Percutaneous mechanical circulatory support in cardiogenic shock

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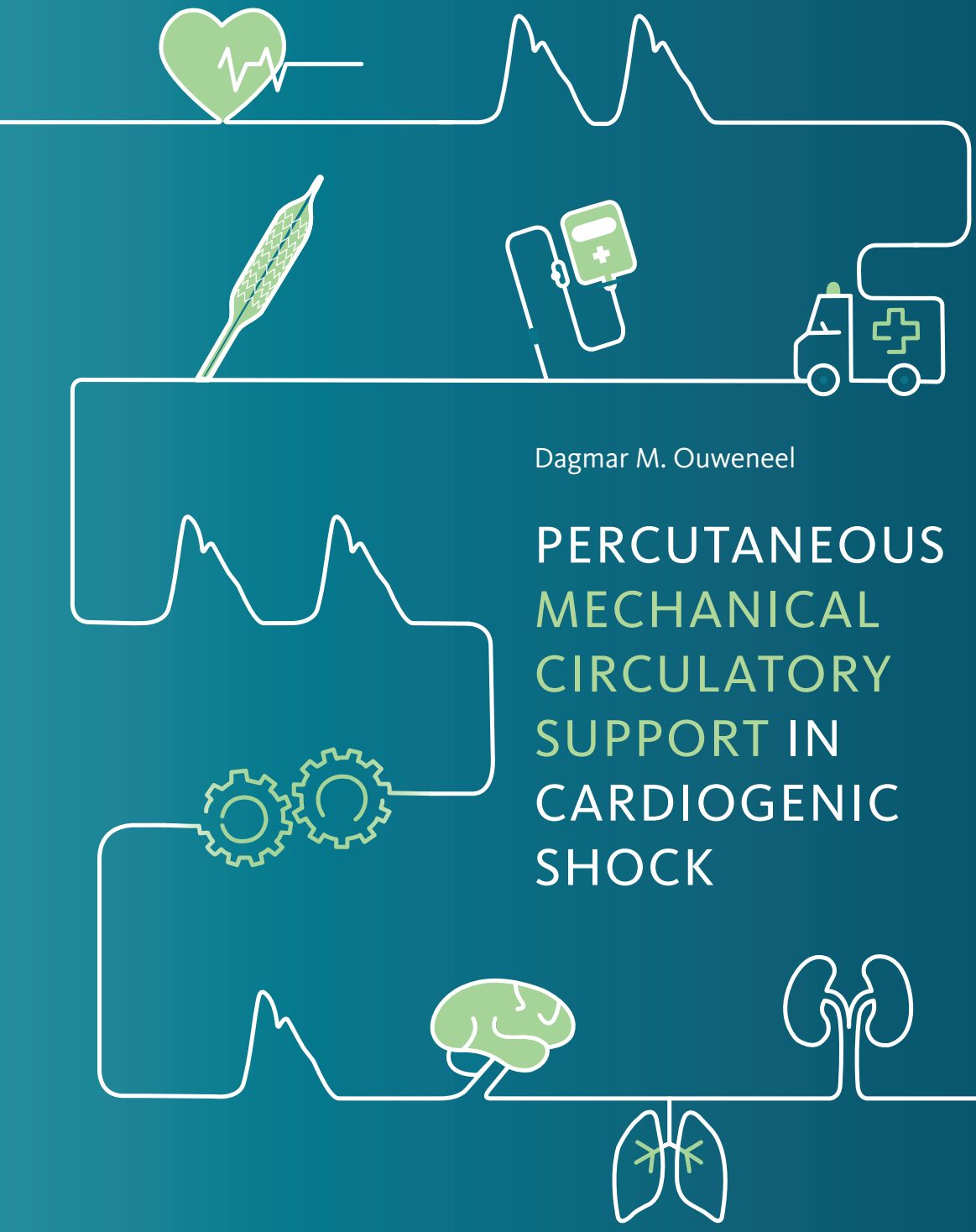

Dagmar M. Ouweneel

PERCUTANEOUS MECHANICAL CIRCULATORY SUPPORT IN CARDIOGENIC SHOCK

Percutaneous mechanical circulatory support in cardiogenic shock

Dagmar M. Ouweneel

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Dissertation, University of Amsterdam, Amsterdam, The Netherlands

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Percutaneous mechanical circulatory support in cardiogenic shock

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Voor alle patiënten en hun familie

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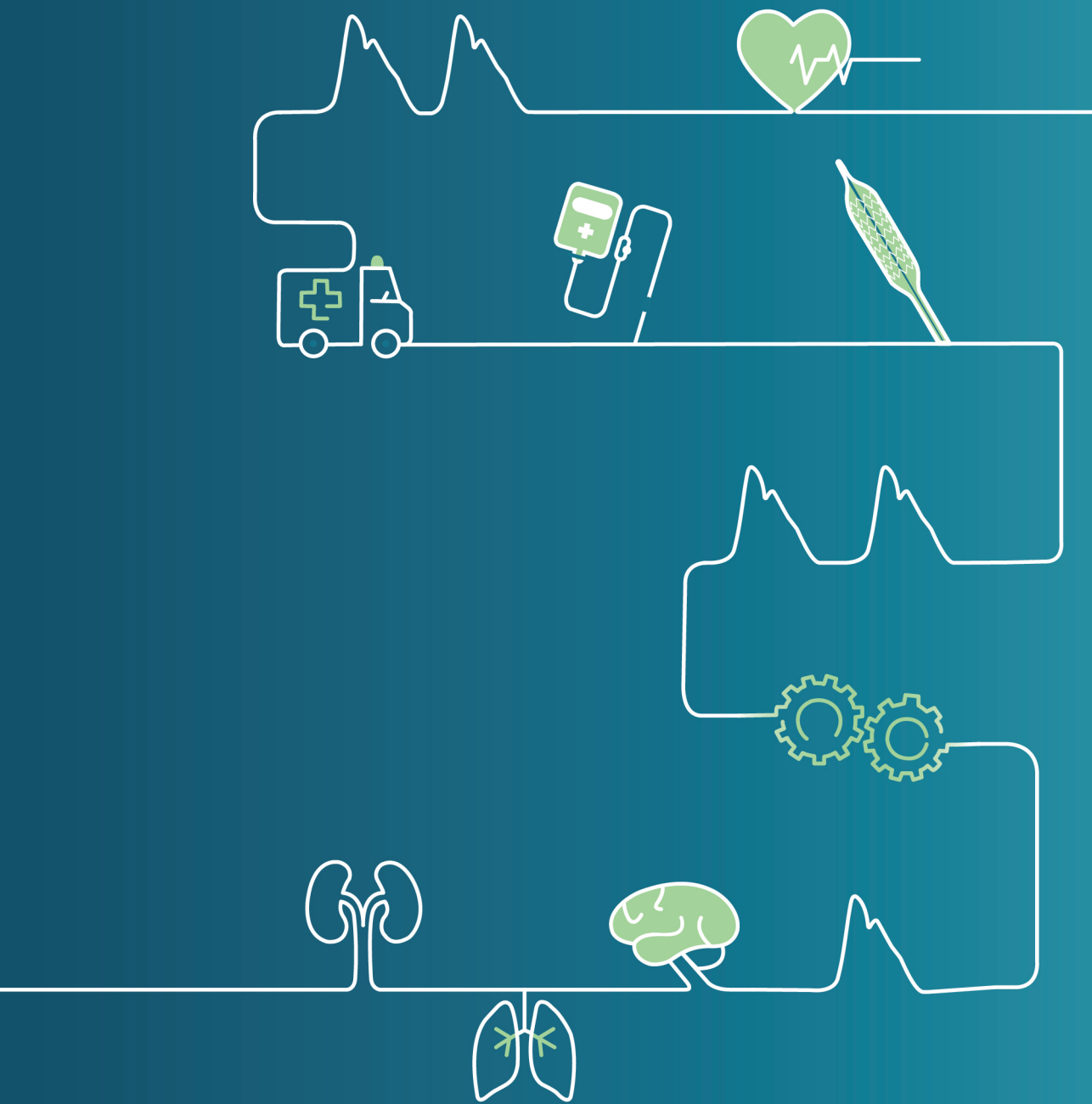
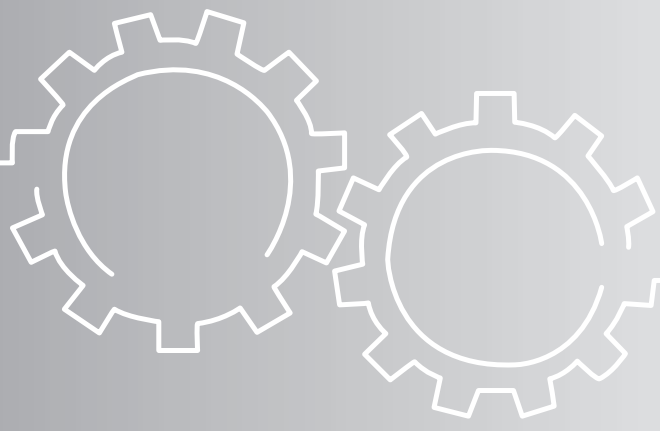
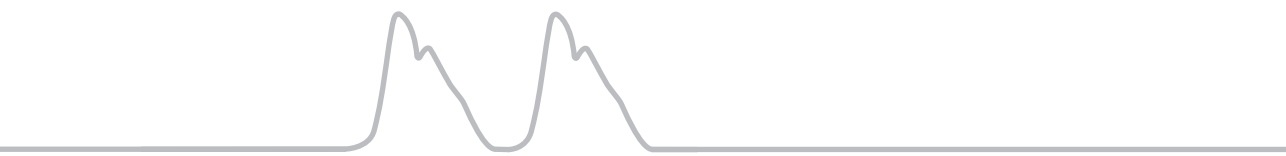


INTRODUCTION

CHAPTER 1



GENERAL INTRODUCTION AND THESIS OUTLINE



BACKGROUND

Cardiogenic shock

Cardiogenic shock is a clinical condition which is the result of decreased organ perfusion due to cardiac failure. It is characterized by reduced systolic blood pressure and signs of organ hypoperfusion despite adequate intravascular volume. Cardiogenic shock is a fatal condition when organ perfusion is not rapidly restored. The most common cause of cardiogenic shock is myocardial ischemia due to an acute myocardial infarction. Other causes of cardiogenic shock include mechanical complications of acute myocardial infarction such as ventricular or septal wall rupture or acute valvular dysfunction, myocarditis, decompensated cardiomyopathy or sustained cardiac arrhythmias.[2]

Cardiogenic shock occurs in around 6-10% of patients with ST-segment elevation myocardial infarction (STEMI).[3-5] It is a consequence of decreased myocardial contractility due to the infarction, which results in a cascade of decreased cardiac output, hypotension, decreased coronary blood flow which will further reduce the cardiac function. This vicious circle may not only lead to further myocardial ischemia, but also to diminished organ perfusion and ultimately results in multiple organ failure and death. In addition to the hemodynamic compromise, cardiogenic shock induces a systemic inflammatory response which can result in further deterioration of the hemodynamic situation. The severity of cardiogenic shock ranges from mild hypoperfusion to profound shock.

