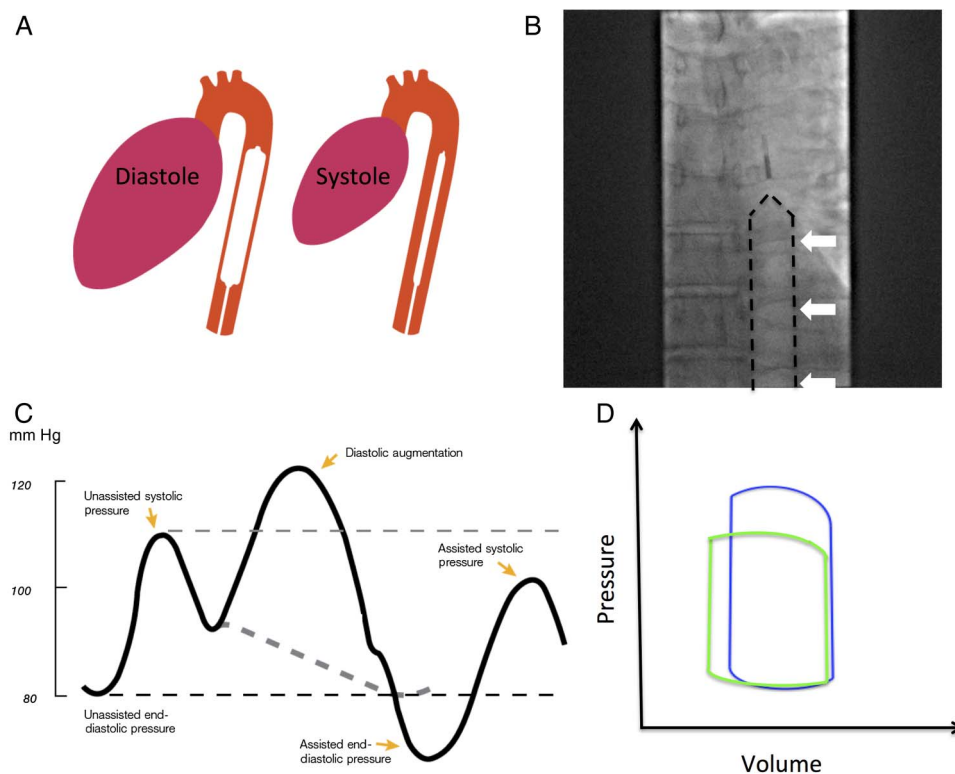
The IABP is the oldest percutaneous MCS device that is widely implanted in both cardiac catheter laboratories and surgical theatres (figure 2). Its primary haemodynamic effects are designed to increase coronary perfusion pressure by augmenting the aorto-coronary perfusion gradient (diastolic augmentation) and to reduce afterload as a result of a diminished LV systolic pressure (systolic unloading). The latter has been postulated to reduce myocardial work by reducing wall tension.<sup>24</sup> These effects are mediated through balloon inflation and deflation, which is timed to ECG and pressure triggers. As a result, profound tachycardia or irregular heart rhythms can limit the effectiveness of counterpulsation therapy. Early clinical physiological studies of balloon counterpulsation performed demonstrated increased coronary flow and reduced afterload with this therapy. One such study enrolled 19 patients who were critically ill with an average ejection fraction measured by ventriculography of 32% (predominantly in the context of AMI and shock), seeking to determine the impact of IABP counterpulsation on systemic coronary haemodynamics.<sup>25</sup> They found that counterpulsation reduced aortic systolic pressure, augmented diastolic pressure and increased coronary flow. Interestingly, the augmentation in flow was greatest in patients with the most compromised haemodynamics. More recent work by De Silva *et al.*,<sup>21</sup> which also applied the method of wave intensity analysis, assessed the impact of IABP therapy on coronary haemodynamics in patients undergoing high-risk PCI. The two main findings were that when coronary autoregulation is intact, counterpulsation does not augment coronary flow. However, when autoregulation was disabled, with intracoronary adenosine, significant augmentation of coronary flow was observed, which correlated with a novel wave profile associated with balloon inflation, known as the IABP-forward compression wave. From a demand perspective, there are several studies showing reduced LV end-diastolic pressure (LVEDP) and volume (LVEDV), with an increase in stroke volume as shown in figure 2.<sup>26 27</sup> A recent analysis of patients with advanced heart failure and CS showed that patients with poor contractile reserve may not stabilise with IABP therapy.<sup>28</sup> The authors specifically showed that reduced right ventricular (RV) or LV cardiac power indexes (cardiac power index=cardiac index×mean arterial pressure/451) identifies patients who are less likely to stabilise with IABP therapy (area under the receiver operating characteristic curve=0.82). The impact of IABP therapy on LV stroke work and myocardial oxygen demand remains poorly understood and is an active area of investigation with preclinical studies showing minimal effect of IABP therapy on cardiac output and PVA.<sup>29</sup>

Whereas registry data of IABP use has largely reflected the physiological benefits seen in animal and clinical studies, this has not been the case with RCTs that have looked at the impact of IABP therapy on outcomes.<sup>30 31</sup> The largest to date was

**Table 1** Summarising strategy, physiological effects and disadvantages of IABP, Impella, TandemHeart and VA-ECMO

Device	Mechanism	Proposed physiology effects	Potential advantages	Potential disadvantages
IABP	Phasic (pulsatile) modulation of aortic pressure by displacing aortic blood volume	Reduces LV afterload Augments aortic diastolic pressure Increases coronary flow during active ischaemia <sup>21</sup>	Ease of insertion No need for intracardiac penetration	Contraindicated in aortic regurgitation Dependent on native contractile function Inefficient during arrhythmia or marked hypotension Modest increase in systemic perfusion and LV unloading
Impella recover	LV to ascending aortic continuous flow microaxial flow pump (intracorporeal)	Reduce LV pressure and volume (PVA) Augments systemic mean pressure Increases coronary flow during active ischaemia <sup>22</sup>	Ease of insertion Independent of native contractile function	Contraindicated in presence of LV thrombus and aortic regurgitation Risk of haemolysis Bleeding complications Vascular complications
TandemHeart	Left atrial to descending aortic non-pulsatile flow, extracorporeal pump	Reduces LV preload thereby reducing LV volumes (PVA) Augments systemic mean pressure	Independent of native contractile function Can be used in the setting of aortic regurgitation <sup>23</sup>	Bleeding complications Vascular complications Requires transeptal puncture Risk of haemolysis
VA-ECMO	Right atrial to descending aortic flow, retrograde if peripheral type Extracorporeal pump with membrane oxygenator	Augments systemic mean pressure Supplements systemic oxygenation	Independent of native contractile function Useful for biventricular failure	Bleeding complications Vascular complications No change in PVA Requires LV venting to reduce any increase in LV afterload Risk of haemolysis

AR, aortic regurgitation; IABP, intra-aortic balloon pump; LV, left ventricular; MAP, mean arterial pressure; PVA, pressure volume area; VA-ECMO, veno-arterial extracorporeal membrane oxygenation.



