

### Novel devices

# Mechanical circulatory support in cardiogenic shock

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Despite advances in coronary revascularization and widespread use of primary percutaneous interventions, cardiogenic shock complicating an acute ST-elevation myocardial infarction (CSMI) remains a clinical challenge with high mortality rates. Conservative management with catecholamines is associated with serious limitations, including arrhythmias, increased myocardial oxygen consumption, and inadequate circulatory support. Clinicians have therefore turned to mechanical means of circulatory support. Circulatory assist systems for CSMI can be distinguished by the method of placement (i.e. percutaneous vs. surgical), the type of circulatory support (i.e. left ventricular, right ventricular, or biventricular pressure and/or volume unloading), and whether they are combined with extracorporal membrane oxygenation (ECMO). The percutaneous assist systems most commonly used in CSMI are the intra-aortic balloon pump (IABP), venoarterial ECMO, the Impella pump, and the Tandem-Heart. Decades of clinical studies and experience demonstrated haemodynamic improvement, including elevation of diastolic perfusion pressure and cardiac output. Recently, the large randomized IABP-Shock II Trial did not show a significant reduction in 30-day mortality in CSMI with IABP insertion. There are no randomized study data available for ECMO use in CSMI. Both the Impella pump and the TandemHeart did not reduce 30-day mortality when compared with IABP in small randomized controlled trials (RCTs). In conclusion, despite the need for effective mechanical circulatory support in CSMI, current devices, as tested, have not been demonstrated to improve short- or long-term survival rates. RCTs testing the optimal timing of device therapy and optimal device design are needed to improve outcomes in CSMI.

**Keywords** 

Cardiogenic shock • Left ventricular assist devices • Mortality • APACHE II score • Interleukin 6 (IL-6)

### Introduction

Cardiogenic shock, the most severe form of acute heart failure, is characterized by (i) myocardial contractile dysfunction resulting in the inability of the left ventricle to maintain adequate cardiac output (i.e.  $CI < 2.2 \text{ L} \text{min}^{-1}$ ) despite normal or elevated pre-load (i.e. normal circulatory blood volume, PCWP greater than or equal to 15 to 18 mmHg) and (ii) clinical signs of peripheral tissue hypoperfusion as evidenced by decreased urine output, altered mental status, and/or cold extremities. In recent studies of cardiogenic shock, eligibility criteria included systolic blood pressure <90 mmHg for >30 min or catecholamines required to maintain systolic pressure >90 mmHg plus clinical signs of pulmonary congestion and impaired organ perfusion with at least one of the following criteria: (i) altered mental status; (ii) cold, clammy skin and extremities; (iii) oliguria with urine output <30 mL h<sup>-1</sup>; or (iv) serum lactate >2.0 mmol L<sup>-1</sup>.

Despite the technical advances in cardiology, cardiogenic shock as a complication of acute myocardial infarction (CSMI) remains an unresolved medical challenge. The last significant innovation resulting in a decline in mortality from cardiogenic shock—early reperfusion of the infarct-related coronary artery by percutaneous coronary intervention (PCI)<sup>2</sup>—is more than 10 years old. Despite use of coronary intervention, improved antithrombotic regimens, and significant advances in cardiac intensive care medicine, mortality rates remain unacceptably high at over 40% (*Figure 1*).<sup>3,4</sup> In contrast to cardiogenic shock due to other causes (e.g. acute myocarditis, acute valvular heart disease, congenital heart disease, etc.), CSMI with severe systolic contractile dysfunction comprises a relatively homogenous population in which treatment options can be tested in randomized trials. Hence, this review will focus on this patient group.

The failure of pharmacological therapy to maintain adequate perfusion and to prevent irreversible end-organ failure in many patients with cardiogenic shock has led to attempts to improve the circulation



**Figure I** Time trends in hospital case fatality rates (CFR) in patients with acute myocardial infarction  $\pm$  cardiogenic shock in the Worcester (MA, USA) metropolitan area. Despite the survival improvement resulting from more widespread use of acute interventional reperfusion strategies, overall cardiogenic shock mortality rates remain high at over 40%. The additional columns (from left to right) represent mortality rates from (A) the SHOCK study<sup>2</sup> (dark grey column: IMS, Initial Medical Stabilisation Group; light grey column: ERV, Early Revascularisation Group); (B) the TRIUMPH Study<sup>52</sup> [all patients with ERV; with (dark grey column) or without (light grey column) the nitric oxide synthase (NOS) inhibitor Tilarginine]; and (*C*) the IABP SHOCK II Trial<sup>4</sup> [all patients with ERV; with (dark grey column) or without (light grey column) intraaortic balloon counterpulsation (IABP)]. Modified from Goldberg et al.<sup>80</sup>

and outcomes by mechanical circulatory support devices.<sup>5</sup> Recently, the IABP-Shock II Trial did not demonstrate improvement in 30-day survival after implantation of an intra-aortic balloon pump (IABP) in patients with CSMI.<sup>4</sup> It is therefore timely to reassess existing and future devices that provide circulatory support. How do they differ in concept? What increase in cardiac output can be achieved? What are the typical device-related complications, and how do they compare with the clinical benefits as seen in prospective trials?

### Prognosis of post-infarction cardiogenic shock and predictors of survival

### Predictors of survival in cardiogenic shock: haemodynamic impairment and/or multiorgan dysfunction syndrome?

Analysing the results of 1600 patients from the SHOCK trial and registry<sup>6</sup> and from the TRIUMPH trial,<sup>7</sup> the following mortality risk factors have been identified by multivariate modelling: age, anoxic brain damage, end-organ hypoperfusion, stroke work, left ventricular (LV) ejection fraction, systolic blood pressure, vasopressor support, and creatinine clearance. However, cardiogenic shock is not a mere decrease in cardiac contractile function, but also a multiorgan dysfunction syndrome (MODS) resulting from peripheral hypoperfusion with microcirculatory dysfunction, often complicated by a systemic inflammatory response syndrome (SIRS) and sepsis (*Figure 2*).<sup>4,8–13</sup> Once MODS has developed, it is difficult to improve prognosis and reduce mortality by simply increasing cardiac output with a circulatory assist device. Prevention of MODS may depend on three critical factors:

- (1) optimal timing (i.e. early initiation) of mechanical circulatory support,
- (2) optimal level of mechanical circulatory support with reestablishment of adequate perfusion of critical organs, and
- (3) optimal prevention and management of potential device-related complications (i.e. device malfunction, infection).