The generally used criteria for the diagnosis of cardiogenic shock are:

- Systolic blood pressure <90 mmHg for >30 min or vasopressors required to achieve a blood pressure ≥90 mmHg;
- Pulmonary congestion or elevated left-ventricular filling pressures;
- Signs of impaired organ perfusion with at least one of the following criteria: (a) altered mental status; (b) cold, clammy skin; (c) oliguria.

Treatment

Advances in treatment of acute myocardial infarction have resulted in a decrease in mortality in patients with acute myocardial infarction.[5,6] The latest significant improvement of therapy of cardiogenic shock patients was the introduction of early reperfusion by percutaneous coronary intervention (PCI) in 1999.[4] Despite early revascularization, the mortality of patients with cardiogenic shock remains around 50%.[7-10]

Standard treatment consists of immediate revascularization of the occluded coronary vessel. In addition, inotropic and vasopressor agents can be administered to increase blood pressure. Although inotropic and vasopressor agents rapidly improve the hemodynamic parameters in cardiogenic shock, it has detrimental effects on the heart and the peripheral circulation.[11] However, the haemodynamic benefits are perceived to outweigh the specific risks of inotropic therapy because organ hypoperfusion itself

also has detrimental consequences. In addition to pharmacological agents, mechanical support devices can be used to provide additional support to the circulation. Typically, cardiogenic shock patients are treated in the intensive care unit with other therapeutic options such as mechanical ventilation, therapeutic hypothermia and renal replacement therapy when necessary.

Mechanical circulatory support

The primary objective of cardiac support is the maintenance or restoration of haemodynamic stability. This is achieved by maintaining or improving coronary and systemic blood flow in order to ensure sufficient cardiac output and adequate organ perfusion. The improvement of coronary and microvascular blood flow could also accelerate recovery of stunned myocardium after ischemia. Some mechanical support devices have the additional property to unload the left ventricle enabling increased myocardial perfusion and lower the oxygen demand. There are several devices available on the market. The devices which are discussed in this thesis will be shortly described. An more comprehensive overview is given in Chapter 2.

Intra-aortic balloon pump

The intra-aortic balloon pomp (IABP) was introduced in 1968 and was the first percutaneous mechanical circulatory support device.[12] The IABP is a catheter-mounted balloon placed in the descending aorta, distal to the left subclavian artery and proximal to the renal artery branches (Figure 1A). The balloon inflates in during cardiac diastole and aims to augment coronary circulation. During systole the balloon deflates with the aim to reduce the afterload of the left ventricle. The IABP is the most widely used percutaneous assist device in the catheterization laboratory.[13] However, in 2009 a meta-analysis of cohort studies showed no improved clinical outcome in patients treated with IABP after acute myocardial infarction.[14] In 2012, the results of a large multicenter randomized trial (the IABP-SHOCK II trial) became available. The trial randomized a total of 600 patients to either IABP or medical therapy.[9,15] The results showed no difference in 30-day mortality nor in other clinical endpoints such as lactate level and renal function. There was also no difference with respect to safety outcomes such as bleeding, stroke, sepsis or vascular complication. The past years, the European guidelines on the role of IABP in patients with STEMI complicated by cardiogenic shock have significantly changed. The European guidelines of 2010 recommended the use of IABP (class I/c) in patients with cardiogenic shock, the recommendation was downgraded in 2012 and the guidelines of 2014 do not recommend routine use of IABP anymore.[16-18]

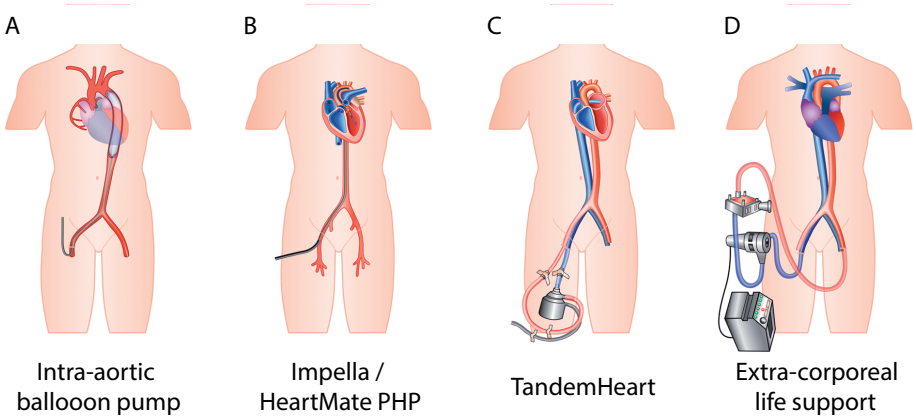


Figure 1 Left ventricular percutaneous mechanical assist devices.
(A) The IABP is poisoned in the descending aorta, distal to the left subclavian artery and proximal to the renal artery branches (B) Impella and PHP pump are both inserted percutaneously and positioned across the aortic valve in the left ventricle; (C) TandemHeart: the inlet is inserted transseptal and via a centrifugal pump connected with the arterial outlet cannula (D) Extracorporeal life support (ECLS): The venous access is connected to an extracorporeal membrane oxygenation (ECMO) system with an integrated centrifugal pump and membrane oxygenator (artificial lung) and connected to the arterial inflow access. Adapted from Werdan et al.[1]

Impella

The Impella (Abiomed, Danvers, MA, USA) device is a percutaneous device, which is inserted via the ascending aorta, placed across the aortic valve, into the left ventricle (Figure 1B and Figure 2A). It is an axial pump which pulls blood from the left ventricles through an inlet area and expels it through a cannula catheter into the ascending aorta. The device has a pigtail-catheter at the tip to ensure stable positioning in the left ventricle and to avoid adhering to the myocardium. The pump is designed for short-term support of several days. Several versions of the Impella system are available. The Impella 2.5 and the Impella CP can provide 2.5 L/min and 3.7 L/min respectively, and both allow percutaneous insertion. The Impella 5.0 can deliver up to 5.0 L/min but requires a surgical cut-down of the femoral or axillary artery. The Impella LD pump is an Impella that can only be inserted via open-chest surgery by way of the ascending aorta, across the valve and into the left ventricle. There is a specific Impella to support the right ventricle, the Impella RP. The Impella RP is placed percutaneously through the femoral vein and advanced in an antegrade fashion across the pulmonic valve into the pulmonary artery (Figure 2B). The Impella RP can provide flow up to 5 L/min for an anticipated duration of 14 days. European guidelines state that short-term mechanical circulatory support devices in patients with acute coronary syndromes with cardiogenic shock may be considered.[17]

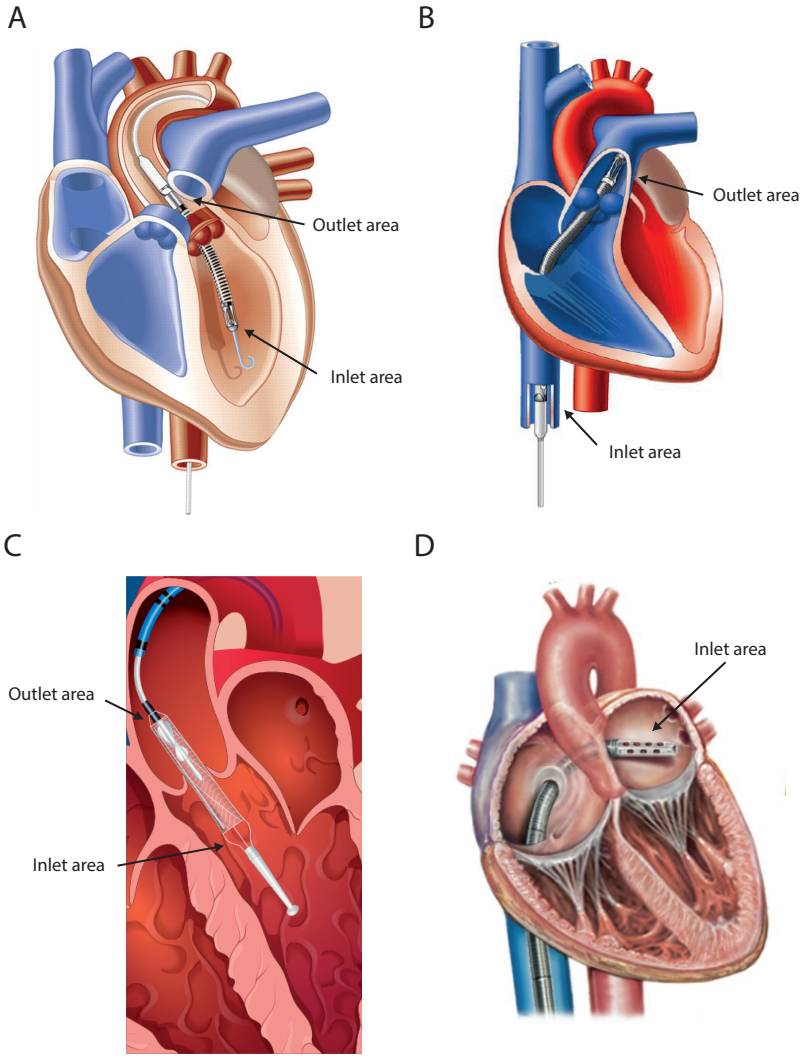


Figure 2 Specific location of several support devices.
(A) Impella for left ventricular support (Impella 2.5, Impella CP or Impella 5.0), placed across the aortic valve; (B) Impella for right ventricular support (Impella RP); (C) HeartMate PHP pump, placed over the aortic valve; (D) TandemHeart inflow cannula, inserted via a transseptal puncture.

Heartmate PHP

The HeartMate PHP (Percutaneous heart Pump, St. Jude Medical, St. paul, Minnesota, USA) is a continuous flow device that is designed for percutaneous entry through the femoral artery (Figure 1B, Figure 2C). Like the Impella device, it is insensate percutaneously and positioned over the aortic valve into the left ventricle. However, the Heart-

Mate PHP has a collapsible axial flow impeller and cannuala at the distal end. When the catheter is placed over the aortic valve, the cannula is unsheathed and fully expands from 13 to 24F, with the inlet within the left ventricle and the outlet in the ascending aorta. The manufacturer reports a flow of more than 4 L/min. It obtained CE mark in July 2015 for support of patients undergoing high-risk PCI. Data on the HeartMate PHP in cardiogenic shock is not yet available. Although it resembles the Impella, the device only recently became available with little clinical experience.