**Figure 2** Balloon counterpulsation therapy. (A) Schematic of balloon counterpulsation. (B) Fluoroscopy image of inflated balloon in the descending aorta with tip just at the level of the carina. (C) Diagram demonstrating physiological mechanism of action (courtesy of Maquet). (D) The impact of intra-aortic balloon pump on the pressure volume (PV) loop, demonstrating a reduction in both end-diastolic and end-systolic pressures with a small reduction in the end-systolic volume. The PV loops are representative, and may vary depending on device-related factors and patient-related factors.

the IABP II SHOCK trial, which was a multicentre, open-label, prospective trial that randomised 600 patients with CS complicating AMI to either receive IABP therapy or no IABP therapy. The trial failed to meet its primary end point, with both the

30 days<sup>32</sup> and 1 year<sup>33</sup> data showing no overall difference in all-cause mortality between groups. There were also no significant differences found in the secondary end points, which included renal function, lactate, C-reactive protein,

cerebrovascular accident, gastrointestinal bleeding, sepsis and peripheral ischaemic complications. Although this was the largest trial to date looking at this high-risk cohort of patients, there are two important points that may have impacted on the outcome. First, there was crossover from both arms (10% of the control group received IABP due to haemodynamic instability), which may have led to an underestimation of the effect of IABP and recognises the presence of a subgroup of patients that do deteriorate when treated without MCS, likely due to the lack of myocardial protection during PCI. Second, the timing of IABP insertion was at the discretion of the operator; in nearly 90% of cases, this was carried out after PCI, whereas the greatest benefit may be expected with preprocedure insertion (whereby the downward spiral of ischaemic LV dysfunction may be prevented). Other large trials looking at the use of IABP in differing patient populations and evaluating IABP from a myocardial protection stand point, including the balloon pump-assisted coronary intervention study-1 (high-risk PCI)<sup>13</sup> and Counterpulsation to reduce Infarct Size Pre-PCI Acute Myocardial Infarction (CRISP-AMI) (high-risk PCI in the context of an anterior myocardial infarction)<sup>34</sup> have also shown no significant impact on mortality or reduction in infarct size.

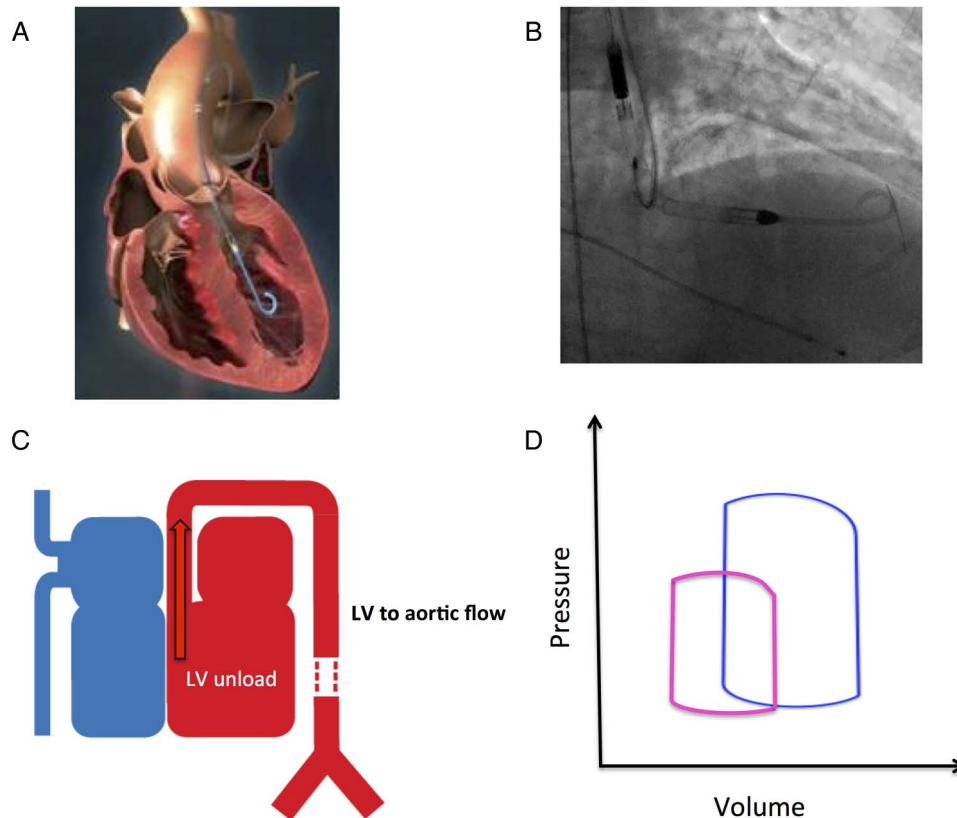
The majority of balloon pump trials that have been performed to date have had significant patient crossover from the no-IABP arm to the IABP arm, which reflects to an extent the limitations of the risk models used in defining the relevant study populations, often due to the need to design pragmatic trials that can be completed in a timely manner. What is clear from all these trials is that routine use of IABP in all patients, identified using broad diagnostic classifications such as CS, high-risk PCI or acute anterior ST segment elevation myocardial infarction (STEMI), does not improve short-term clinical outcomes. However, the high crossover rate that exist in these trials, coupled with the signal of benefit in certain subgroups in smaller observational studies or subsets of RCTs underlines the need for further studies into this clinical conundrum. An example of such an evolution of study design is the RCT Survival Improvement in extensive Myocardial Infarction with PERsistent Ischaemia Following Intra-aortic Balloon Pump Implantation (SEMPER FI), which followed the publication of the substudy of patients with persistent ST elevation in the CRISP-AMI trial.<sup>17</sup> SEMPER FI is currently enrolling patients and will investigate the impact of IABP therapy in a cohort of patients that have an AMI and persistent ST elevation following revascularisation.<sup>35</sup> The development and introduction to clinical practice of a larger capacity (50cc) balloon (MEGA IABP) has been a more recent addition to the family of balloon pumps commercially available. The underlying theoretical premise is that a larger balloon will displace more blood in the descending aorta, therefore, providing superior haemodynamic support compared with the standard balloon.