Intuitively, one would expect that haemodynamic parameters would best discriminate between survivors and non-survivors, and at least for the calculated pressure-flow-product 'cardiac power output/index', this has been demonstrated.<sup>14,15</sup> However, in the IABP-Shock study,<sup>10</sup> cardiac index itself was unrelated to patient survival beyond the first 24 h of CSMI. Likewise, biomarkers of heart failure (e.g. BNP) were unrelated to prognosis in the first 96 h of CSMI.

On the other hand, MODS severity (as indicated by the APACHE II or SAPS II scores<sup>10</sup>) and biomarkers of SIRS (like Interleukin 6 and receptor of advanced glycation end-products, RAGE) can predict mortality more accurately than haemodynamic indices (*Table 1*).<sup>16</sup> What do these unexpected findings imply for mechanical circulatory support in CSMI?

### Consequence of multiorgan dysfunction syndrome as predictor of survival for mechanical circulatory support

Although LV contractile failure and low cardiac output are the primary cause of cardiogenic shock, improving cardiac output alone may not reverse or even halt the progression of MODS if initiated too late. Therefore, the haemodynamic improvement of cardiac index may be a measure of *technical success* of mechanical circulatory support; however, without limiting the progression of SIRS



Figure 2 Prognostically relevant components of cardiogenic shock complicating myocardial infarction. In addition to severe systolic and diastolic cardiac dysfunction compromising macro- and microcirculation, also systemic inflammatory response syndrome and even sepsis may develop, finally resulting in multiorgan dysfunction syndrome. The pro- and anti-inflammatory cytokines mentioned have prognostical significance, with either higher  $(\uparrow)$  or lower  $(\downarrow)$  serum levels in non-survivors compared with survivors. G-CSF, granulocyte colony-stimulating factor; IF, interferon; IL, interleukin; MCP, monocyte chemotactic protein; MIP, macrophage inflammatory protein. Modified from Hochman<sup>13</sup> and supplemented with results from the first randomized IABP-Shock trial.<sup>10-12</sup>

and MODS within the first few days, these haemodynamic improvements may be futile and may not translate into improved survival.

# Pharmacological therapy in cardiogenic shock

Current guidelines on the use of inotropes in cardiogenic shock are very careful in evaluating the risk–benefit ratio of inotropes and vasopressors. The recent *ESC Guideline on Acute and Chronic Heart Failure* states that 'Inotropes cause sinus tachycardia and may induce myocardial ischaemia and arrhythmias. There is long-standing concern that they may increase mortality'.<sup>17</sup>

### **Inotropic therapy**

Dobutamine is regarded as the initial treatment of choice in cardiogenic shock with low-output syndrome and preserved systolic blood pressure.<sup>18</sup> Because dobutamine does not increase blood pressure *per se*, it may be combined with vasopressors to maintain adequate mean arterial pressure. All catecholamine-based inotropes cause tachycardia, increase myocardial oxygen demand, and can trigger arrhythmias—both supraventricular and ventricular. In a special subset—patients with post-cardiotomy cardiogenic shock—highdose inotropes were clearly related to higher in-hospital mortality.<sup>19</sup>

Because of these side effects, other inotropes have been evaluated in cardiogenic shock. Phosphodiesterase inhibitors (e.g. milrinone) have fewer adverse chronotropic and arrhythmogenic effects but can cause significant vasodilation and hypotension and are therefore not a preferred therapeutic option in cardiogenic shock. Calcium sensitizers such as levosimendan do not increase myocardial oxygen consumption and may be less arrhythmogenic. Small studies have confirmed the haemodynamic benefit of levosimendan in CSMI,<sup>20</sup> which may exceed the effects of dobutamine<sup>21</sup> and enoximone.<sup>22</sup> Nevertheless, at least in patients with acute heart failure, survival was not superior.<sup>23</sup>

Istaroxime is a novel inotropic agent with positive inotropic and lusitropic effects through inhibition of the Na<sup>+</sup>/K<sup>+</sup>-ATPase and activation of the sarcolemmal calcium ATPase (SERCA).<sup>24</sup> In the HORIZON-HF study in patients with acute heart failure, reduced LV ejection fraction, and preserved systolic blood pressure (90–150 mmHg), istaroxime reduced PCW pressure, increased cardiac output, and improved diastolic LV function.<sup>25</sup> It has not yet been tested in CSMI.

### Vasopressor therapy

Despite their widespread use in cardiogenic shock, there are limited numbers of prospective randomized studies comparing different vasopressor treatment strategies in shock patients. Most recently, De Backer *et al.*<sup>26</sup> compared dopamine and norepinephrine in shock and found that there was no significant between-group difference in the rate of death at 28 days but more arrhythmic events among the patients treated with dopamine. A subgroup analysis showed that dopamine, compared with norepinephrine, was

Biomarker	Area under the curve (Selejan et <i>al.</i> 2012) <sup>81</sup>	Area under the curve (Prondzinsky et al., 2010, Intra-Aortic Balloon counterpulsation Pump SHOCK Trial) <sup>10</sup>
RAGE expression on monocytes	0.943, <i>P</i> < 0.001	
Soluble RAGE in plasma	0.815, <i>P</i> = 0.004	
SAPS score	0.873, <i>P</i> < 0.001	
APACHE score		0.850, <i>P</i> < 0.001
Cardiac power index	0.742, <i>P</i> = 0.025	
Cardiac index		0.771, <i>P</i> = 0.088
Interleukin-6 in plasma	0.747, <i>P</i> = 0.025	0.769, <i>P</i> = 0.011
Pro-BNP	0.674, <i>P</i> = 0.149	
BNP		0.502, <i>P</i> = 0.987
C-reactive protein	0.505, P = 0.963	