TandemHeart

TandemHeart (TandemLife, Pittsburgh, PA, USA) is a trans-septal ventricular assist device that can be inserted in the catheterisation laboratory under fluoroscopy. This device is inserted via the femoral vein and right atrium into the left atrium via an atrial septum puncture (Figure 1C, Figure 2D). The outflow cannula is inserted through the femoral artery and positioned at the level of the aortic bifurcation. It can deliver up to 4 L/min.

Extracorporeal life support

Extracorporeal life support (previously called extra-corporeal membrane oxygenation (ECMO)) is a percutaneous heart-lung machine which can be used for several days (Figure 1D). The ECLS system generally consists of a centrifugal pump, a heater and an oxygenator. Venous blood flows from the right atrium into a centrifugal pump and oxygenator and is guided via an outflow cannula in the femoral artery into the descending aorta. The advantage of ECLS over the other percutaneous devices is the ability to support the right ventricular as well as the left ventricle, is has higher blood flow rates (up to 4.5 L/min depending on the cannula size) and the ability to oxygenate the blood. Its peripheral approach and the retrograde flow in the aorta may lead to overloading the left ventricle in contrast to the other devices that aim at unloading the left ventricle. It is currently unclear whether this effect has clinical relevance in the overall outcome when comparing its efficacy with the other devices.

In conclusion, there are several percutaneous mechanical support devices on the market. Chapter 2 describes a more detailed introduction of mechanical support devices in cardiogenic shock. During an acute critical situation, a quick and easy deployment of the device is preferable. The ideal device should enable both haemodynamic support and myocardial protection. 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 mechanical assist device may include limb ischaemia, embolisation of atherosclerotic and/or thrombotic material, stroke, infection and haemolysis.[19]

THESIS OUTLINE

Part I of this thesis describes the experience of the Academic Medical Center (AMC) with the Impella device. The Impella system was first used in the AMC in 2004. In the beginning Impella was only used in the elective setting, to provide hemodynamic support during high-risk percutaneous coronary interventions. After experience with the device was gained in the elective setting, the Impella was used in the acute setting in patients with acute myocardial infarction. In **Chapter 3** we evaluate if the learning curve of handling the Impella influences the clinical results of patients who are supported with a mechanical assist device during elective high-risk PCI. When a patient in cardiogenic shock is treated with a mechanical assist device, it is important to evaluate if the device is in the correct position. Its efficacy greatly depends on proper position in the left ventricle. For the Impella it is important that the inlet area is located in the left ventricle, and the outlet is located above the aortic valve in the ascending aorta. The current method to evaluate the Impella position is by echocardiography. In **Chapter 4** we evaluate a new method to evaluate the position of the device by using supine chest X-ray. In **Chapter 5** we describe the experience of the AMC with the use of Impella in cardiogenic shock patients. We evaluate the mortality in patients with different etiologies of cardiogenic shock. In patients who are treated with Impella after an acute myocardial infarction, we evaluate the influence of patient characteristics, the choice of Impella device and the timing of Impella placement on mortality. In **Chapter 6** we give a brief overview of treatment with Impella technology over time from the early phase of its introduction until the current status with reimbursement in the Netherlands and recent FDA approval.

Part II of this thesis describes the result of randomised controlled trials comparing Impella with IABP. In **Chapter 7** we describe a randomised trial comparing Impella 2.5 and IABP in patients with cardiogenic pre-shock. In **Chapter 8** we evaluate the Impella CP in a randomised trial in patients with severe cardiogenic shock. In **Chapter 9** we pool the results of all available randomised controlled trials comparing Impella with IABP in a meta-analysis. In **Chapter 10** we pool all data of randomised controlled trials with active mechanical support devices such as Impella and TandemHeart to evaluate mortality, device related complications as well as effects on lactate levels and hemodynamic variables.

In **Part III** describes the role of extracorporeal life support in patients with cardiogenic shock and cardiac arrest. **Chapter 11** describes a meta-analysis comparing ECLS treated patients with patients who were not treated with ECLS in de setting of refractory cardiac arrest and cardiogenic shock after acute myocardial infarction. **Chapter 12** describes the current state and future perspectives of the role of extracorporeal life support.

A summary of this thesis and the future perspectives of mechanical circulatory support in patients with cardiogenic shock can be found in **Chapter 13**.

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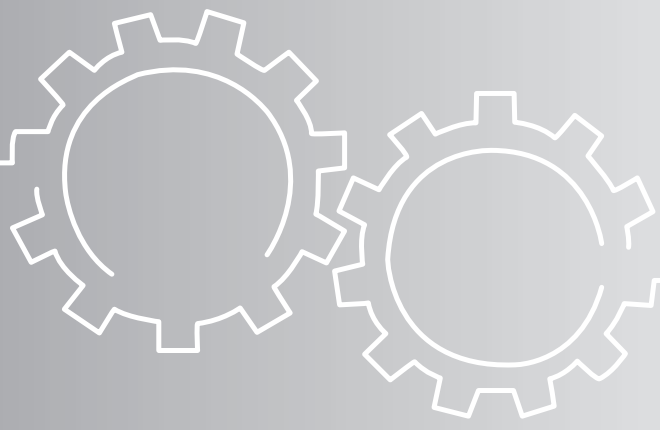
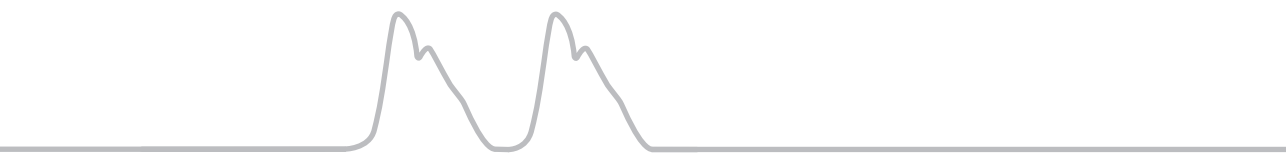
CHAPTER 2



PERCUTANEOUS CARDIAC SUPPORT DEVICES FOR CARDIOGENIC SHOCK: CURRENT INDICATIONS AND RECOMMENDATIONS

Dagmar M. Ouweneel, José P. S. Henriques



Heart. 2012 Aug;98(16):1246-54.

Cardiogenic shock (CS) is a physiological state in which inadequate tissue perfusion results from cardiac dysfunction, most commonly following acute myocardial infarction. Non-ischaemic causes include myocarditis, end-stage cardiomyopathy or sustained arrhythmias.

The use of reperfusion therapy has substantially reduced 30-day mortality in acute ST-segment elevation myocardial infarction (STEMI) patients.[1-3] Currently, the optimal reperfusion therapy is timely primary percutaneous coronary intervention (PCI). The improvement in clinical outcome has been mostly observed in STEMI patients without cardiogenic shock. Despite reperfusion therapy, approximately 6-10% of STEMI patients develop cardiogenic shock during initial hospitalisation.[4-6] The large multicentre Should we Emergently Revascularise Occluded Coronaries for Cardiogenic Shock? (SHOCK) trial and registry demonstrated that early revascularisation, including PCI or coronary artery bypass grafting, in cardiogenic shock patients improves clinical outcome, but the overall 6-month mortality of cardiogenic shock patients remained 50% in accordance with other reports.[4,5,7] Despite reperfusion by primary PCI, cardiogenic shock remains the leading cause of death for hospitalised STEMI patients.[5,8]

Cardiogenic shock after STEMI is mostly a consequence of decreased myocardial contractility due to the infarction, resulting in a cascade of decreased cardiac output, hypotension and decreased coronary blood flow (CBF), which will further reduce contractility and cardiac output. This vicious circle may not only lead to further myocardial ischaemia, but also to diminished organ perfusion and may ultimately result in multiple organ failure and death. Additional aggravation of the downward spiral is caused by a systemic inflammatory response and excess nitric oxide synthesis induced by the myocardial infarction, which further induces vasodilatation.[6]

Clinically, cardiogenic shock is characterised by hypotension and defined by a systolic blood pressure of less than 90 mm Hg for at least 30 min or the need for supportive measures to maintain a systolic blood pressure of 90 mm Hg, heart rate of more than 60 beats/min and end-organ hypoperfusion with cool extremities or a urine output of less than 30 ml/h. Haemodynamic criteria for cardiogenic shock include cardiac index less than 2.2 l/min per square metre and a pulmonary capillary wedge pressure (PCWP) of at least 15 mm Hg.[7,9]

There are currently two therapeutic options for patients with cardiogenic shock to support the circulation: pharmacological inotropic and/or vasopressor therapy and mechanical support. The recently updated 2011 American College of Cardiology Foundation/American Heart Association/ Society for Cardiovascular Angiography and Interventions (ACCF/AHA/SCAI) guidelines for PCI recommend the use of a haemodynamic support device for patients with cardiogenic shock who do not quickly stabilise with pharmacological therapy.[10]

PHARMACOLOGICAL INOTROPIC SUPPORT

Inotropic and vasopressor agents can be used to improve the haemodynamic parameters rapidly in cardiogenic shock. They are generally administered under the assumption that short-term clinical recovery will be facilitated by enhancement of cardiac output or vascular tone.[11] Although these agents all increase myocardial oxygen consumption and can cause ventricular arrhythmias, contraction band necrosis and infarct expansion, the haemodynamic benefits are perceived to outweigh the specific risks of inotropic therapy because hypotension itself also compromises myocardial perfusion.[11] The increased myocardial oxygen consumption and vascular tone may have detrimental consequences that may negatively impact clinical outcome, such as impairment of peripheral organ perfusion and an increase in myocardial ischaemia. Although survival in the case of acute myocardial infarction has improved, many patients are left with sizeable infarcts and organ dysfunction, which limits long-term survival and quality of life despite good short-term outcomes. The use of pharmacological inotropic circulating support is recommended, although inotropes and vasopressors have not been shown to improve patient outcomes in randomised controlled studies.

MECHANICAL SUPPORT

The aim of mechanical cardiac assistance is to support the endangered circulation by providing increased systemic blood flow to prevent organ hypoperfusion and allow organ recovery. In addition to haemodynamic support, mechanical cardiac assistance may also provide myocardial protection by unloading the ventricle. It is hypothesised that this left ventricular unloading may result in infarct size reduction and increased left ventricular recovery.[12]

Haemodynamic support

In patients with cardiogenic shock, the maintenance of haemodynamic stability is the primary objective of cardiac support. This includes appropriate mean arterial pressure (MAP) and cardiac output to ensure adequate organ perfusion at the tissue level. The SHOCK trial investigators have shown that cardiac power output (CPO) is the best haemodynamic parameter to predict mortality in the case of cardiogenic shock.[13] CPO can also be used to predict worsening heart failure in patients with heart failure or pre-shock.[14,15]

$$CPO = \frac{MAP * CO}{451}$$

The parameter takes both the systemic flow, cardiac output and the MAP into account and is divided by a conversion factor of 451 to get the CPO in Watts, assuming that cardiac output alone is necessary but not sufficient for end-organ perfusion and also adequate blood pressure is required. The ideal device would be able to maintain both cardiac output and blood pressure without concomitant vasopressor or inotrope therapy and thereby avoid the possible cardiotoxicity and long-term morbidity of these agents.