Clinical studies performed have demonstrated the 50cc balloon provides greater systolic unloading and greater diastolic augmentation compared with the standard 40cc balloon.<sup>36 37</sup> Whether this translates into greater increases in coronary flow or a greater reduction in myocardial oxygen demand is yet to be elucidated.

#### DIRECT LV UNLOADING – IMPELLA AND HEARTMATE PHP

The Impella device (Abiomed, Danvers, Massachusetts, USA) is an axial flow catheter, which directly transfers blood from the LV into the ascending aorta, leading to continuous flow augmentation (figure 3).<sup>38</sup> The device consists of a microaxial pump that is mounted onto a pigtail catheter. Current percutaneous iterations include the 2.5 L/min, CP (up to 3.5 L/min) and 5.0 L/min devices, inserted via 13, 14 and 22 French (Fr) arterial sheaths, respectively. The device is passed retrogradely across the aortic valve and unloads the LV directly, thereby increasing cardiac output, reducing myocardial oxygen consumption (by reducing both LV pressure and volume) and decreasing pulmonary capillary wedge pressure. Animal models of CS have shown improvements in many systemic haemodynamic parameters and LV unloading,<sup>39–41</sup> and also reduced infarct size with the use of Impella.<sup>41 42</sup> More recently, both preclinical and clinical data suggest that primarily unloading the LV before coronary reperfusion may reduce infarct size and improve both in-hospital and short-term mortality.<sup>41 43</sup> Rummelink *et al*<sup>22</sup> demonstrated that when autoregulation is intact, the Impella 2.5L has minimal impact on coronary flow in a group of patients undergoing high-risk PCI. However, when autoregulation is disabled (which mimics clinical situations such as CS, ST-elevation myocardial infarction and persistent ischaemia) with the administration of adenosine, coronary flow significantly increases in direct correlation with Impella flow rates. The impact of Impella therapy on coronary flow and LV unloading were further confirmed by Sauren *et al* using a preclinical model of acute myocardial ischaemia.<sup>29</sup> While animal models have demonstrated a reduction in myocardial demand through a shift in the PV loop downwards and left, reflecting reductions in both LVEDP and LVEDV (see figure 3),<sup>41</sup> this has not been borne out in a clinical physiological study.<sup>44</sup>

Initial studies and registries have demonstrated the safety and haemodynamic efficacy of Impella 2.5L in patients undergoing high-risk PCI, myocardial infarction and CS.<sup>45–50</sup> The PROTECT II study was a multicentre RCT that compared MCS during high-risk PCI using IABP versus Impella on the incidence of major adverse cardiac events at 30 days.<sup>15</sup> While the haemodynamic benefits of Impella were confirmed in this trial, there was no difference in the occurrence of the primary end point, to the extent that the trial was discontinued early (after 452 of 600 patients had been enrolled) due to futility and anticipated equipoise between IABP and Impella. Based on the PROTECT II study and several subsequent analyses,



**Figure 3** Left ventricular (LV) unloading (Impella). (A) Schematic of the Impella catheter within the LV (courtesy of Abiomed). (B) Fluoroscopy image of Impella in the LV. (C) Diagram demonstrating physiological mechanism of action, with the predominant effect of direct LV unloading with flow direction LV to aorta. (D) The impact of direct LV unloading on the pressure volume (PV) loop. Effects such as a reduction in LV pressure and volume can be seen here, with a reduction in the PV area.<sup>44</sup> The PV loops are representative, and may vary depending on device-related factors and patient-related factors.

the Food and Drug Administration (FDA) has approved the Impella device for use during high-risk PCI.<sup>43 51–55</sup> There are no published randomised studies to date on the higher performance Impella devices. Furthermore, despite the appealing physiological profile when treating CS, there have been no published randomised trials of Impella use powered for hard outcomes in this setting to date and none that has evaluated the Impella CP. The Impella LP 2.5 vs. IABP in Cardiogenic SHOCK (ISAR SHOCK) trial did demonstrate in a randomised prospective fashion the haemodynamic superiority of the Impella 2.5L compared with the IABP in the setting of CS.<sup>47</sup>

Impella devices are sometimes used to support haemodynamics during high radiofrequency ablation procedures<sup>56</sup> and during STEMI. A recent animal study in a swine model of an acute infarct secondary to an occluded left anterior descending artery demonstrated effective LV unloading with the Impella CP prior to revascularisation leading to reduced infarct size and reperfusion injury.<sup>41</sup>

The HeartMate Percutaneous Heart Pump (PHP) (St Jude Medical, formally Thoratec) is a new LV unloading device being currently introduced into the clinical arena. Like the Impella device it is an LV to aortic unloading device, but theoretically provides greater flow rates (up to 5 L/min) through a 14 Fr sheath. The PHP device has collapsible impeller blades across the aortic valve, which can facilitate

larger flow rates despite the use of a 14 Fr percutaneous vascular access sheath. Notably, unlike the Impella devices, the PHP has an extracorporeal motor that is connected to the impeller via a cable. Therefore, the PHP uses an over-the-wire delivery approach that requires intermittent purge and flushes, while the Impella devices are based on a monorail system with a built-in continuous purge system. The recently presented SHIELD I (Coronary InterventionS in HIgh-Risk PatiEnts Using a Novel Percutaneous Left Ventricular Support Device) registry, which was a prospective non-randomised, open-label multicentre trial that assessed its use in 46 patients undergoing protected PCI demonstrated the feasibility of implantation and safety, and efficacy particularly during periods of haemodynamic collapse during high-risk PCI (presented at the Transcatheter Cardiovascular Therapeutics conference in San Francisco, California in 2015 by Professor Dariusz Dudek). The SHIELD II trial is a randomised study currently enrolling comparing the PHP and Impella 2.5L devices in patients referred for high-risk PCI. Future studies examining the clinical utility of the PHP device in CS are needed.