#### Table I Prognostic biomarkers in patients with cardiogenic shock complicating acute myocardial infarction

APACHE, Acute Physiology and Chronic Health Evaluation; BNP, B-type natriuretic peptide; RAGE, receptor for advanced glycation end-products; SAPS, Simplified Acute Physiology Score. From Werdan.<sup>16</sup>

associated with an increased rate of death at 28 days among the 280 patients with cardiogenic shock (P = 0.03; the percentage of CSMI patients within this cardiogenic shock subset is not given), but not among the 1044 patients with septic shock (P = 0.19) or the 263 patients with hypovolemic shock (P = 0.84). The European STEMI guidelines<sup>27</sup> prefer dopamine (IIaC) over norepinephrine (IIbC) but state that norepinephrine is preferred over dopamine when blood pressure is low. The German–Austrian CSMI guideline<sup>28</sup> states that 'Norepinephrine should be given as vasopressor ( $\uparrow$ )'.

### Conclusions

Taken together, the current pharmacological inotropic and vasopressor therapy in CSMI should be regarded as symptomatic therapy to counteract the cardiac low output failure and peripheral hypoperfusion. However, inotropes are potentially hazardous in ischaemic heart failure due to the increased myocardial oxygen demand, and vasopressors can worsen peripheral tissue perfusion and microcirculation. It is therefore generally recommended to aim for the desired therapeutic effect at the lowest possible dose. The lack of clear evidence on the efficacy of pharmacological inotropic support and the limited or even adverse effect of catecholamine therapy on survival in CSMI are the driving forces behind further exploration of mechanical means of circulatory support.

### Mechanical circulatory support

Despite the large number of devices for mechanical circulatory support used in cardiogenic shock<sup>5,29–32</sup> (*Figure 3, Table 2*), there are few well-conducted prospective randomized studies allowing an evidence-based judgement on their therapeutic effectiveness. In this report, we focus on evidence-based application of percutaneous devices in cardiogenic shock, whereas for surgical ventricular assist devices, the reader is referred to the relevant literature.<sup>29,33–37</sup>

Ouweneel and Henriques<sup>32</sup> defined the 'ideal device for cardiogenic shock' as follows: '... during an acute critical presentation, only those assist devices allowing percutaneous access are suitable due to the invasiveness of surgical devices. The ideal device should enable both haemodynamic support and myocardial protection. Also, a percutaneous approach is preferable to provide for a quick and easy deployment. In addition, the ideal device should be associated with a low complication rate, as complications may sometimes outweigh the potential beneficial effect. Complications associated with any (percutaneous) LV assist device may include limb ischaemia, embolisation of atherosclerotic and/or thrombotic material, stroke, infection and haemolysis'.

In line with these demands for mechanical circulatory support in CSMI, different technical strategies have been developed over the past decades to (i) improve cardiac output and (ii) unload the critically damaged left ventricle by either afterload or pre-load reduction (i.e. pressure or volume unloading, respectively).

Additionally, circulatory support may be provided to the left ventricle alone, the right ventricle alone, or to both ventricles. Biventricular assist devices may be combined with replacement of pulmonary gas exchange (i.e. extracorporal membrane oxygenation, ECMO) or be administered as pure right and LV haemodynamic support.

Based on the different physiological concepts outlined above, we propose to distinguish among four categories of percutaneous circulatory support devices in CSMI:

- (1) mechanical LV support by LV pressure unloading—the IABP;
- (2) mechanical LV support by LV volume unloading—the TandemHeart<sup>™</sup>, the Impella Recover LP<sup>®</sup> micro-axial rotary pump;
- (3) mechanical biventricular support—combination of right ventricular circulator support using a modified TandemHeart and one of the LV circulatory assist devices (e.g. Impella pump); and
- (4) mechanical biventricular support with membrane oxygenation— ECMO.

Mechanical biventricular support without simultaneous replacement of pulmonary gas exchange plays a significant role in cardiac surgery,





with combined right ventricular assist device (RVAD) and left ventricular assist device (LVAD) therapy or the fully implantable total artificial heart. Although it is possible to insert axial flow pumps in both the right and the left ventricle, this therapeutic strategy has not gained any significant role in CSMI. We will therefore focus on (1), (2), and (4).

### Mechanical left ventricular support by left ventricular pressure unloading: the intra-aortic balloon pump

#### Intra-aortic balloon pump: the concept

With the IABP in place in the descending thoracic aorta, inflation of the balloon in diastole and active deflation in systole induce higher diastolic perfusion pressures in the coronary arteries and unload the diseased heart by reducing LV afterload during systole. Volume shifting of ~40 mL per beat by the IABP increases LV stroke volume and cardiac output by up to  $1 \text{ L min}^{-1}$  (15–30%, respectively), with the largest increases seen in patients with severely reduced CO.

The haemodynamic effects of IABP in CSMI<sup>38</sup> include

- an increase in stroke volume and CO,
- an increase in systemic blood pressure with increased coronary blood flow in open coronary arteries,<sup>39</sup>
- a reduction in LV pre-load, LV end-diastolic pressure, and pulmonary capillary wedge pressure,
- a decrease in LV wall stress and myocardial oxygen demand, and
- improved reperfusion after thrombolysis in STEMI patients.