Myocardial protection

To protect the myocardial tissue, the optimal device should be able to reduce oxygen demand and increase oxygen delivery to prevent (further) myocardial damage. Myocardial tissue depends exclusively on aerobic metabolism, extracting most of the oxygen provided by the coronary system. Because oxygen extraction cannot substantially be increased, the oxygen supply can only be increased by augmentation of the CBF. CBF is related to the pressure difference between the proximal and distal vascular bed and is inversely related to myocardial microvascular resistance. Coronary flow occurs mainly during diastole, when coronary vascular resistance is minimal due to extravascular compression during systole. The pressure gradient is the MAP in diastole minus the downstream pressure, which is related to the end-diastolic filling pressure. Myocardial microvascular resistance is related to the wall tension, which is also closely related to the end-diastolic filling pressure. To increase the oxygen supply, the CBF can be increased by decreasing the end-diastolic pressure and thereby affecting both the microvascular resistance and the perfusion pressure.

Reducing the oxygen demand is another way to protect the cardiac tissue. The pressure-volume area (PVA) is the parameter that correlates with the oxygen consumption per beat. The PVA is the area of the pressure-volume loop bounded by the end-diastolic pressure volume relation, the end-systolic pressure volume relation and the systolic portion of the loop, and has been considered to represent the total mechanical energy generated by the left ventricle.[16,17] The ideal device decreases preload and unloads the ventricle, which results in shifting of the pressure-volume loop downwards and to the left, reducing the PVA and therefore the oxygen consumption.

In conclusion, devices that affect both the oxygen supply by increasing CBF and decrease the oxygen consumption simultaneously will have the best advantage by providing myocardial protection.

MECHANICAL ASSIST DEVICES

Many left ventricular support devices have been developed over the past decades. Surgical ventricular assist devices may improve clinical outcome in STEMI patients with

cardiogenic shock.[18,19] However, 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) left ventricular assist device (LVAD) may include limb ischaemia, embolisation of atherosclerotic and/or thrombotic material, stroke, infection and haemolysis.

INTRA-AORTIC BALLOON PUMP

The intra-aortic balloon pump (IABP) is a percutaneous cardiac assist device that is most frequently used and has been broadly available in clinical practice since its introduction in 1968.[20] The IABP is inserted percutaneously in the femoral artery and the balloon is positioned in the descending thoracic aorta distal to the left subclavian artery and proximal to the renal artery branches. The balloon is synchronised to the cardiac cycle and is rapidly inflated during diastole and rapidly deflated immediately before systole, aiming for augmentation of the CBF and systemic blood flow during diastole. Immediately before or during early systole the balloon rapidly deflates, decreasing afterload and thereby increasing cardiac output, decreasing ventricular wall tension and reducing myocardial oxygen demand. The IABP generates an increase in cardiac output up to approximately 0.3-0.5 l/min. Also the IABP is assumed to increase CBF due to increased diastolic pressure and reduction of left ventricular end-diastolic pressure, and a decrease in oxygen demand by decreased afterload and decreased ventricular wall tension.[21-23] However, the Counterpulsation to Reduce Infarct Size Pre-PCI Acute Myocardial Infarction (CRISP AMI) randomised trial concluded that in 337 anterior segment STEMI patients without shock, IABP therapy complementing PCI alone did not result in reduced infarct size.[24] Also, a small randomised trial recently reported no significant difference in cardiac index and acute physiology and chronic health evaluation II score using IABP therapy.[25]
There are several limitations to the IABP aside from the limited proof of effectiveness. The augmentation of cardiac output of approximately 0.3-0.5 l/min is likely to be insufficient for patients with severe cardiogenic shock. Additional use of possible deleterious vasoactive agents might be necessary to maintain adequate CPO. Also, the function of the IABP relies on synchronisation with the cardiac cycle, which might not be reliable in the case of cardiac arrhythmia in the critically ill patient and it requires a certain level of left ventricular function.

There are only a few relatively small randomised clinical trials that have studied IABP therapy in STEMI complicated by cardiogenic shock. A meta-analysis published in 2009 of cohort studies of STEMI patients showed no improved outcome in patients treated with IABP.[26] A recently published Cochrane individual patient data meta-analysis of randomised controlled trials on patients with myocardial infarction complicated by cardiogenic shock included six eligible and two ongoing studies with a total of 190 patients.[27] This study concluded that the small number of randomised trials that were available were not able to show convincing evidence, for either benefit or harm, supporting the use of IABP-therapy. A large randomised trial, IABP-SHOCK II, started in 2009 and is expected to be completed early in 2012 with reporting late in 2012.

LEFT VENTRICULAR ASSIST DEVICES

Several efforts have been made to develop cardiac assist devices with more haemodynamic support, but as non-invasive as the IABP. They can be used as a bridge to recovery for several days or as a bridge to surgery when no recovery occurs. Currently, three percutaneous devices are commonly used, TandemHeart (Cardiac Assist Inc, Pittsburgh, Pennsylvania, USA), extracorporeal membrane oxygenation (ECMO) and Impella (Abiomed Europe GmbH, Aachen, Germany). These devices differ in the insertion technique and working mechanism (Table 1).

TandemHeart

The TandemHeart is a trans-septal ventricular assist device that can be inserted in the catheterisation laboratory under fluoroscopy. This device is inserted via the femoral vein and right atrium into the left atrium via an atrial septum puncture (Figure 1). The outflow cannula is inserted through the femoral artery and positioned at the level of the aortic bifurcation. It has a continuous flow centrifugal pump with a maximal rotation speed of 7500 revolutions/min, which can deliver up to 4 l/min. The haemodynamic effects of the TandemHeart are an increase in cardiac output and MAP and a decrease in PCWP, central venous pressure and pulmonary artery pressure, which results in reduced filling pressures in the left and right ventricle, reduced cardiac workload and reduced oxygen demand. [28-30] However, it should be noted that without direct left ventricular unloading, increases in MAP translate to increases in the left ventricular afterload, which partly offset the potential cardiac workload benefits. Thiele et al also found an increase in the cardiac power index of 0.15 W/m^2[28]. Kar et al implanted the TandemHeart in 117 patients with severe refractory cardiogenic shock refractory to IABP and vasopressor support resulting in a significant improvement in haemodynamic values, mixed venous oxygen saturation and urine output[31]. Two randomised controlled trials in patients

Table 1 Comparison of devices.

	IABP	ECMO	TandemHeart	Impella 2.5	Impella cVAD	Impella 5.0
Pump mechanism	Pneumatic	Centrifugal	Centrifugal	Axial flow	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	14 Fr	22 Fr Surgical cut-down
Insertion technique	descending aorta via the femoral artery	inflow cannula into the right atrium via the femoral vein, outflow cannula into descending aorta via femoral artery	21 F inflow cannula into left atrium via femoral vein and trans-septal puncture and 15-17 F outflow cannula into femoral artery	12 F catheter placed retrograde across the aortic valve via the femoral artery	14 F catheter placed retrograde across the aortic valve via the femoral artery	21 F catheter placed retrograde across the aortic valve via a surgical cut-down of the femoral artery
Haemodynamic support	0.5 L/min	> 4.5 L/min	4 L/min	2.5 L/min	3.7 L/min	5.0 L/min
Implantation time	+	++	++++	++	++	++++
Risk of limb ischaemia	+	+++	+++	++	++	++
Anticoagulation	+	+++	+++	+	+	+
Haemolysis	+	++	++	++	++	++
Requires stable heart rhythm	Yes	No	No	No	No	No
Post implantation management complexity	+	+++	++++	++	++	++

ECMO, extracorporeal membrane oxygenation; IABP, intra-aortic balloon pump.

with STEMI complicated by cardiogenic shock confirmed the superior improvement of haemodynamic parameters with TandemHeart support compared with IABP therapy.[28,30] However, complications such as severe bleeding, arrhythmias and limb ischaemia occurred more often using the TandemHeart than IABP. Although both studies were not powered to detect differences in mortality, no difference in mortality was found.

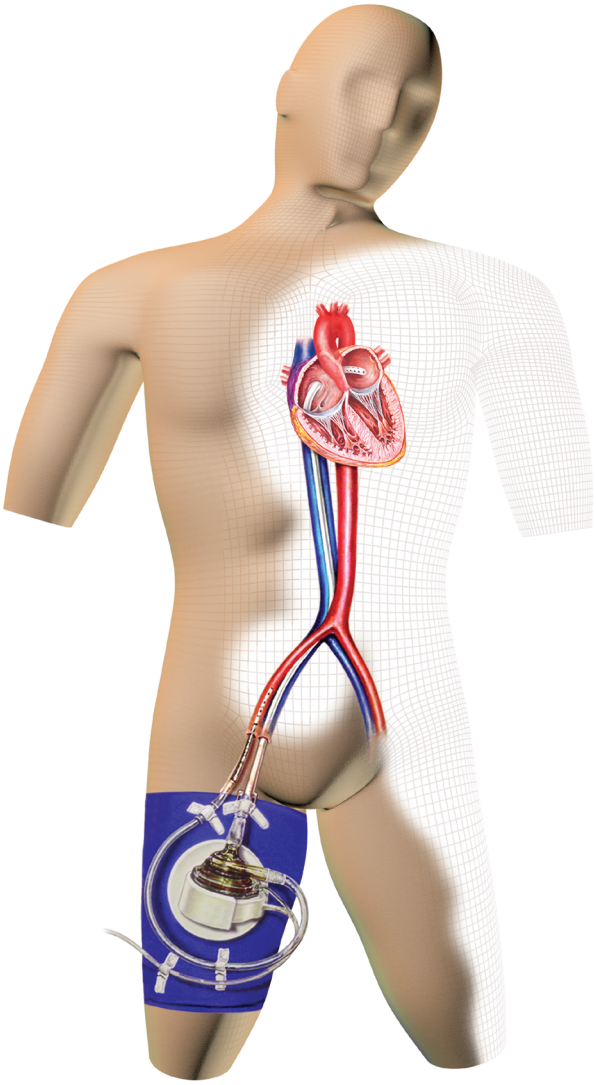


Figure 1 TandemHeart
The TandemHeart ventricular assist device which is placed in the left ventricle using a trans-septal cannula.

In conclusion, the TandemHeart provides both haemodynamic support and myocardial protection in patients with STEMI complicated by cardiogenic shock, although several complications such as severe bleeding and limb ischaemia can occur when using this invasive treatment. Also, the insertion procedure is complex.