#### LEFT ATRIAL UNLOADING—TANDEMHEART

TandemHeart (CardiacAssist, Pittsburgh, Pennsylvania, USA) is a percutaneous extracorporeal pump that can provide temporary LV or RV unloading. For LV

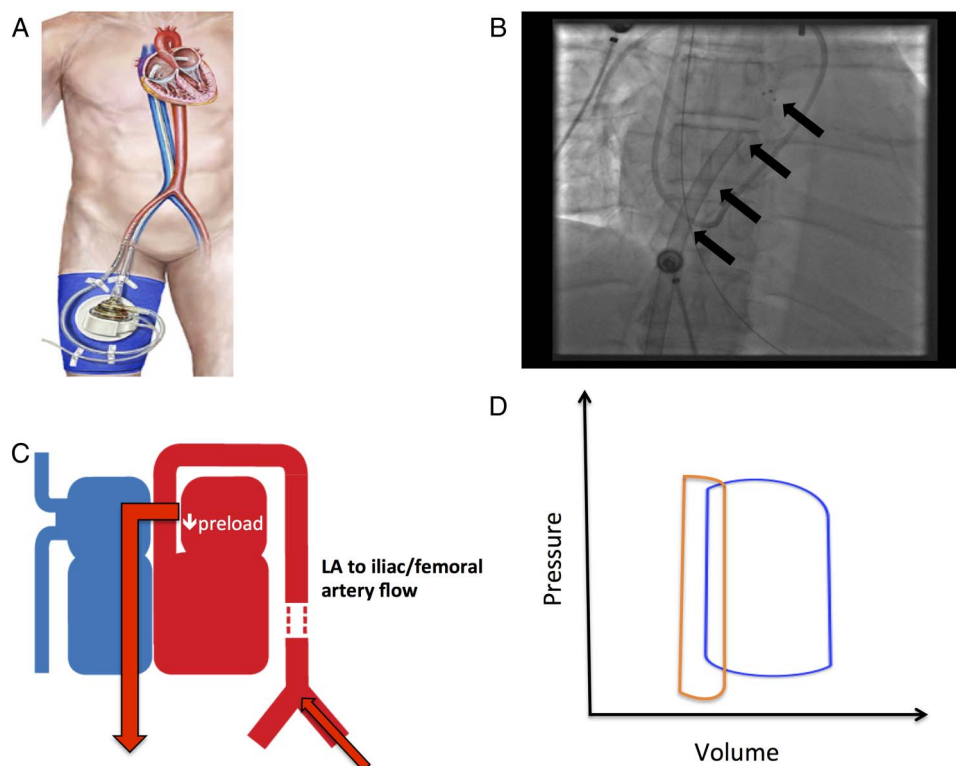
support, the TandemHeart pump is used to create a left atrial to femoral artery bypass circuit with continuous flow rates of up to 5 L/min (figure 4). The benefit of this device is that it can be deployed percutaneously, providing indirect LV unloading with lower rates of haemolysis, and depending on arterial cannula placement does not greatly increase LV afterload. It can also be inserted in the presence of aortic regurgitation or an LV thrombus,<sup>57</sup> which is a limitation of the Impella and PHP devices. It consists of a 21 Fr venous cannula inserted via a femoral vein into the left atrium via a transeptal puncture technique, and a 15–19 Fr return cannula inserted into a femoral artery, with both the cannulae connected to an external hydrodynamic centrifugal pump. Left atrial unloading leads to reduced preload, LV wall stress and filling pressures with a reduction in myocardial oxygen demand<sup>58</sup> (figure 4).

Registry data have demonstrated its feasibility and safety.<sup>59–61</sup> Although small numbers of patients, a trial performed by Burkhoff *et al*<sup>62</sup> demonstrated that the TandemHeart provided greater increases in cardiac index and mean arterial blood pressure and reduction in pulmonary capillary wedge pressures compared with IABP. However, no overall difference in 30-day mortality was observed. Although this device can provide up to 5 L/min of flow, the major limitations to achieving maximal flow include the size of the left atrium

and the calibre of the femoral arterial cannula for retrograde perfusion. Due to the technical aspects of insertion, in particular the need for transeptal puncture and left atrial cannulation, this device is not as widely used as the other MCS devices such as Impella. Major potential complications include vascular access complications, cardiac tamponade and the potential for a large right to left shunt and severe systemic desaturation if the left atrial cannula displaces into the right atrium.<sup>63</sup>

### RV SUPPORT

In 2006, the first successful implantation of a percutaneously delivered RV assist device (RVAD) in the setting of RV failure after AMI<sup>64</sup> using the TandemHeart centrifugal flow pump was reported (figure 4). Percutaneous application of a MCS device provides the opportunity for early intervention in the cascade of refractory RV failure without the need for surgery. Since then, the TandemHeart RVAD (TH-RVAD) has been implanted for RV failure in the setting of: AMI,<sup>65</sup> post-left ventricular assist device (LVAD) implantation,<sup>66</sup> severe pulmonary hypertension<sup>67</sup> and cardiac rejection after orthotopic heart transplantation.<sup>68</sup> Several clinical studies have reported that early application of the TandemHeart RVAD may improve clinical outcomes.<sup>69 70</sup> The TandemHeart in Right VENTRICULAR support study was a retrospective, observational registry of 46 patients receiving a TH-RVAD for



**Figure 4** TandemHeart. (A) Schematic of a TandemHeart device. (B) Fluoroscopy image of the TandemHeart cannula in left atrium. (C) Diagram demonstrating physiological mechanism of action, with blood drawn from left atrium, and then inserted back into the descending aorta after passing through an external centrifugal pump. (D) The impact of TandemHeart on the pressure volume (PV) loop. The main mechanism of action is a reduction in left ventricular (LV) preload, and through return of blood to the descending aorta, an increase in systolic pressure. There is also a reduction in stroke volume.<sup>58</sup> The PV loops are representative, and may vary depending on device-related factors and patient-related factors. LA, left atrial.