However, in severe coronary artery stenosis or acute coronary syndrome, more findings argue against<sup>39–41</sup> than for<sup>42</sup> a clinically relevant increase in coronary blood flow after IABP insertion beyond critical stenoses, despite an increase in coronary perfusion pressure. The IABP can increase mean blood pressure in CSMI by markedly increasing diastolic pressure in the upper part of the body. In IABP patients with CSMI, a mild improvement of microcirculatory flow was documented<sup>43</sup>; however, microvascular density, which is better related to prognosis, remained unchanged.<sup>44</sup>

Detailed information on IABP insertion and removal techniques, care of the patient with an IABP, and contraindications and complications may be found in *The ESC Textbook of Intensive and Acute Cardiac Care.*<sup>38</sup>

#### Clinical studies with surrogate endpoints

A review of the evidence from non-randomized and small randomized clinical trials that studied the use of IABP in CSMI has recently been published.<sup>45</sup> As expected, these trials do not provide conclusive evidence whether IABP might reduce mortality in CSMI. 'Real world' clinical practice patterns and outcomes are better reflected by the Euro Heart Survey on PCI<sup>46</sup>: of 654 CSMI patients, 25% were treated with IABP; in-hospital mortality, with and without IABP, was 56.9 and 36.1%, respectively. In the multivariate analysis, the use of IABP was not associated with improved survival (OR 1.47; P = 0.07).

In the first randomized study comparing IABP therapy with conservative management in 40 CSMI patients—the IABP SHOCK trial<sup>10–12,47</sup>—IABP treatment did not improve haemodynamics or reduce systemic inflammation or the severity of MODS. BNP levels were significantly lower in the IABP group at 48 and 72 h, indicating unloading of the left ventricle. However, this did not translate into better clinical outcomes, including survival in this small study.

### Clinical outcome studies

There are three meta-analyses that address the role of IABP in CSMI.  $^{\rm 48-50}$  In the Cochrane Database Systematic Review,  $^{\rm 49}$  six

### Table 2 Comparison of devices

	IABP	ЕСМО	TandemHeart	Impella 2.5	Impella 5.0
Pump mechanism	Pneumatic	Centrifugal	Centrifugal	Axial flow	Axial flow
Cannula size	7.9 Fr	18–21 Fr inflow;15–22 Fr outflow	21 Fr inflow; 15–17 Fr outflow	13 Fr	22 Fr
Insertion technique	Descending aorta via the femoral artery	Inflow cannula into the right atrium via the femoral vein, outflow cannula into the descending aorta via the femoral artery	21 Fr inflow cannula into left atrium via femoral vein and transseptal puncture and 15–17 Fr outflow cannula into the femoral artery	12 Fr catheter placed retrogradely across the aortic valve via the femoral artery	21 Fr catheter placed retrogradely across the aortic valve via a surgical cutdown of the femoral artery
Haemodynamic support	$0.5 - 1.0 \text{ Lmin}^{-1}$	$>4.5 \text{ Lmin}^{-1}$	$4 \mathrm{Lmin}^{-1}$	2.5 L min <sup>-1</sup>	5.0 L min <sup>-1</sup>
Implantation time	+	++	+++	++	++++
Risk of limb ischaemia	+	+++	+++	++	++
Anticoagulation	+	+++	+++	+	+
Haemolysis	+	++	++	++	++
Post-implantation management complexity	+	+++	++++	++	++
Optional active cooling in post- cardiopulmonary resuscitation patients	No	Yes	(Yes)	No	No

ECMO, extracorporeal membrane oxygenation; IABP, intra-aortic balloon pump; +, ++, +++, relative qualitative grading concerning time ('implantation time'), risk ('risk of limb ischaemia'), intensity ('anticoagulation', 'post-implantation management complexity'), and severity ('haemolysis'). Modified from Ouweneel and Henriques.<sup>32</sup>

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IABP	ECMO	TandemHeart	Impella
Reduced	Increased	Increased	Neutral
Slight increase	Reduced	Reduced	Reduced
Slight increase	Unknown	Unknown	Unknown
Slightly reduced	Reduced	Reduced	Slightly reduced
Slightly reduced	Reduced	Reduced	Slightly reduced
No significant increase	Improved	Improved	Improved
	IABP Reduced Slight increase Slight increase Slightly reduced Slightly reduced No significant increase	IABPECMOReducedIncreasedSlight increaseReducedSlight increaseUnknownSlightly reducedReducedSlightly reducedReducedNo significant increaseImproved	IABPECMOTandemHeartReducedIncreasedIncreasedSlight increaseReducedReducedSlight increaseUnknownUnknownSlightly reducedReducedReducedSlightly reducedReducedReducedSlightly reducedReducedReducedNo significant increaseImprovedImproved

Table 3 Propo	ed haemod	ynamic	effects o	f the mec	hanical	circulatory	/ support	device
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eligible and two ongoing randomized controlled trials (RCTs) were identified from a total of 1410 references, with inclusion of 190 patients (105 patients treated with IABP and 85 controls—40 without devices and 45 with LVAD). The reported hazard ratio for all-cause 30-day mortality was 1.04 (95% confidence interval 0.62–1.73), demonstrating no evidence for a survival benefit when using IABP in CSMI. A subset analysis of 62 patients in the two studies<sup>10,51</sup> comparing IABP vs. no IABP without LVAD showed that IABP did not significantly reduce in-hospital, 30-day, or 6-month all-cause mortality rates.

Nine cohorts of STEMI patients with cardiogenic shock (n = 10,529) were included in the meta-analysis of Sjauw et al.<sup>48</sup> In patients treated with thrombolysis, IABP was associated with an 18% decrease in 30-day mortality (P < 0.0001), although this may be due to significantly higher revascularization rates compared with patients without LV support. In contrast, in patients treated with primary PCI, IABP was associated with a 6% (P = 0.0008) increase in 30-day mortality. This meta-analysis indicates that immediate revascularization may have a greater impact on survival in CSMI than IABP use.

A 2012 meta-analysis including 6 cohorts with a total of 24,541 patients calculated a 28% reduction in mortality in the IABP group in CSMI patients.<sup>50</sup> However, this meta-analysis did not discriminate between CSMI patients treated by thrombolysis vs. PCI vs. no reperfusion therapy. The divergent findings of the meta-analyses may be related to the heterogeneity of the included patient populations and to publication bias leading to overrepresentation of studies with positive findings regarding IABP effectiveness.