Impella

The Impella is a micro-axial rotary pump that is placed across the aortic valve expelling aspirated blood from the left ventricle into the ascending aorta (Figure 2). Two versions of the Impella system are currently available. The Impella 2.5 can provide up to 2.5 l/min and can be percutaneously inserted. The Impella 5.0 can deliver up to 5.0 l/min but requires a surgical cutdown of the femoral or axillary artery. Maximum flow in the Impella 2.5 and 5.0 is generated at a maximal rotational speed of 50,000 and 33,000 revolutions/min, respectively. The device has a pigtail-catheter at the tip to ensure stable positioning in the left ventricle and to avoid adhering to the myocardium.

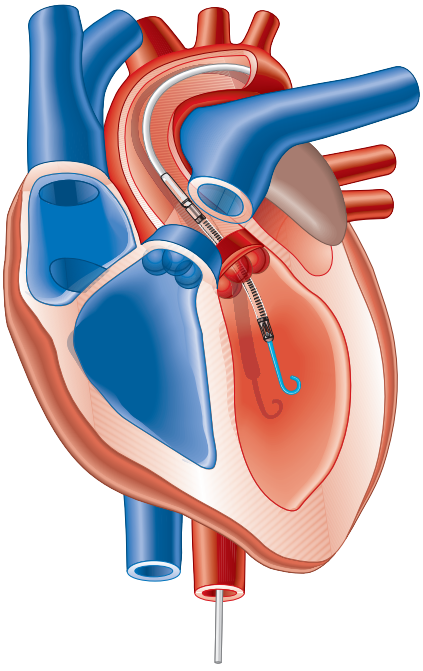


Figure 2 Impella
The Impella 2.5 is inserted percutaneously and positioned across the aortic valve in the left ventricle.

Several studies have demonstrated that the Impella device is feasible and safe in STEMI and high-risk PCI patients, but in cardiogenic shock patients, only a few studies have been

reported. [32-34] Meyns et al. showed initial safety and feasibility in six patients with severe cardiogenic shock after maximal inotropic support and IABP therapy.[35] They showed decreased PCWP and blood lactate levels and increased MAP and cardiac output. The ISAR-SHOCK randomised trial compared IABP with Impella 2.5 in cardiogenic shock patients.[36] They found increased cardiac index, cardiac output and MAP in patients treated with Impella compared with IABP-treated patients. Also, they found the overall cardiac power index was slightly higher in Impella patients but the endogenous cardiac output of the left ventricle was significantly lower at all time points because of the additional work of the device. Serum lactate levels were lower in the Impella group than the IABP group. No difference in mortality, major bleeding, distal limb ischaemia, arrhythmias and infections was found. The long-term effects of the Impella are only described by usage after PCI by STEMI and showed no aortic valve abnormalities.[37] Also, the Impella group patients showed more left ventricular ejection fraction recovery compared with control patients.

The IMPRESS in STEMI trial, comparing mechanical support by IABP versus Impella 2.5 in STEMI patients with signs of pre-shock, has recently been stopped because of a low inclusion rate due to the targeted pre-shock population, which is not an easily assessed clinical condition.[38] Also the RECOVER II trial, comparing IABP and Impella 2.5 in haemodynamically unstable STEMI patients, has been terminated due to insufficient patient enrolment.[39]

The direct unloading of the left ventricle is an important feature of the Impella. The unloading effect is demonstrated by reduced end-diastolic wall stress and an immediate decrease in PCWP by using the Impella 2.5.[40,41] There is also an increase in coronary perfusion pressure and coronary flow.[42] Measured pressure volume loops show a decreased PVA, which indicates a reduced oxygen consumption of the myocardium.[42] The Impella-induced increase in coronary flow probably results from both an increased perfusion pressure and a decreased left ventricular volume-related intramyocardial resistance. In an experimental setting in sheep, the Impella support has been demonstrated to reduce infarct size.[35] The Impella 5.0 should result in even larger unloading due to the substantially larger contribution to overall circulation.

In severe cardiogenic shock, the Impella 5.0 may result in superior haemodynamic support. Engstrom et al described the experience with the use of the Impella 2.5 and 5.0 and suggested that Impella 5.0 placement should be considered for profound cardiogenic shock patients.[43]. Either immediate insertion or quick upgrade, after initial Impella 2.5 to Impella 5.0 may be considered in cases with severe shock without signs of recovery. Also, in patients with post-cardiotomy low-output syndrome with a residual cardiac function of 1 l/min a significant reduction in mortality was observed with Impella 5.0 support.[44,45]

In conclusion, the less invasive Impella 2.5 support is able to unload the ventricle, improves coronary circulation and gives haemodynamic support up to 2.5 l/min with a low complica-

tion rate. However, the Impella 2.5 may not be sufficient to provide enough cardiac output to preserve or restore organ perfusion in the case of severe and profound cardiogenic shock. In these cases, the Impella 5.0 may be able to provide additional support although a drawback of this device is the requirement of femoral artery surgical cutdown. In 2012, the Impella cVAD is expected to be clinically available. The Impella cVAD is smaller than the Impella 5.0 (14 Fr pump vs 21 Fr) and can deliver at least 3.7 l/min. Due to its smaller size, it can be inserted percutaneously like the Impella 2.5. A randomised controlled trial using the Impella cVAD should give more insight into the feasibility of the Impella cVAD in cardiogenic shock. The IMPRESS in Severe Shock Trial using the Impella cVAD is planned to start as soon as the Impella cVAD is clinically available.

Percutaneous ECMO

ECMO can be achieved percutaneously and is a modified heart-lung machine, which can be used for several days. The ECMO system generally consists of a centrifugal pump, a heater and an oxygenator. Via the femoral artery, venous blood flows from the right atrium into a centrifugal pump and oxygenator and is guided via an outflow cannula into the descending aorta via the femoral artery (Figure 3). The usage of percutaneous ECMO in cardiogenic shock has been described in postcardiotomy[46], STEMI[47] and myocarditis[48]. ECMO is the only percutaneous assist device that also oxygenates the blood. It can give haemodynamic support more than 4.5 l/min depending on the cannula size. Complications associated with ECMO use are a systemic inflammatory response, renal failure, limb ischaemia and bleeding complications. Although ECMO can provide substantial haemodynamic support, it also increases both afterload and preload of the left ventricle, increasing the oxygen demand and impeding myocardial protection.[49]
However, the European Society of Cardiology/ European Association for Cardio-Thoracic Surgery (ESC/EACTS) guidelines recommend consideration of ECMO implantation for temporary support in patients who continue to deteriorate after IABP implantation and adequate circulation cannot be maintained.[50] This strong recommendation is, however, not substantiated by any robust clinical evidence and should therefore be re-evaluated.

PERCUTANEOUS LVAD VERSUS IABP

A meta-analysis compared the safety and efficacy of percutaneous LVAD with IABP in patients with cardiogenic shock using two TandemHeart studies and one Impella study and concluded that LVAD patients had a higher cardiac index and MAP and lower PCWP compared with IABP patients.[28,29,36,51] Although none of the included studies was powered to detect mortality differences, the authors reported similar mortality and incidence of leg ischaemia, but more bleeding in LVAD patients compared with patients treated with IABP.

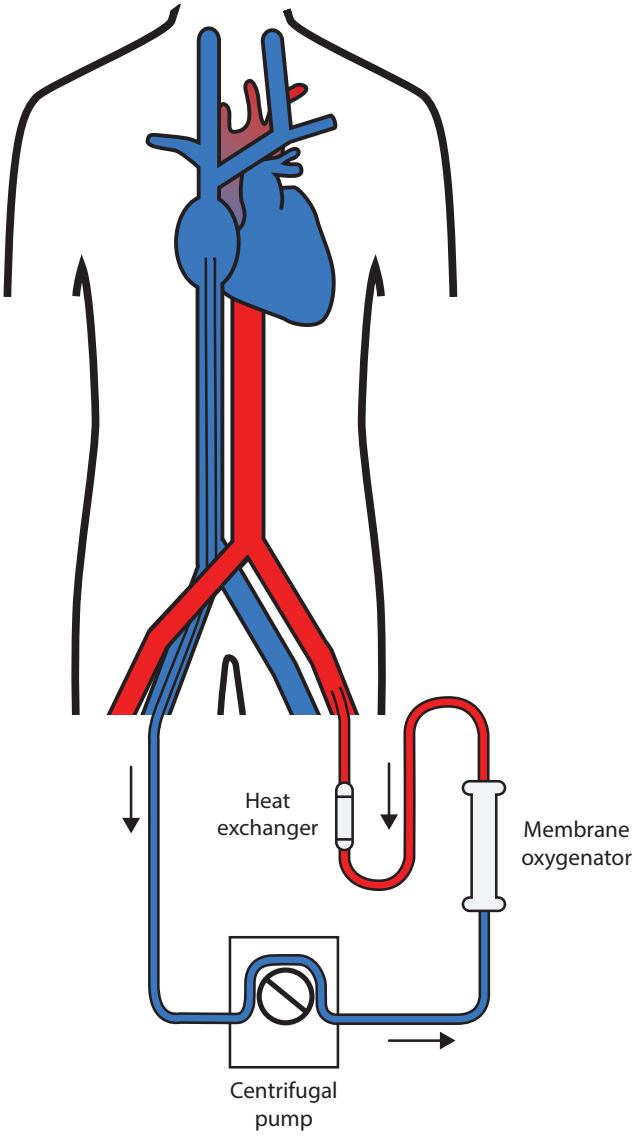


Figure 3 ECMO
A percutaneous veno-arterial access. The venous access is connected to an ECMO system with an integrated centrifugal pump and membrane oxygenator (artificial lung) and connected to the arterial inflow access.

In the case of cardiogenic shock, especially full-blown cardiogenic shock, haemodynamic support is the main concern, to prevent organ dysfunction. In these patients, the Impella 2.5 may be insufficient and the TandemHeart or Impella 5.0 device would be superior to increase CPO to avoid organ failure, despite the longer implantation time and higher complication rates. Of note, the Impella 2.5 clearly improves various clinical

parameters when compared with IABP therapy in a variety of clinical conditions.[36] A more complete review on the technical details between the TandemHeart and Impella devices is described by Naidu.[52]

GUIDELINES

The ESC/EACTS guidelines on myocardial revascularisation recommend early reperfusion as well as haemodynamic support to prevent end-organ failure.[50] The use of an IABP is recommended only in the presence of haemodynamic impairment. Although not supported by evidence, insertion is recommended before angiography. It is also stated that after failure of initial therapy including reperfusion and revascularisation to stabilise haemodynamics, temporary mechanical support using an extracorporeal membrane oxygenator should be considered. The recently updated 2011 ACCF/AHA/SCAI guidelines for PCI for cardiogenic shock recommend PCI as soon as possible if the patient is a suitable candidate.[10] A haemodynamic support device, specifically including the IABP, Impella and TandemHeart, is recommended if the patient does not stabilise quickly with pharmacological therapy, although it is mentioned that no data support a reduction in mortality rates when using the IABP or percutaneous LVAD. An overview of recommendations of using mechanical assist devices is shown in Table 2.[10,50,53]

FUTURE PERSPECTIVES

Despite prompt revascularisation, pharmacological treatment and the use of IABP therapy, the mortality in cardiogenic shock patients remains high. Currently available percutaneous LVADs are promising and safety and feasibility is encouraging in patients with cardiogenic shock. The experience in LVAD therapy is expanding rapidly. The indications include not only acute cardiogenic shock patients, but also prophylactic support during high-risk PCI or as a bridge to transplant in advanced heart failure patients. Therefore, in the forthcoming years, the development and usage of percutaneous LVADs will increase and haemodynamic support will be used more frequently as an additional treatment in several patient groups. In patients with cardiogenic shock, mechanical cardiac assistance can provide immediate circulatory support to prevent organ failure and to provide time to await myocardial recovery. Also, if myocardial recovery is not expected to occur rapidly, percutaneous LVADs may select patients who may benefit from long-term (surgical) LVAD therapy. In STEMI patients with cardiogenic shock, mechanical circulatory support may even become as equally important as opening the occluded artery. In the future, the focus of these patients may therefore shift from door-to-balloon time to door-to-circulatory support time.