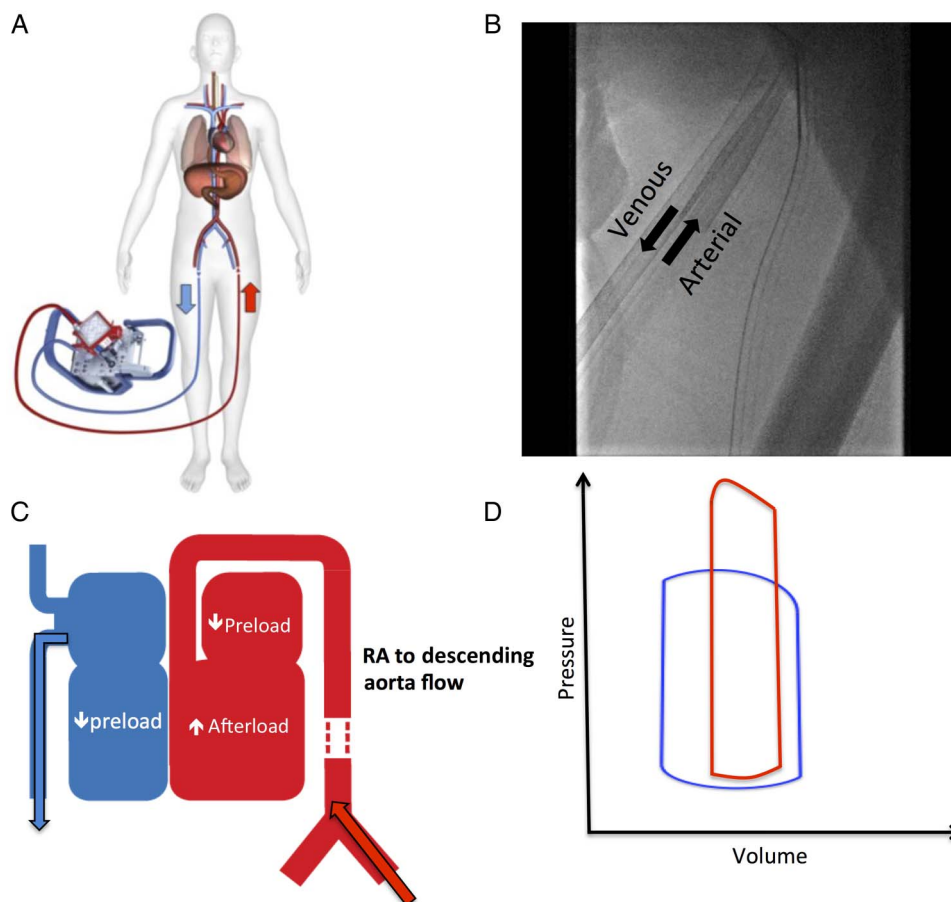
RV failure in eight tertiary care centres in the USA.<sup>71</sup> The central finding of this report was that implantation of the TH-RVAD is clinically feasible via both surgical and percutaneous routes and is associated with acute haemodynamic improvement in RV failure across a broad variety of clinical presentations. This study also identified that evaluation of RV failure in real-world practice did not always involve quantitative measures of RV function and further does not always include comprehensive evaluation and management of concomitant LV dysfunction. In-hospital mortality varied widely among different indications for mechanical RV support and was lowest among patients with RV failure in the setting of AMI or after LVAD implantation. Increased age, biventricular failure and thrombolysis in myocardial infarction major bleeding were more commonly observed in patients not surviving to hospital discharge.

#### TOTAL RESPIRATORY AND CIRCULATORY SUPPORT – VA-ECMO

VA-ECMO provides continuous non-pulsatile flow of oxygenated blood giving total respiratory and

cardiac support<sup>72</sup> (figure 5). Deoxygenated blood is drawn from the right atrium and inferior vena cava, which is then oxygenated and returned to the aorta. Essential circuit components include a centrifugal pump, membrane oxygenator and a heat exchanger. VA-ECMO can be provided centrally (with cannulae inserted surgically following sternotomy in the ascending aorta and right atrium) or peripherally (arterial cannula inserted via the femoral or axillary arteries percutaneously with a venous cannula inserted into the right atrium). Peripheral VA-ECMO provides retrograde flow in the aorta. VA-ECMO has been shown to improve end-organ perfusion through an increase in mean arterial blood pressure and increased oxygen delivery.<sup>73</sup> Common complications are predominantly due to the large vascular access required, including bleeding and limb ischaemia. Haemolysis can also occur, and should be monitored in all patients on VA-ECMO.

While the benefits of VA-ECMO in improving distal organ perfusion are well recognised, its effects on the physiology of the heart are not entirely understood. Animal studies have shown a reduction



**Figure 5** Veno-arterial extracorporeal membrane oxygenation (VA-ECMO). (A) Schematic of VA-ECMO set up (courtesy of Maquet). (B) Fluoroscopy of femoral cannulae. (C) Diagram demonstrating physiological mechanism of action. Through removal of venous blood from the right atrium, there is an immediate reduction in right ventricular (RV) preload, and subsequent left ventricular (LV) preload. With return of blood to the femoral artery (after passing through a centrifugal pump and oxygenator), there is an increase in afterload, which is dependent on return cannula placement and flow rates. (D) The impact of VA-ECMO on the pressure volume (PV) loop. This demonstrates increased LV pressures and a smaller stroke volume. Without unloading the LV, there can also be progressive increases in LV volumes with further shifts in the PV loop to the right.<sup>74</sup> The PV loops are representative, and may vary depending on device-related factors and patient-related factors. RA, right atrial.

in preload, which leads to a reduction in LV end-diastolic pressure, and hence a reduction in myocardial oxygen demand. However, there is a well-documented increase in afterload, which can result in increased LV end-diastolic volume, LV end-diastolic pressure, LV wall stress and conversely an increase in myocardial oxygen demand<sup>73</sup> (figure 5). In sheep models of myocardial ischaemia, VA-ECMO has been demonstrated to increase LV wall stress.<sup>75</sup> A more recent swine model demonstrated decreasing native cardiac output, increasing LV volumes and increasing LV stroke work with increasing ECMO flow rates.<sup>74</sup> Animal studies looking at the impact of VA-ECMO on coronary perfusion are conflicting, with some demonstrating improved coronary flow,<sup>76 77</sup> and others demonstrating a reduction in coronary flow with peripheral VA-ECMO.<sup>78</sup> The well-documented increase in afterload is problematic for patients with a poorly functioning or non-contracting left ventricle, resulting in profound LV dilatation. In these cases, surgical or percutaneous approaches to unload the LV are required<sup>79</sup> including implantation of devices such as the Impella or TandemHeart to offload the left ventricle or left atrium. IABP counterpulsation has also been used in a similar fashion, and studies involving sheep models have demonstrated improvement in wall stress, elastance and LV oxygen consumption with a combination of IABP and VA-ECMO.<sup>75</sup> To date, no invasive studies have been performed in humans looking at the devices interplay and their impact on the underlying physiology.