In the randomized, prospective, open-label, multicentre IABP-SHOCK II Trial,<sup>4</sup> a total of 600 patients with CSMI were assigned—after best medical therapy and early revascularization, predominantly with PCI (95.8%)—to additional intra-aortic balloon counterpulsation (IABP group, 301 patients) or no intra-aortic balloon counterpulsation (control group, 299 patients). No difference was found in the primary endpoint—30-day all-cause mortality—with 39.7% mortality in the IABP group and 41.3% mortality in the control group (relative risk with IABP 0.96, 95% confidence interval 0.79–1.17, P = 0.69). The authors concluded that the use of IABP did not significantly reduce 30-day mortality in patients with CSMI for whom an early revascularization strategy was planned.

Of note, no significant survival benefit could be detected in any of the subgroups: contrary to expectation, patients with severely reduced systolic blood pressure (<80 mmHg) did not derive

significant survival benefit from IABP placement. The IABP-SHOCK II Trial also has its limitations: inclusion criteria were based on readily available clinical assessments such as systolic blood pressure <90 mmHg for >30 min, pulmonary congestion, and signs of end-organ hypoperfusion. It may be argued that a metabolic parameter such as a serum lactate level >2 mmol L<sup>-1</sup> might have been useful to confirm the diagnosis and severity of cardiogenic shock. However, the high 30-day mortality rate of 39.7-41.3% is consistent with previous randomized studies in CSMI.<sup>52</sup> Between 20.4 and 23.7% of the patients had suffered a previous myocardial infarction, which may have negatively influenced their potential to benefit from circulatory support. Only data on 30-day mortality are available so far, one-year-mortality will follow. The study was conducted in Germany, a region with a high density of catheterization laboratories and perhaps more aggressive primary revascularization in ST-elevation myocardial infarction than in other regions.

### Recommendations for the use of intra-aortic balloon pump in patients with cardiogenic shock

There is a large indication list for the adjunctive use of IABP in heart failure and shock states including cardiac surgery,<sup>38</sup> with little convincing evidence of proven benefit. On the other hand, those indications with evidence from large RCTs are all negative: (i) CSMI, (ii) elective high-risk PCI in patients with LV dysfunction and extensive coronary artery disease,<sup>53</sup> and (iii) acute anterior STEMI without cardiogenic shock.<sup>54</sup>

The American College of Cardiology/American Heart Association STEMI guidelines recommend the use of IABP as a class IIa indication for patients with CSMI,<sup>58</sup> whereas the recent European guidelines state that 'intra-aortic balloon pumping may be considered (IIb/B)' (*Table 4*). The *German-Austrian S3 Guideline on Cardiogenic Shock*<sup>28</sup> (*Table 4*) differentiates between those CSMI patients having been treated with early systemic fibrinolysis and those having been treated by primary PCI. In patients who have undergone systemic fibrinolysis, a weak recommendation ( $\uparrow$ ) is given for adjunctive IABP treatment, mainly based on the positive findings of the meta-analysis of Sjauw et al.<sup>48</sup>; but in patients with PCI, the German–Austrian guidelines find 'no evidence-based recommendation possible ( $\Leftrightarrow$ )'. In patients with mechanical complications like ventricular septal defect, a weak indication ( $\uparrow$ ) for the IABP use is given.

### **Personal conclusions**

In summary, published meta-analyses, one small and one large RCT consistently document the absence of benefit of routine IABP insertion on morbidity and mortality in patients with CSMI. Given the

Indication	Assist device		European Guidelines	American Guidelines	German–Austrian Guidelines
Cardiogenic shock	IABP	IIb/B	Intraaortic balloon pumping may be considered in patients with cardiogenic shock (Killip class IV)	IIa/B Haemodynamic support for patients with cardiogenic shock after STEMI who do not quickly stabilize with pharmacological therapy	<ul> <li>↑ In patients undergoing</li> <li>↑ In patients</li> <li>↓ undergoing PCI</li> <li>↑ In patients with</li> <li>↑ mechanical</li> <li>↓ complications</li> </ul>
	Left ventricular assist devices	IIb/C	LV assist devices may be considered for circulatory support in refractory shock in patients with cardiogenic shock (Killip class IV)	IIb/C Alternative left ventricular (LV) assist devices for circulatory support may be considered in patients with refractory cardiogenic shock.	Routine use not recommended

results exist that demonstrate either a beneficial or harmful no recommendation ('may'; no confirmed study | '); ↑ recommended ('should'); ⇔ Recommendation grades of the German-Austrian Guidelines $^{22} \Uparrow \mathbb{R}$  strongly recommended ('shall effect);  $\Downarrow$  rejected ('should not');  $\Downarrow$   $\Downarrow$  strongly rejected ('shall not'). LVAD, left ventricular assist device; BiVAD, biventricular assist device. widespread familiarity with the IABP, the easy insertion, and handling of the device, the lack of any survival benefit comes as a disappointment to many cardiologists and leaves them uncertain as to which device to choose as an alternative. Extracorporal membrane oxygenation and Impella are usually not available outside tertiary care centres with cardiac and/or vascular surgery expertise. To rely on pharmaceutical inotropic support only seems futile and is against our inherent impetus 'to do something'. As a consequence, the IABP will continue to be used in CSMI—perhaps in declining frequency—because of belief in a certain understanding of pathophysiology and anecdotal experience of improved clinical status that has not, however, been confirmed by clinical benefit in randomized trials.

# Mechanical left ventricular support by left ventricular volume unloading The TandemHeart<sup>TM</sup>, a left atrial-to-aortic left ventricular assist device

### TandemHeart<sup>™</sup>: the concept

The TandemHeart<sup>TM</sup> (*Figure 3*) provides mechanical circulatory support of up to 4 L min<sup>-1</sup> blood with a continuous flow centrifugal pump.<sup>32–34</sup> Oxygenized blood is aspirated from the left atrium and injected into the lower abdominal aorta or iliac arteries via a femoral artery cannula.