Table 2 Guideline recommendations on mechanical assist devices.

Indication	Assist device	ESC/EACT Guidelines[50]		ACCF/AHA/SCAI Guidelines[10,53]	
Cardiogenic shock	IABP	Class I [Level of Evidence C]	IABP insertion is recommended in patients with haemodynamic instability (particularly those in cardiogenic shock and with mechanical complications)	Class I [Level of Evidence B]	A haemodynamic support device is recommended for patients with cardiogenic shock after STEMI who do not quickly stabilise with pharmacological therapy
	TandemHeart	Class III [Level of Evidence B]	Routine use of percutaneous centrifugal pumps is not recommended		
	Impella	No recommendation	No recommendation		
	ECMO	No recommendation	ECMO implantation should be considered for temporary support in patients with AHF with potential for functional recovery following revascularisation	No recommendation	No recommendation
High risk PCI	IABP	Class III [Level of Evidence B]	The systematic use of balloon counterpulsation, in the absence of haemodynamic impairment, is not recommended.	Class IIb [Level of Evidence C]	Elective insertion of an appropriate haemodynamic support device as an adjunct to PCI may be reasonable in carefully selected high-risk patients
	TandemHeart	Class III [Level of Evidence B]	Routine use of percutaneous centrifugal pumps is not recommended		
	Impella	No recommendation	No recommendation		
	ECMO	No recommendation	No recommendation	No recommendation	No recommendation
Unstable Angina/NSTEMI	IABP	Class I [Level of Evidence C]	IABP insertion is recommended in patients with haemodynamic instability (particularly those in cardiogenic shock and with mechanical complications)	Class IIa [Level of Evidence C]	Intra-aortic balloon pump (IABP) counterpulsation is reasonable in UA/NSTEMI patients for severe ischaemia that is continuing or recurs frequently despite intensive medical therapy, for haemodynamic instability in patients before or after coronary angiography, and for mechanical complications of MI
	TandemHeart	Class IIa [Level of Evidence C]	LVADs have been used in patients not responding to standard treatment including IABP and as a bridge to transplantation but the experience is limited	No recommendation	No recommendation
	Impella				
	ECMO	No recommendation	No recommendation		

Table 2 Guideline recommendations on mechanical assist devices. (continued)

Indication	Assist device	ESC/EACT Guidelines[50]		ACCF/AHA/SCAI Guidelines[10,53]	
CABG	IABP	No recommendation	If repeat PCI fails to abort evolving significant MI, immediate CABG is indicated. When severe haemodynamic instability is present, IABP should be inserted prior to emergency revascularisation. Cardiopulmonary assistance may be considered if the patient does not stabilise prior to emergency CABG	Class IIa [Level of Evidence B]	In the absence of severe, symptomatic aorto-iliac occlusive disease or peripheral artery disease, the insertion of an intra-aortic balloon is reasonable to reduce mortality rate in CABG patients who are considered to be at high risk (e.g., those who are undergoing reoperation or have LVEF <30% or left main CAD)
	TandemHeart	No recommendation	No recommendation	No recommendation	No recommendation
	Impella				
	ECMO				

ACCF/AHA/SCAI, American College of Cardiology Foundation/American Heart Association/Society for Cardiovascular Angiography and Interventions; AHF, advanced heart failure; CABG, coronary artery bypass grafting; CAD, cardiac assist device; ECMO, extracorporeal membrane oxygenation; ESC/EACT, European Society of Cardiology/European Association for Cardio-Thoracic Surgery; IABP, intra-aortic balloon pump; LV, left ventricular; LVADs, left ventricular assist devices; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NSTEMI, non-ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction; UA, unstable angina

However, large randomised trials need to be performed to show the effect of different LVADs and IABP on hard clinical endpoints and preferably on survival. Future developments need to focus on minimising insertion point-related complications such as limb ischaemia and severe bleeding by reducing the device size while maintaining sufficient haemodynamic support. Also thromboembolic complications should be reduced and the associated morbidity needs to be minimised.

As described before, the amount of cardiogenic support and ventricular unloading varies between different mechanical support systems. The choice of support system may depend on the amount of support needed. In consequence, subgroups of patients have to be defined regarding the severity of cardiogenic shock to allow a better discrimination between patient groups and devices to detect beneficial or harmful effects on outcome in different subgroups. Whether device therapy will ultimately prove beneficial and whether one device is superior to the other in each situation remains to be seen. The usage of percutaneous right ventricular assist devices in the case of right ventricular failure is in development and only little experience is available. Developments of both the TandemHeart and Impella systems are in progress and a percutaneous right ventricular assist device might become clinically available in the future.[54]

There is a critical need for studies regarding the optimal timing of percutaneous cardiac support device implantation, which may prevent the need for potentially deleterious pharmacotherapy. Intuitively, by placing the assist device early in the course of cardiogenic shock, systemic perfusion may be preserved while unloading the heart, resulting in less myocardial damage and multiorgan failure. This would be expected to improve survival although evidence is currently lacking.

CONCLUSION

In conclusion the experience and usage of percutaneous cardiac assist devices in cardiogenic shock has increased over the past years. The ideal device generates sufficient haemodynamic support to prevent end-organ failure, but also myocardial protection to prevent myocardial ischaemia, and has a low complication rate. In the future, mechanical circulatory support may even become equally important as opening the occluded artery in STEMI patients with cardiogenic shock. Eventually, the focus of these patients may therefore shift from door-to-balloon time to door-to-circulatory support time but only in the light of clinical evidence.

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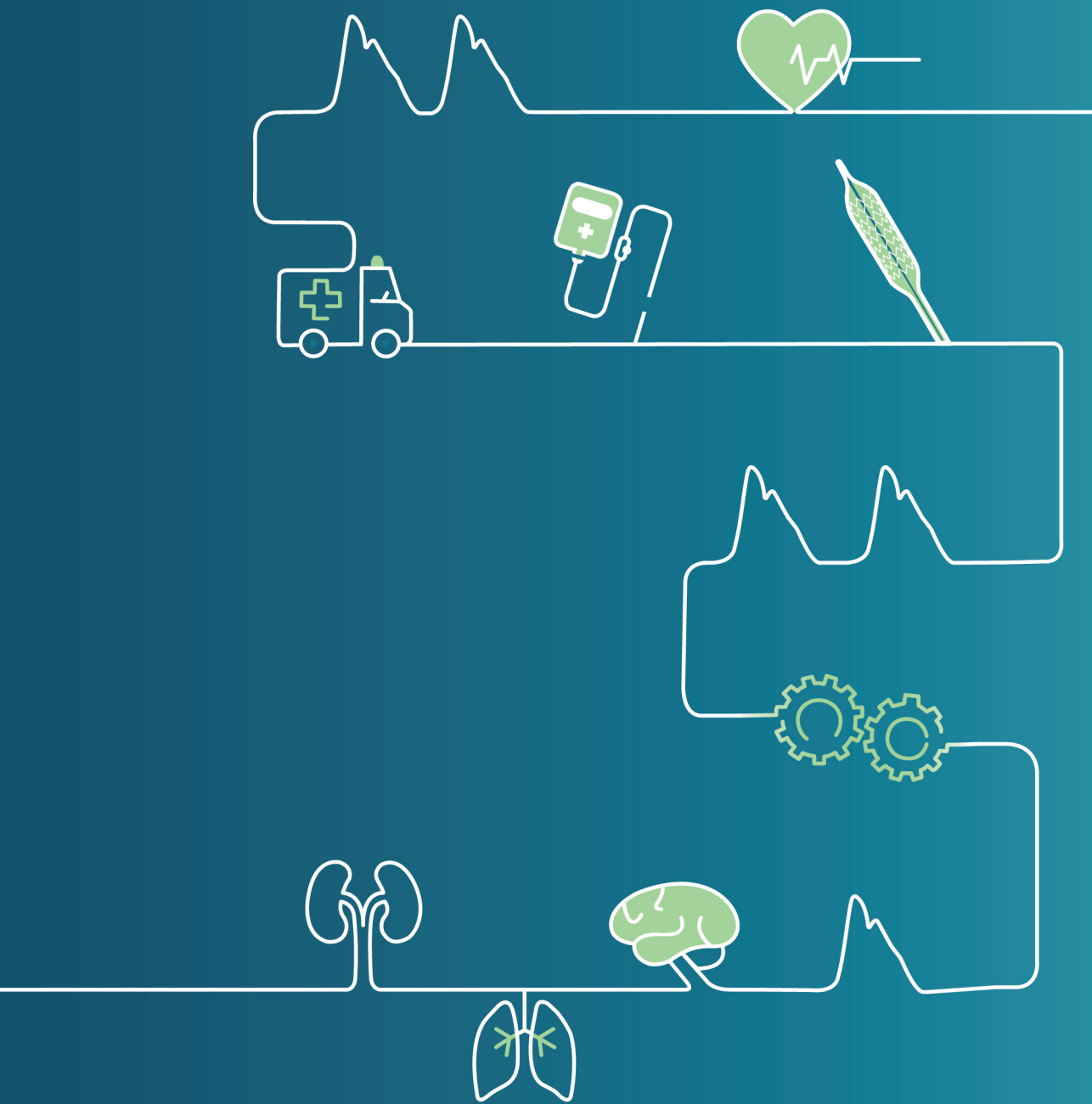
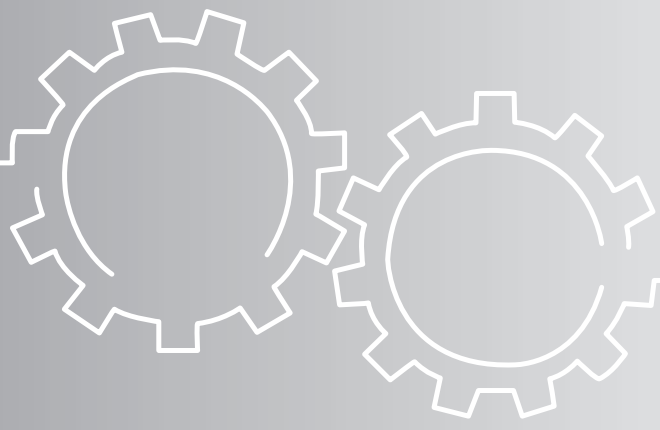


PART I

HEMODYNAMIC SUPPORT WITH IMPELLA: CLINICAL EXPERIENCE

CHAPTER 3



EVALUATING THE LEARNING CURVE IN THE PROSPECTIVE RANDOMIZED CLINICAL TRIAL OF HEMODYNAMIC SUPPORT WITH IMPELLA 2.5 VERSUS INTRA-AORTIC BALLOON PUMP IN PATIENTS UNDERGOING HIGH-RISK PERCUTANEOUS CORONARY INTERVENTION: A PRE-SPECIFIED SUB-ANALYSIS OF THE PROTECT II STUDY

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ABSTRACT

Background

The introduction of new medical devices may be accompanied by a learning curve.