Several retrospective and prospective studies have investigated VA-ECMO, which have shown varying outcomes with its use with significant rates of complications.<sup>80–84</sup> A recently published retrospective study on 57 patients treated for fulminant myocarditis with VA-ECMO demonstrated high rates of survival to hospital discharge with VA-ECMO (71.9%), however, with a high rate of major complications including bleeding and neurological pathology (70.1%).<sup>85</sup> A similar retrospective study from a higher volume VA-ECMO centre showed similar survival outcomes, with ischaemic heart disease being independently associated with reduced survival.<sup>86</sup> The recently published mechanical CPR, Hypothermia, ECMO and Early Reperfusion (CHEER) trial was an observational prospective study examining the use of a protocol for treating refractory cardiac arrest that involved the use of mechanical cardiopulmonary resuscitation (CPR), hypothermia, VA-ECMO (labelled extracorporeal CPR in this context) and early reperfusion where indicated. Survival to discharge with full neurological recovery in this group was 54%, with an average time of collapse to instigation of ECMO therapy being 54 min.<sup>87</sup> Survival was better in those with a smaller time delay to starting ECMO therapy. There have been no RCTs of the use of VA-ECMO in patients with CS.

#### CURRENT GUIDELINES FOR USE OF MCS

For many years, due to its physiological mechanisms and observational data supporting its use,

alongside its ease of insertion and low complication rate, the balloon pump had a class I indication in the management of CS.<sup>88–90</sup> However, the publication of several neutral trials evaluating IABP therapy has resulted in a downgrading of the indication to class IIa level evidence B (American Heart Association (AHA))<sup>91</sup> and class IIIa (European Society of Cardiology (ESC)),<sup>92</sup> with the former stating that IABP should only be considered in patients with STEMI who do not stabilise quickly on pharmacological therapy and those with haemodynamic instability/CS due to mechanical complications (class IIa) level of evidence B. With regards to percutaneous LVADs, the 2014 ESC myocardial revascularisation guidelines state they may be considered in patients presenting with an acute coronary syndrome and shock (class IIb level evidence C).<sup>92</sup> The latest AHA STEMI guidelines published in 2013 state that percutaneous LVADs can be considered for patients in refractory CS, with a class IIb level evidence C.<sup>91</sup> The AHA/American College of Cardiology (ACC) non-STEMI guidelines published in 2014 recommend a class I indication for revascularisation in heart failure and further state that percutaneous ventricular assist devices be considered for patients with a large amount of myocardium at risk and severely impaired cardiac function.<sup>93</sup> This recommendation for MCS is further supported by the recent FDA approval of the Impella device for high-risk PCI.

Dramatic changes in guidance across the international societies and overall lack of evidence on the role of percutaneous MCS in CS prompted the formation of a Society for Cardiac Angiography and Interventions (SCAI)/American College of Cardiology (ACC)/Heart Failure Society of America (HFSA)/Society of Thoracic Surgeons (STS) Clinical Expert Consensus Group. This group published a statement in several major journals earlier this year reviewing the use of percutaneous MCS in cardiovascular care.<sup>63</sup> The main conclusions from the expert consensus statement were that MCS: (1) provides superior haemodynamic support compared with pharmacological therapy, (2) should be considered early in patients in CS, (3) that in setting of profound CS, IABP is less likely to be of benefit, (4) higher support devices should be considered early if required and severe biventricular failure may require the use of both right-sided and left-sided devices, and (5) that these devices may be used in patients who have failed to wean off cardiopulmonary bypass, for valvular implants and for patients undergoing an electrophysiological procedure where prolonged periods of hypotension are predicted. A collaborative viewpoint on Impella support specifically in clinical practice has been recently published by a European expert user group.<sup>38</sup>

#### SUMMARY AND CLINICAL ALGORITHM FOR DEVICE THERAPY

Although at present there is a lack of randomised clinical trials that support the use of MCS in CS, high-risk PCI or AMI, clinicians continue to use



these devices because of their haemodynamic effects, favourable registry data and the results of several subanalyses of RCTs (such as PROTECT-II and CRISP-AMI trials<sup>17 51</sup>). A recently published observational study using data taken from the Nationwide Inpatient Sample sought to evaluate the use of short-term MCS in the context of STEMI complicated by CS in the USA between 2003 and 2012. The investigators found that IABP use increased steadily until 2009, with a decrease in its use since then. Concurrently, there was a significant increase in the use of other percutaneous assist devices such as Impella and TandemHeart, with the higher volume PCI centres using more MCS devices.<sup>94</sup> Although, the use of the latter, more haemodynamically effective MCS devices appears to be on the increase in the USA, this may not be reflected internationally, most often due to lack of centre expertise, cost and lack of definitive RCT data to support their use.

When considering device therapy, there are several factors that need to be addressed including the patient's physiology, planned procedure and MCS device-related factors. In CS, this physiological evaluation includes assessment of distal organ perfusion (through monitoring of indices such as lactate, urine output and mixed venous oxygen saturation), as well as the cardiac status in terms of myocardial supply and demand and establishing whether there is primarily univentricular or biventricular failure. In the latter case, biventricular support strategies should be considered. Another key factor to consider is the safety of the device, and feasibility of rapid insertion and subsequent monitoring, which in part will vary depending on the treating centre. Currently, when severe hypotension develops the initial therapeutic strategy is inotropic and vasopressor therapy, due to their rapid onset of action. However, the detrimental effects of pharmacologic therapy alone on the heart must not be forgotten, and there needs to be a paradigm shift whereby device therapy is considered quickly if inotropes/vasopressors fail to stabilise the patient. When there is an indication that escalating doses or multiple inotropes/vasopressors are required to support the circulation, an MCS should be instigated quickly, to avoid these high doses of pharmacotherapy. This is often an IABP or Impella CP depending on local familiarity and insertion times. However, it is important that the patient's haemodynamic and metabolic condition is closely monitored for signs of deterioration and device therapy rapidly escalated to more powerful haemodynamic devices if needed, to prevent the downward spiral of CS. In some cases of CS, upfront device therapy may be preferable to pharmacologic therapy as an initial stabilisation method. **Table 2** displays what each goal of support is and how each device meets them, as a framework for device selection. **Figure 6** provides a clinical algorithm to aid physicians in selecting the optimal acute circulatory support device for CS. The key is continued assessment during support, and escalating therapy when required early, including

**Table 2** Summary of the overall goals of mechanical circulatory support, and how each device impacts on these, as a guide for device selection

	A: Myocardial protection		B: Organ perfusion	C: Ease of use
	Supply	Demand		
Inotropes/vasopressors	?	--	(-)	++
IABP	+	(+)	(+)	++
Impella	+	++	+	+
TandemHeart	?	++	+	-
VA-ECMO	?	-	+	-