### Clinical studies with surrogate endpoints

The haemodynamic effects of the TandemHeart are superior to the IABP,  $^{55,57-59}$  leading to a greater increase in CO and MAP and a decrease in PCWP, central venous pressure, and pulmonary artery pressure, resulting in reduced filling pressures in the left and right ventricle, reduced cardiac workload and reduced oxygen demand,  $^{55,56}$  as well as an increase in cardiac power index (*Figure 4*).

Complications are an issue for the TandemHeart. In the registry of 117 patients,<sup>57</sup> 1 patient died after post-operative revision of a wire-related perforation of the left atrium following transseptal puncture; other complications included right common femoral artery dissection (0.85%), groin haematomas (5.1%), bleeding around cannula site (29.1%), device-related limb ischaemia (3.4%), sepsis/SIRS (29.9%), gastrointestinal bleeding (19.7%), coagulopathy (11%), and stroke (6.8%), as well as blood transfusions in 71%. Furthermore, the complexity of the insertion procedure limits the use of the device to centres experienced in transseptal puncture.

### **Clinical outcome studies**

No meta-analysis or RCT examining mortality has been published exclusively for the TandemHeart. A combined meta-analysis assessing the effects of percutaneous LV assist devices (TandemHeart and Impella) will be discussed at the end of the paragraph on the Impella family.

### Recommendations for the use of the TandemHeart in patients with cardiogenic shock

In the European guidelines a class IIB recommendation is given for LV assist devices in CSMI<sup>27</sup> (*Table 4*). The 2013 AHA/ACC Guideline for the Management of ST-Elevation Myocardial Infarction assigns a level IIb/C indication for LV assist devices in refractory cardiogenic shock.



**Figure 4** Time course of change in haemodynamic parameters expressed as a percentage of patient's baseline in TandemHeart (squares) and IABP (circle) groups of a randomized prospective multicentre trial with 42 patients. Patients presented within 24 h of developing cardiogenic shock, with cardiogenic shock due to myocardial infarction in 70% and decompensated heart failure in most of the remaining patients. Using random effects linear regression analysis, compared with IABP, TandemHeart resulted in a (A) 20% higher cardiac index (P = 0.13), (B) an 18% higher MAP (P = 0.16), and (C) an 18% lower PCWP (P = 0.12). From Burkhoff et al.<sup>56</sup>

This includes centrifugal pump systems such as the TandemHeart and ECMO.  $^{\rm 58}$ 

### **Personal conclusions**

Percutaneous circulatory assist device insertion in CSMI is rarely performed as an elective procedure when experienced interventionalists are readily available. However, to perform fluoroscopy-guided transseptal puncture and to advance a 21 Fr inflow cannula into the left atrium requires courage and skills and cannot be done under CPR conditions. Although the concept of the TandemHeart is intriguing, the challenges of device insertion may limit emergency use of the device.

### Mechanical left ventricular support by left ventricular volume unloading: The Impella family

### The Impella family: the concept

Axial flow pumps<sup>30,32</sup> like the Impella Recover LP® micro-axial rotary pump (*Figure 3*) are positioned across the aortic valve to provide active support by transvalvular LV assistance, expelling aspirated blood from the left ventricle into the ascending aorta (*Figure 3*). Two versions are currently available: the Impella Recover LP® 2.5 can provide up to 2.5 L min<sup>-1</sup> and can be inserted percutaneously. The Impella Recover LP® 5.0 can deliver up to 5.0 L min<sup>-1</sup> but requires surgical cutdown of the femoral or axillary artery.

#### Clinical studies with surrogate endpoints

Several studies have demonstrated that the Impella device is safe and haemodynamically effective in STEMI and high-risk PCI patients.<sup>32</sup> The unloading of the left ventricle is associated with reduced enddiastolic wall stress and an immediate decrease in PCWP.<sup>32</sup> Coronary perfusion pressure and coronary flow are reported to be increased and myocardial oxygen consumption reduced.<sup>32</sup> Clinical trials with the Impella Recover LP® 2.5 applied in a STEMI population with preshock (IMPRESS trial) as well as in haemodynamically unstable STEMI population (RECOVER II trial) had to be terminated due to insufficient patient enrolment.<sup>32</sup>

With respect to the role of the Impella pump in cardiogenic shock and especially in CSMI, an initial report of the experience in

six patients<sup>61</sup> was followed by two relevant studies. The multicentre Impella EUROSHOCK-Registry<sup>62</sup> included 120 patients with CSMI receiving temporary circulatory support with the Impella-2.5-pLVAD. Thirty-day mortality was 64.2%. After Impella-2.5-pLVAD-implantation, lactate levels decreased from 5.8 ± 5.0 to 4.7 ± 5.4 (P = 0.28) and 2.5 ± 2.6 mmol L<sup>-1</sup> (P = 0.023) at 24 and 48 h, respectively. The ISAR-SHOCK randomized trial compared the Impella 2.5 with the IABP in cardiogenic shock patients.<sup>63</sup> As illustrated in *Table 5*, CI and MAP increased more in the Impella group; furthermore, serum lactate levels were lower in the Impella group than in the IABP group. No differences in mortality, major bleeding, distal limb ischaemia, arrhythmias, and infections were found.