Methods

To evaluate the impact of the device learning curve on the outcomes of PROTECT II trial, comparing Impella 2.5 versus the intra-aortic balloon pump (IABP) during high-risk percutaneous coronary intervention, we report on a prespecified analysis, excluding the first Impella 2.5 and IABP patients at each site.

Results

A total of 448 patients were enrolled at 74 sites. Among these, 58 patients were the first to receive Impella 2.5 at their site, 62 were the first to receive IABP. A trend toward higher major adverse events (MAEs) at 30 days was observed for the subgroup of first versus remaining Impella 2.5 patients: 44.8% versus 31.7%, p=0.072. MAE rates for the first and remaining IABP patients were similar at 30 days. After exclusion of the first patient in each group, MAE rates for Impella 2.5 and IABP were 31.7% versus 40.0% (p=0.119) at 30 days and 38.0% versus 50.0% (p=0.029) at 90 days.

Conclusions

Significantly lower 90-day MAE rates were observed with the use of Impella 2.5 compared to the use of IABP after excluding the first patient per group at each site. This pre-specified analysis suggests a learning curve associated with initial introduction of the Impella 2.5. Clinical trials should better address the training aspect of new devices, especially when compared with more established devices.

New cardiovascular medical devices require specific training, even when perceived as relatively simple. This training, from device deployment to post-implant management, is relevant not only to the physician but also to other personnel exposed to new technology. The training process is characterized by a learning curve, which has been shown to affect clinical outcomes during early use of devices.[1-3] Clinical trials designed to assess device safety and efficacy may include a roll-in or training phase.[4] Frequently, the results of these roll-in or training patients are excluded from the endpoint analysis.[5]

The prospective, multi-center, randomized controlled PROTECT II trial was designed to assess the safety and efficacy of the Impella 2.5 percutaneous left ventricular assist device against the intra-aortic balloon pump (IABP) in the setting of non-emergent high-risk percutaneous coronary intervention (PCI). The study was powered to demonstrate superiority of Impella.[6]

Before the start of the PROTECT II study, the PROTECT I study was performed as a pre-IDE trial and consisted of 20 patients in 7 sites. Therefore, at the start of the PROTECT II trial, the clinical experience with the Impella was limited to 7 sites. Of those sites, only 5 participated in the PROTECT II study. The PROTECT II study had a targeted enrollment of 654 patients in 112 sites, most of which had no experience with the Impella.[6]

Although a learning curve was expected, PROTECT II did not include a roll-in phase due to the large number of sites and the expected low enrollment rate. Instead, a prespecified subgroup analysis was incorporated in the statistical analysis plan to evaluate the effect of the device learning curve on the outcomes of the study.

We report the results of a prespecified subgroup analysis, in which the outcomes of PROTECT II were evaluated after excluding the first Impella and IABP patients at each site.

METHODS

Study Design

The PROTECT II trial was a prospective, multi-center, randomized controlled trial that compared the outcomes of patients supported with the Impella 2.5 percutaneous left ventricular assist device to those supported with the IABP during high-risk PCI, as published previously[6]. The trial was conducted at 112 sites in the United States, Canada, and Europe. Patients eligible for enrollment required hemodynamic support, as determined by the treating physician, during non-emergent PCI. Eligible patients were scheduled for PCI of an unprotected left main artery or last patent coronary vessel and had a left ventricular ejection fraction (LVEF) ≤35%, or had 3-vessel disease and a LVEF ≤30%.

Device Description

The Impella 2.5 (Abiomed, Danvers, MA) is a 12 F intravascular micro-axial blood pump mounted on a 9 F catheter.[6,7] The device is inserted percutaneously through the femoral artery and positioned with the pump inlet in the left ventricle and pump outlet in the ascending aorta, providing up to 2.5 L/min of continuous blood flow. The device provides direct left ventricular unloading by aspirating blood from the left ventricle and expelling it into the aorta, thus increasing total cardiac output, reducing myocardial oxygen consumption and decreasing the pulmonary capillary wedge pressure.[8-10]

Study Procedures

After providing informed consent, patients underwent right and left heart catheterization and vascular access suitability was assessed. Patients were randomized to either the Impella 2.5 or a commercially available IABP. Revascularization was performed using standard equipment and techniques, leaving the use of drug-eluting or bare metal stents as well as adjunctive therapies such as rotational atherectomy and antiplatelet therapy to the discretion of the treating physician. Hemodynamic support was discontinued in the catheterization laboratory if the patient was deemed hemodynamically stable. According to the study protocol, follow-up was performed at 30 and 90 days postprocedure. Study procedures and details have been described previously.[6]

Endpoints

The primary endpoint of the PROTECT II trial was the composite rate of 10 major adverse events (MAEs) at discharge or 30-day follow-up, whichever was longer.[6] According to the study protocol, additional follow-up of the composite endpoint was performed at 90 days. The composite endpoint components included: all-cause mortality, Q-wave or non–Q-wave myocardial infarction (MI), stroke or transient ischemic attack, any repeat revascularization procedure, need for cardiac or vascular operation, acute renal insufficiency, severe intraprocedural hypotension requiring therapy, cardiopulmonary resuscitation or ventricular tachycardia requiring cardioversion, aortic insufficiency, and angiographic failure of PCI. Definitions of the MAEs are attached in the supplementary files.

Statistical analyses

The primary endpoint analysis was reported for all randomly assigned patients who underwent high-risk PCI on the intent-totreat principle regardless of protocol compliance. In accordance with the protocol, the endpoint analysis was also reported for the prespecified per-protocol population, which included only patients meeting the protocol eligibility criteria. As outlined in the prespecified statistical analysis plan, a subanalysis was performed excluding the first Impella and IABP patients within the

PROTECT II study at each site. The first IABP study patients were excluded not due to inexperience using the IABP, but rather to generate comparable, randomized treatment groups. The first patient in each group at each site was excluded from both the intent-to-treat and per-protocol patient populations. Treatment comparisons on the 30-day and 90-day MAE were performed using the X^2-test. As a supportive analysis, Kaplan–Meier estimates of the cumulative incidence of MAE through 30 and 90 days were performed, and a log-rank test was used to compare the curves between the 2 study arms at these time points. Data are expressed as mean ± standard deviation (SD), median (range), or proportion. Univariate parametric analysis was performed using a 2-tailed unpaired t-test or a nonparametric Mann-Whitney U test for continuous outcomes. Fisher exact or X^2-tests were used as appropriate for nominal data. All probability values were 2-tailed and considered significant when <0.05. Statistical analyses were performed by the Harvard Clinical Research Institute using SAS version 9.2 (SAS Institute Inc, Cary, NC). The authors had full access to the data and take responsibility for its integrity. This study was funded by Abiomed (Danvers, MA). The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the manuscript, and its final contents.

RESULTS

The PROTECT II trial enrolled 452 patients between November 27, 2007 and December 6, 2010. A total of 226 patients were randomized to Impella and 226 patients to IABP support, representing 69% of the planned 654 patient enrollments. After review of the planned interim data (n = 327), the Data and Safety Monitoring Board (DSMB) recommended early discontinuation of the study for futility based on the observed conditional power of the 30-day results of the first 327 patients and the assumed similar trend for the remaining 327 patients to be included in the study. The executive committee accepted the DSMB recommendation. An additional 125 patients were enrolled during the ensuing 9 months between the halfway enrollment point and the DSMB analysis and recommendation which resulted in a total cohort of 452 patients. Four patients were not included in the primary analyses due to informed consent withdrawal (3 patients, IABP arm) and death before undergoing PCI (1 patient, Impella arm), resulting in a cohort of 448 patients of whom 225 were assigned to Impella and 223 to IABP.

Patients were enrolled at 74 sites. Among these, 58 patients were the first to receive Impella at their site. There were 62 patients treated with IABP for the first time within the study at each site.

Since the PROTECT I study only included 20 patients at 7 sites (of which only 5 were included in the PROTECT II trial), and the Impella 2.5 did not have 510(k) clearance until

7 months after initiating the PROTECT II trial, the first Impella uses in the PROTECT II trial were mostly the first ever uses of the device at the enrolling center. In contrast, all sites had wide experience with IABP prior to their first IABP enrollment in PROTECT II.
The prespecified per-protocol population included only patients who met the protocol eligibility criteria. The per-protocol population included 427 patients (216 Impella patients and 211 IABP patients), of which 54 and 59 were the first Impella and IABP patients treated within this study at their sites, respectively.
At the conclusion of the study, 38 of the participating 112 sites had not enrolled any patients. Sixteen sites enrolled only IABP patients, and twelve sites enrolled only Impella patients.

First treated patient at each site

Impella patients
Baseline characteristics were similar between the first and remaining Impella patients, except for the higher incidence of cardiomyopathy in the first Impella patients (Supplementary Table 1).
During the procedures of the first Impella patients compared to the remaining patients, there was more use of heparin, longer procedure duration, more blood transfusions, a higher percentage of post-procedural New York Heart Association (NYHA) class III or IV, and fewer patients with additional lesions treated than pre-procedurally planned (Supplementary Table 2).
In the group of the first Impella patients at each site, there was a trend toward higher MAE at 30 and 90 days compared to the remaining patients (44.8% vs 31.7%, p=0.072 at 30 days, 48.3% vs 38.0%, p=0.168 at 90 days) (Figure 1, Supplementary Table 3). All adverse events in the first Impella patients are depicted in the supplementary files.

IABP patients
Baseline and procedural characteristics were similar between the first and remaining IABP patients (Supplementary Tables 1 and 2). The first IABP patients experienced a similar MAE rate compared to the remaining patients (40.3% vs 40.0%, p=0.965 at 30 days, 47.5% vs 50.0%, p=0.744 at 90 days) (Figure 1, Supplementary Table 4).