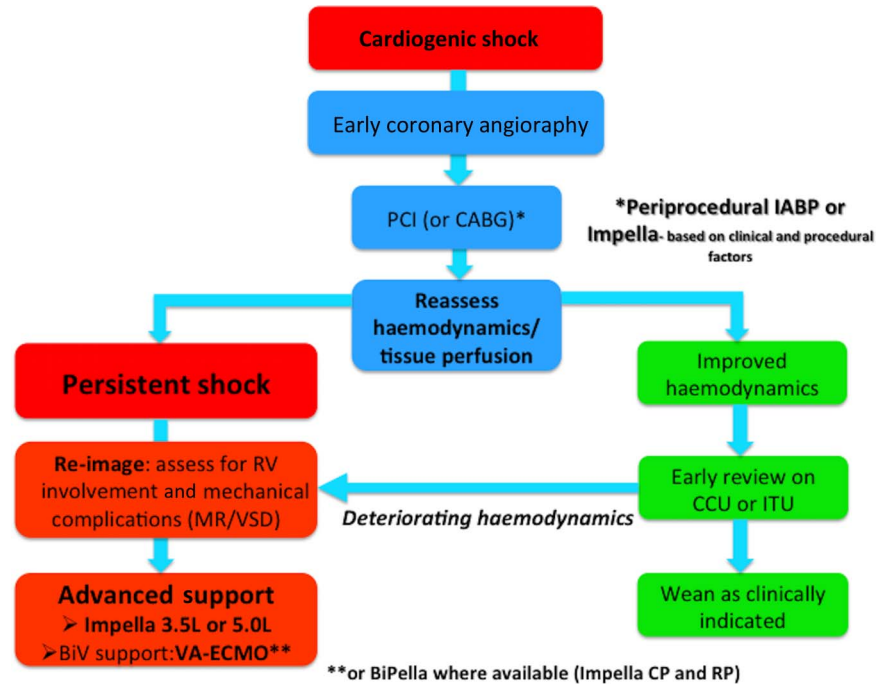
+, desired effects; -, undesired effects; ?, missing/equivocal data.  
IABP, intra-aortic balloon pump; VA-ECMO, veno-arterial extracorporeal membrane oxygenation.

consideration of advanced surgical VAD therapies and cardiac transplantation in those without contraindications.<sup>95</sup>

With respect to the stable, high-risk patient undergoing PCI, procedural characteristics need to be considered, including the need for rotational atherectomy, PCI on the last remaining conduit, left main stem PCI and PCI in context of STEMI. Patient characteristics that also need to be considered include presence of depressed LV function, ongoing ischaemia and other comorbidities. Using such a model, risk is a continuous parameter, with the degree of risk being proportional to the number of coexistent risk factors. This concept is illustrated graphically in **figure 7**.

As with any new technology, there is an inevitable learning curve associated with its introduction. A subanalysis of the PROTECT II trial found that after excluding the first patients receiving an Impella in each centre, there was a significant reduction in major adverse events in the Impella-treated arm compared with the IABP-treated arm at 90 days.<sup>53</sup> This learning curve extends to all the physicians, catheter laboratory and nursing staff that implant and manage these device patients. While balloon pumps are well established in most centres that have an on-site catheter laboratory, the newer higher support devices are less widely available, and in general are reserved for tertiary and quaternary cardiac centres. Although in general not difficult to implant, as they use standard Seldinger techniques for vascular access, the challenge lies in the ongoing management of a patient with the device, including troubleshooting issues and decisions surrounding escalating and de-escalating support when required. In the USA, broader adoption of Impella in primary PCI centres has led to early device utilisation (elevation of support as opposed to stepwise escalation) in CS as an approach to achieve earlier haemodynamic stability. Transfer to advanced heart failure centres occurs if early stabilisation is not achieved. In the UK, we recommend the adoption of a hub and spoke approach for these high-risk patients. Patients in CS in local district general hospitals should be swiftly stabilised on inotropes (and where possible

**Figure 6** Clinical algorithm for management of cardiogenic shock with respect to mechanical circulatory support. CABG, coronary artery bypass grafting; CCU, coronary care unit; IABP, intra-aortic balloon pump; ITU, intensive care unit; MR, mitral regurgitation; PCI, percutaneous coronary intervention; VA-ECMO, veno-arterial extracorporeal membrane oxygenation; VSD, ventricular septal defect.



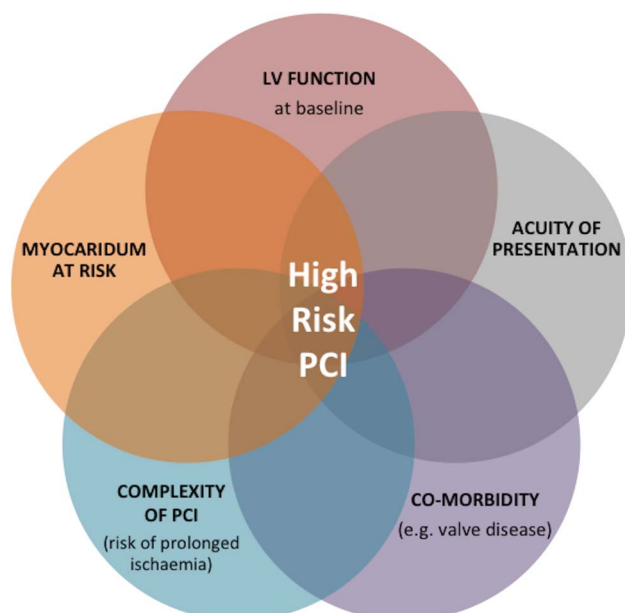
implantation of an IABP), and if no significant improvement, should be referred early to a centre that can provide the full range of percutaneous MCS devices. This hub and spoke approach has been shown to be of benefit in studies, particularly in the cohort of patients requiring VA-ECMO. A recent study has shown benefit in retrieving these patients in their local hospital and initiating VA-ECMO at the referring centre prior to transfer,<sup>96</sup> which is very similar to veno-venous (VV)-ECMO services that are currently available in the UK. It is likely that in the next few years we will see the development of comprehensive MCS

centres that do not offer transplant, which will supplement the capacity of transplant centres and reflect the fact that heart transplants are a limited resource and the need for MCS far outweighs their availability. It is also anticipated that patients with a potentially reversible aetiology can avoid the need for transplantation by timely use of MCS.