It has been suggested that, in severe cardiogenic shock, the Impella 5.0 device may provide superior haemodynamic support.<sup>32,64</sup> A lower mortality rate has been reported for Impella 5.0 in patients with post-cardiotomy low-output syndrome with a residual CO of  $1 \text{ Lmin}^{-1} \text{ vs. IABP.}^{65,66}$ 

### **Clinical outcome studies**

No meta-analysis is available for the Impella pump family alone, nor has there been an RCT with mortality as an endpoint. The most important meta-analysis included three controlled trials involving a relatively small total of 100 patients with cardiogenic shock mainly due to myocardial infarction; it compared the effects of LVADs-two trials with TandemHeart and one trial with the Impella PL2.5 pump-with the effects of IABP with respect to haemodynamics and 30-day survival (Table 5).60 In total, LVAD patients had higher CI  $(+0.35 \text{ Lmin}^{-1} \text{ m}^{-2})$ , higher MAP (+12.8 mmHg) and lower PCWP (-5.3 mmHg) compared with IABP patients. The 30-day mortality rate was similar between the two circulatory support groups (RR 1.06 for LVAD patients vs. IABP patients, CI 0.68-1.66). No significant difference was observed in the incidence of leg ischaemia (RR 2.59, CI 0.75-8.97) and fever of sepsis (RR 1.11, CI 0.43-2.90) for LVAD patients vs. IABP patients, whereas bleeding was significantly more frequent (RR 2.35, CI 1.40-3.93) in LVAD patients vs. IABP. Adverse events (leg ischaemia, bleeding) were reported more frequently in the TandemHeart trials than in the Impella trial (Table 5).

A subgroup evaluation—including the same LVAD trials—of a Cochrane analysis<sup>49</sup> further supports the finding that TandemHeart and Impella 2.5LP pump support improve haemodynamics, but do not improve survival in comparison with IABP support in small trials of patients with CSMI.

### Recommendations for the use of an Impella device in patients with cardiogenic shock

The European guidelines give a class IIb/C recommendation for the use of LV assist devices in refractory  $CSMI^{27}$  (*Table 4*).

### **Personal conclusions**

The concept of a transaortic LV assist device is intriguing; however, limitations include the high rotational speed of the axial flow pump with consecutive haemolysis, the high risk of femoral bleeding and limb ischaemia, and the absence of improved pulmonary oxygenation.

### Mechanical biventricular support

In principle, percutaneous biventricular support is feasible using a modified TandemHeart, with an inflow cannula placed in the right atrium and a long outflow cannula in the pulmonary artery.<sup>67</sup> This technique was first applied in right ventricular failure secondary to large right ventricular infarction.<sup>67</sup> It may be combined with IABP or Impella support for the left ventricle.<sup>68</sup> A case of biventricular support using the Impella LVAD and RVAD device was reported by Jurmann *et al.*<sup>66</sup> in a patient with post-transplant graft failure.

# Mechanical biventricular support with membrane oxygenation

### Percutaneous venoarterial extracorporeal membrane oxygenation: the concept

The complete percutaneous ECMO system (*Figure 3*)—a modified heart–lung machine—generally consists of a centrifugal pump, a heat exchanger, and a membrane oxygenator. Venous desaturated blood is aspirated from the right atrium into a centrifugal pump through a long steel wire-reinforced canulla inserted into the right atrium via the femoral vein. The pump outflow is directed into a membrane oxygenator and is guided via an outflow cannula into the descending aorta via the femoral artery.

Though ECMO can provide substantial haemodynamic support and reduce LV pre-load, it also increases LV afterload, thereby increasing oxygen demand and impeding myocardial protection.<sup>69</sup> Observational studies and case reports indicate an improvement in microcirculatory flow as measured by sidestream dark field imaging or orthogonal polarization spectral imaging.<sup>70,71</sup>

Typical ECMO complications are SIRS, renal failure, limb ischaemia and bleeding.

#### Clinical studies with surrogate endpoints

Extracorporal membrane oxygenation has been applied in STEMI,<sup>72</sup> myocarditis,<sup>73</sup> post-cardiotomy,<sup>74</sup> interhospital transfer,<sup>75,76</sup> and also in the cardiac catheterization laboratory in patients who developed cardiorespiratory arrest during PCI and TAVI.<sup>77</sup>

There are no meta-analyses for ECMO systems or RCT with a mortality endpoint. In a single-centre retrospective comparison of 219 patients with CSMI treated with primary PCI and adjunctive ECMO between 2002 and 2009 with a historical control group of 115 shock patients treated between 1993 and 2002 without ECMO,<sup>72</sup> the 30-day survival in the ECMO group was ~60% compared with 35% in the historical non-ECMO group (P = 0.003).

### Recommendations for the use of extracorporal membrane oxygenation in patients with cardiogenic shock

There is a class IIb/C recommendation in the European STEMI guidelines<sup>27</sup> to consider an LV assist device for circulatory support in patients with refractory cardiogenic shock (*Table 4*). The European guidelines on myocardial revascularization recommend considering—without a definite recommendation—ECMO implantation for temporary support in CSMI patients who continue to deteriorate due to inadequate circulatory support of the IABP. This recommendation is based on expert consensus.

### **Personal conclusions**

Intra-aortic balloon pump is in widespread clinical use for CSMI. However, the IABP-Shock II Trial failed to confirm improved survival with its routine use in a population that underwent PCI. Among the other mechanical circulatory support devices for cardiogenic shock, we believe that ECMO is likely to have the greatest potential for wider clinical use. Its major advantages are

- quick and easy percutaneous insertion of inflow and outflow cannulas,
- full circulatory support with up to 4.0 L min<sup>-1</sup>,
- extracorporeal membrane oxygenation rapidly improves tissue oxygenation in situations of cardiogenic shock combined with severe pulmonary oedema.

However, it does not reduce afterload. There are no RCTs that demonstrate improved clinical outcomes with ECMO, and hospitals without access to perfusionists are understandably hesitant to use a more complex device. More user-friendly ECMO systems have been developed for ICU use and these issues will be addressed in the near future.

### **Future aspects**

Despite optimal up-to-date therapy of CSMI (including early resuscitation early primary PCI, medical treatment with recently developed antithrombotic medications, and aggressive management of complications), mortality of cardiogenic shock continues to remain unacceptably high. Limited data may support the use of levosimendan,<sup>22</sup> but innovations in pharmacological therapy are not forth-coming. Mild therapeutic hypothermia is promising as a potential therapeutic strategy for CSMI.<sup>78</sup> It has multiple potentially beneficial effects, including the potential to improve post-ischaemic cardiac function and haemodynamics, decrease myocardial damage, and reduce end-organ injury from prolonged hypoperfusion. Data on animal models of post-MI cardiogenic shock and ischaemia/reperfusion injury and small case series of patients with cardiogenic shock are encouraging.<sup>78</sup>

	Thiele et al. <sup>55</sup>		Burkhoff et al. <sup>56</sup>		Seyfarth et al. <sup>63</sup>		Pooled (fixed effect model)		Pooled (random effects model)	
	LVAD (n = 21)	IABP (n = 20)	LVAD (n = 19)	IABP (n = 14)	LVAD (n = 13)	IABP (n = 13)	Mean difference/ relative risk	P-value	Mean difference/ relative risk	P-value
Haemodynamics										
$\begin{array}{c} CI \pm SD \\ (L \min^{-1} m^{-2}) \end{array}$	2.3 ± 0.6	1.8 ± 0.4	$2.2\pm0.6$	2.1 ± 0.2	$2.2\pm0.6$	1.8 ± 0.7	0.35 (0.14; 0.55)	< 0.001	0.35 (0.09; 0.61)	< 0.01
MAP $\pm$ SD (mmHg)	76 <u>+</u> 10	70 <u>+</u> 16	91 + 16	72 ± 12	$87\pm18$	71 <u>+</u> 22	12.1 (6.3; 17.9)	< 0.001	12.8 (3.6; 22.0)	< 0.01
PCWP $\pm$ SD (mmHg)	16 <u>+</u> 5	22 <u>+</u> 7	16 <u>+</u> 4	25 ± 3	19 <u>+</u> 5	$20 \pm 6$	-6.2 (-8.0; -4.3)	< 0.001	-5.3 (-9.4; -1.2)	< 0.05
Clinical outcome										
30-day mortality, <i>n</i> (%)	9 (43)	9 (45)	9 (47)	5 (36)	6 (46)	6 (46)	1.06 (0.68; 1.66)	0.80	1.06 (0.68; 1.66)	0.80
Reported adverse events										
Leg ischaemia, n (%)	7 (33)	0 (0)	4 (21)	2 (14)	1 (8)	0 (0)	2.59 (0.75; 8.97)	0.13	2.59 (0.75; 8.97)	0.13
Bleeding, n (%)	19 (90)	8 (40)	8 (42)	2 (14)			2.35 (1.40; 3.93)	< 0.01	2.35 (1.40: 3.93)	< 0.01
Fever of sepsis, n (%)	17 (81)	10 (50)	4 (21)	5 (36)			1.38 (0.88; 215)	0.16	1.11 (0.43; 290)	0.83
Fever of sepsis, n (%)	17 (81)	10 (50)	4 (21)	5 (36)			1.38 (0.88; 215)	0.16	1.11 (0.43; 290)	

**Table 5** Meta-analysis of RCTs: effects of left ventricular assist devices—TandemHeart<sup>55,56</sup> and Impella PL2.5 pump<sup>63</sup>—in comparison with the effects of IABP on haemodynamics; 30-day-mortality and adverse events in patients with cardiogenic shock, mainly due to myocardial infarction

Cl, cardiac index; IABP, intra-aortic balloon pump; LVAD, left ventricular assist device; MAP, mean arterial pressure; PCWP, pulmonary capillary wedge pressure. From Cheng *et al.*<sup>60</sup> For details on the statistical analysis please refer to the original publication.

The neutral results of the IABP-SHOCK II Trial remind us that immediate haemodynamic improvement may not automatically translate into improved survival. However, many believe that mechanical circulatory support may be the best therapy for the future. What is the future direction of device-related therapy in CSMI and which areas need further clinical research?

# (1) Physiological concept of left ventricular support

The IABP concept of primary afterload reduction with modest increases in stroke volume and cardiac output has failed to translate into survival benefits. It is therefore logical to focus now on devices with higher cardiac output support. However, more cardiac output may be a necessary prerequisite, but no guarantee for success.

# (2) Reduction of device-related complications

Clinical success of device therapy in CSMI does not depend on the mechanical qualities of the device alone. The ease and safety of device implantation—especially under emergency conditions and during cardiopulmonary resuscitation—will also greatly influence patient outcome. Additionally, the rates of device-related complications such as limb ischaemia, access site bleeding, haemolysis, and infection are still too high, and the contact of blood with these devices may cause/worsen SIRS and MODS. Patients with CSMI have minimal reserve to tolerate operator error or device complications.

# (3) Timing of mechanical circulatory support

Data from morbidity studies with a focus on the time course of SIRS and MODS development indicate that haemodynamic support has limited ability to change outcome if initiated when overt MODS has already developed. Mechanical circulatory support should not be considered the treatment of last resort for CSMI, but should probably be initiated early in the disease course to minimize the negative effects of high-dose catecholamine therapy on microcirculation and before end-organ dysfunction with MODS. No randomized clinical trials have been initiated to study the optimal timing of circulatory support in CSMI, but they are needed.

# (4) Improvements in revascularization therapy

There is continuing debate whether culprit lesion revascularization or complete revascularization is the preferred immediate interventional treatment strategy in CSMI. The CULPRIT-SHOCK Trial (Coordinating Investigator: H. Thiele) is under way.

In view of the dissociation between improvements in haemodynamic parameters and clinical outcomes, including mortality, as evidenced by the neutral results of the IABP-SHOCK II Trial, device therapy must not only improve haemodynamics, but prevent or reduce MODS and ultimately, mortality. The final pathway of CSMI is the microcirculation. We know how to measure microcirculatory function in shock patients, and we know that impaired microcirculation predicts poor outcome of patients with CSMI.<sup>79</sup> Optimizing outcomes in CSMI is not only a matter of better devices, but also of better patient monitoring. We need to go beyond CI measurements and focus on other prognostically relevant information. Perhaps monitoring of microcirculation<sup>79</sup> would help to optimize circulatory support in the future. The failure of IABP in CSMI is not the end of device therapy for this condition; it is the dawn of a new and more systematic era of clinical research on circulatory support and outcome measures in cardiogenic shock—an important frontier of cardiology today.

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