### FUTURE PERSPECTIVES

There is a pertinent need to continue to evaluate the utility of different types of MCS, in various clinical settings by performing RCTs as well as detailed physiological studies. However, this is one area of medicine in which such randomised data are particularly difficult to collect as the patients who usually need MCS are profoundly unwell and hence are difficult to recruit to studies. Two important ongoing clinical trials are the Danish Cardiogenic Shock Trial (NCT01633502), which compares conventional circulatory support with the Impella in patients presenting within 36 hours of a STEMI and CS of <24 hours in duration,<sup>97</sup> and the IMPRESS in Severe Shock (IMPella vs IABP Reduces mortality in STEMI patients treated with primary PCI IN SEVERE and deep cardiogenic SHOCK, NTR3450) trial, of which the results of both are eagerly anticipated. Table 3 provides a summary of currently recruiting and previously terminated clinical trials of MCS.

There is also much research interest in exploring new indications for these devices, including the use of IABP in the no-reflow phenomena and the use of Impella CP to accomplish LV unloading before reperfusion during STEMI, ventricular tachycardia ablation, valvular treatments such as transcatheter aortic valve interventions and decompensated chronic heart failure (particularly as an alternative to surgical LVADs). This is a rapidly



**Figure 7** Venn diagram of what constitutes high-risk percutaneous coronary intervention.

**Table 3** Terminated and currently recruiting trials in mechanical circulatory support

Trial name	Device	Study design	Clinical setting	NCT/NTR no.	Status
ExtraCorporeal Membrane Oxygenation in the Therapy of Cardiogenic Shock	VA-ECMO	RCT, ECMO vs conservative strategy	CS	02301819	Recruiting
Danish Cardiogenic Shock trial	Impella	RCT	CS	01633502	Recruiting
TandemHeart Experiences and Methods (THEME registry)	TandemHeart	Observational, prospective	All settings where TandemHeart may be required	02326402	Recruiting
TRIS trial	TandemHeart	RCT	STEMI	02164058	Withdrawn
IMPRESS in severe shock	Impella/IABP	RCT	CS secondary to STEMI	3450	Recruitment completed
IMPRESS in STEMI	Impella/IABP	RCT	STEMI	1079	Terminated
Comparison of standard treatment vs standard treatment plus ECLS in myocardial infarction complicated by CS	VA-ECMO, Impella	RCT	CS	00314847	Terminated
RECOVER II	Impella	RCT	AMI	00972270	Terminated
MINI-AMI	Impella	RCT	AMI	01319760	Terminated
SHEILD II	Impella, PHP	RCT	High-risk PCI	02468778	Recruiting
SEMPER FI	IABP	RCT	AMI with ongoing ischaemia and no reflow following revascularisation		Recruiting

AMI, acute myocardial infarction; CS, cardiogenic shock; ECLS, extra-corporeal life support; IABP, intra-aortic balloon pump; PCI, percutaneous coronary intervention; RCT, randomised clinical trial; STEMI, ST segment elevation myocardial infarction; VA-ECMO, veno-arterial extracorporeal membrane oxygenation.

### Key messages

- ▶ Cardiogenic shock secondary to a variety of different aetiologies (including haemodynamic deterioration during high-risk percutaneous coronary intervention (PCI)) continues to be a significant clinical problem with high morbidity and mortality.
- ▶ Inotropes and vasopressors are often instigated early, at the expense of worsening myocardial oxygen demand.
- ▶ Percutaneous mechanical circulatory support (MCS) devices have been developed to help maintain distal tissue perfusion in the face of profound cardiac failure, while simultaneously favourably impacting on the myocardial supply-and-demand ratio to support myocardial recovery.
- ▶ The current devices in clinical practice have varying physiological mechanisms of action that provide univentricular (intra-aortic balloon pump (IABP), Impella, TandemHeart) or biventricular support (veno-arterial extracorporeal membrane oxygenation or BiPella).
- ▶ Animal models and registry data have demonstrated feasibility, haemodynamic efficacy and safety of these devices; however, randomised trials where performed have not demonstrated an improvement in mortality with their use. This in part reflects the difficulty in conducting trials in these patient populations, with many trials terminated early due to slow recruitment.
- ▶ The use of IABP is declining despite its ease of use and availability in the majority of catheter laboratories globally, due to the neutral results of several randomised controlled trials. This is reflected by the current guidelines advising against its routine use in high-risk PCI or cardiogenic shock. There is a lack of definitive randomised clinical trials data to support the use of acute MCS devices, and their global clinical use is limited by centre expertise and cost.
- ▶ Elective patients undergoing high-risk PCI should be assessed in relation to both the likelihood and consequence of haemodynamic compromise during the procedure, to decide which device is most suitable. In patients with an urgent or emergent indication such as in cardiogenic shock, MCS should be considered early and the correct device targeted to each individual presenting haemodynamics, with frequent re-assessment of the haemodynamic efficacy of the devices and consideration of upgrading support, if required.

evolving field as new devices are continually being evaluated and introduced into the clinical arena. One of these is the Impella RP, which is a percutaneous device that has FDA approval for Humanitarian Device Exemption for implantation of up to 14 days in patients with acute right heart failure. It is the first axial flow catheter designed to support the RV.<sup>98 99</sup> The RECOVER RIGHT trial was recently published and confirmed the haemodynamic efficacy and safety of the Impella RP.<sup>99</sup> There have also been reports of the use of both an Impella 5.0 and an Impella RP (referred to as BiPella) to support biventricular failure, which now opens the possibility of biventricular support for CS.<sup>100</sup> The iCOR device is another newly developed device that is similar to an ECMO circuit; however, it is an axial flow pump that can provide pulsatile circulatory support. It consists of a novel diagonal pump, providing up to 8 L/min of support and also allowing the synchronisation of the rotational timing of the pump to the ECG, providing greater physiological support. The first-in-human study of 15 patients showed that haemodynamics significantly improved on the iCOR system with significant increases in glomerular filtration rate.<sup>101</sup> However, this was at the cost of a significant rate of limb ischaemia (20%), and a large proportion of the patients required a blood transfusion (73%), reflecting the increased vascular access complications and haemolysis.

### CONCLUSION

MCS can provide superior haemodynamic support compared with conventional inotropic/vasopressor therapy, without the deleterious effects inotropes/vasopressors have on the heart. The different devices available clinically have varying physiological mechanisms of action, provide differing levels of support, have different safety profiles and

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also vary in their availability across centres. They should not be thought of as being in direct competition with one another, but rather as representing a continuum of options, allowing clinicians to provide the correct device for the appropriate patient. There is still a lack of randomised, controlled clinical data, supporting the use of acute circulatory support devices, which is necessary to advance the management of CS, to assess whether the beneficial physiological effects translate into improved clinical outcomes in a condition that continues to have a poor prognosis.

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# Percutaneous mechanical circulatory support: current concepts and future directions

Natalia Briceno, Navin K Kapur and Divaka Perera

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