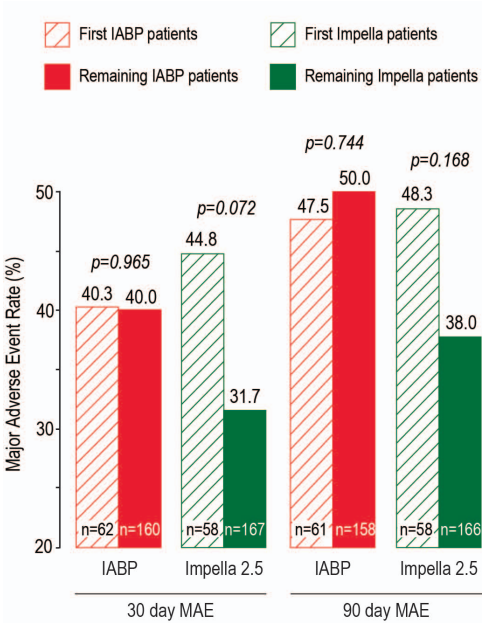

Figure 1 Composite 30-day and 90-day MAE rates for the first Impella and IABP patients at each site versus the remaining Impella and IABP patients (intent-to-treat population).
IABP: intra-aortic balloon pump. MAE: major adverse event.

Table 1 Patient baseline characteristics.
Excluding first IABP and Impella patients at each site, intent-to-treat population.

	IABP patients, excluding first patients at each site	**Impella 2.5 patients, excluding first patients at each site**	
	(n=161)	(n=167)	*p*
Age, y	67 ± 11	68 ± 11	0.355
Sex, male, %	80.1	80.2	0.979
Weight, kg	83.6 ± 20.7	83.1 ± 19.3	0.817
History of CHF, %	83.2	91	0.035
Current NYHA (class III/IV), %	60.4	63.6	0.600
Cardiomyopathy, %	68.3	65.3	0.557
Diabetes mellitus, %	52.2	52.1	0.989
Renal insufficiency, %	29.4	22.2	0.135
Valve disease, %	66.3	65.3	0.852
Peripheral vascular disease, %	25.5	26.2	0.877
Pacemaker/AICD, %	27.3	32.9	0.269
Previous CABG, %	26.7	37.7	0.033
LVEF, %	24.1 ± 6.1	23.2 ± 6.6	0.178
STS mortality score	5.7 ± 5.8	5.8 ± 6.1	0.859
SYNTAX score	28.7 ± 13.5	29.8 ± 12.9	0.522
Not surgical candidate, %	60.9	60.5	0.942

AICD: automated implantable cardioverter-defibrillator; CABG: coronary artery bypass graft; CHF: congestive heart failure; IABP: intra-aortic balloon pump; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association; PCI: percutaneous coronary intervention; STS: Society of Thoracic Surgery; SYNTAX: Synergy Between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery trial.

Table 2 Procedural characteristics.
Excluding first IABP and Impella patients at each site, intent-to-treat population.

	IABP patients, excluding first patients at each site	**Impella 2.5 patients, excluding first patients at each site**	
	(n=161)	(n=167)	*p*
No. of lesions attempted	2.9 ± 1.6	2.8 ± 1.3	0.645
No. of stents placed	3.0 ± 2.0	3.1 ± 1.80	0.688
Total length of all lesion treated, mm	37.0 ± 28.8	37.0 ± 26.9	0.982
Use of heparin, %	86.3	91	0.174
Glycoprotein IIb/IIIa inhibitors, %	25.5	12.6	0.003
Rotational atherectomy, %	8.7	14.4	0.108
Median no. of passes/lesion (IQR)	1(1-2)	4(2-5)	0.001
Median no. of passes/patient (IQR)	2.0(2.0-3.0)	5.0(3.5-9.0)	0.006
Median RA time/lesion (IQR), s	40(25-47)	64(40-134)	0.019
Saphenous vein graft treatment, %	8.7	9.6	0.768
Total support time, h	8.0 ± 18.2	1.9 ± 3.0	< 0.001
Duration of index procedure, h	1.0 ± 0.7	1.0 ± 0.7	0.877
Discharge from cath lab on device, %	37.3	6.1	< 0.001
MAP before procedure, mmHg	89.7 ± 16.3	89.0 ± 14.5	0.695
PAP (sys) before procedure, mmHg	42.3 ± 15.4	43.1 ± 14.9	0.669
PCWP before procedure, mmHg	17.4 ± 8.7	19.7 ± 9.5	0.049
Cardiac index before procedure, mmHg	2.4 ± 0.8	2.2 ± 0.6	0.061
Contrast administered during the procedure, mL	243 ± 121	267 ± 137	0.092
IV fluid administered during the procedure, mL	417 ± 392	549 ± 649	0.06
Transfusion required during the procedure or at pump removal, %	1.9	1.8	0.964
Post-procedural NYHA Class III/IV, %	47.4	40.2	0.338
More lesions treated than planned pre-procedurally, %	27.5	31.1	0.47
Patients with complications during the procedure, %	6.9	10.2	0.286
SYNTAX score post-PCI	13.9 ± 12.4	15.0 ± 12.8	0.505
Difference SYNTAX score pre-post PCI	-14.9 ± 9.4	-14.8 ± 9.5	0.966

Data are expressed as mean ± standard deviation except when mentioned otherwise. *When reporting median and interquartile range (IQR), Wilcoxon rank-sum test p-values are used. IABP: intra-aortic balloon pump; IV: intravenous; MAP: mean arterial pressure; NYHA: New York Heart Association; PAP: pulmonary artery pressure; PCI: percutaneous coronary intervention; PCWP: pulmonary capillary wedge pressure; SYNTAX: Synergy Between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery trial.*

Baseline and procedural characteristics excluding the first Impella and IABP patients

After excluding the 58 first Impella and 62 first IABP patients treated at their respective sites, baseline characteristics were similar between the remaining Impella and IABP patients (Table 1). The number of lesions attempted and the number of stents placed were similar between the two arms, but there were significant differences in the use of adjunctive therapies (Table 2).

Heparin was used more frequently in the Impella arm, while glycoprotein IIb/IIIa inhibitors were used more frequently in the IABP arm. There was a strong trend toward higher incidence of rotational atherectomies in the Impella arm, and among patients who underwent atherectomy the Impella patients experienced more passes overall, more passes per lesion, and more rotational atherectomy time per lesion. The volume of contrast media used and the volume of IV fluids given during the procedure was significantly larger in the Impella arm. IABP patients experienced a longer duration of hemodynamic support and were more likely to be discharged from the catheterization laboratory on support. Clinical outcomes excluding the first Impella and IABP patients Excluding the first patients, a strong trend toward fewer MAEs was observed in Impella patients compared to IABP patients at 30 days: 31.7% versus 40.0%, p=0.119 (intent-to-treat), 32.1% versus 42.1%, p=0.066 (per-protocol) (Figure 2, Table 3). At 90 days, the MAE rate was significantly lower for the Impella patients compared to the IABP patients: 38.0% versus 50.0%, p=0.029 in the intent-to-treat population, and 38.5% versus 52.0%, P = .017 in the per-protocol population. As depicted in the Kaplan–Meier curves for both all randomised patients (Figure 3A) and the first patients excluded (Figure 3B), patients treated with Impella experienced fewer MAEs over the course of the study compared with those treated with IABP. Most of the differences in MAEs between the first and remaining Impella patients occurred on the day of the procedure.

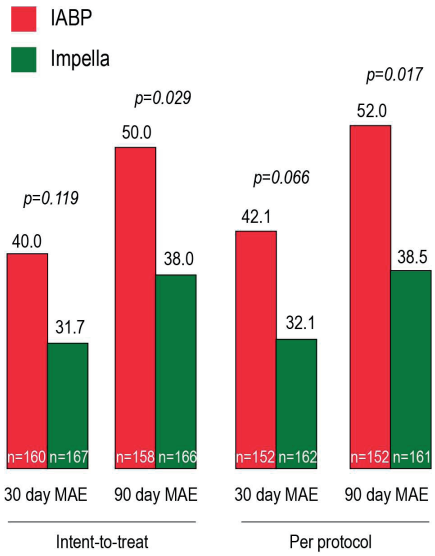

Figure 2 Composite 30- and 90-day MAE rates for the IABP and Impella patients, excluding the first IABP and Impella patients at each site for the intent-to-treat population and the per-protocol population. IABP: intra-aortic balloon pump. MAE: major adverse event.

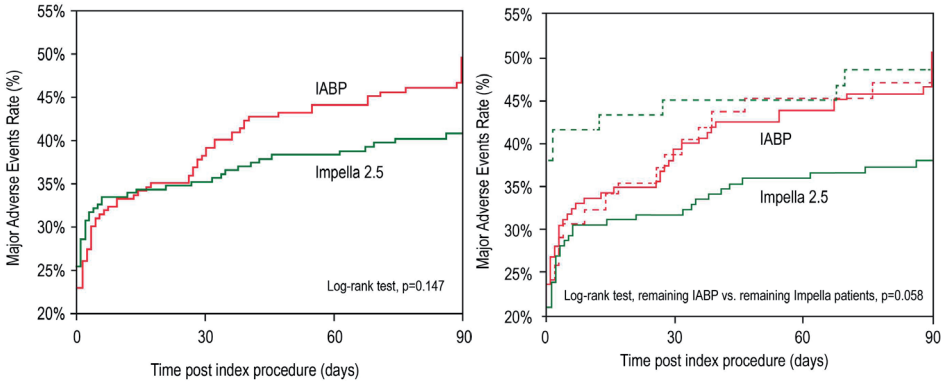

Figure 3 Kaplan-Meier curves of major adverse events to 90 days.
A) all IABP patients (red line) and all Impella patients (green line) (intent-to-treat population). Adapted from O'Neill et al.[6] B) first IABP patients at each site (red dashed line), remaining IABP patients (red solid line), first Impella patients at each site (green dashed line), and remaining Impella patients (green solid line) (intent-to-treat population).

Table 3 Major adverse events (hierarchical).
IABP patients compared to Impella 2.5 patients, excluding first Patients at each site, intent-to-treat population.

	30 Days			90 Days		
	IABP patients excluding first patients at each site (n=160)	Impella 2.5 patients excluding first patients at each site (n=167)	*p*	IABP patients excluding first patients at each site (n=158)	Impella 2.5 patients excluding first patients at each site (n=166)	*p*
Composite of major adverse events, % (n)	40.0(64)	31.7(53)	0.119	50.0(79)	38.0(63)	0.029
Death, % (n)	5.6(9)	6.0(10)	0.888	8.2(13)	10.8(18)	0.424
Stroke/TIA, % (n)	1.9(3)	0.0(0)	0.075	2.5(4)	0.6(1)	0.159
Myocardial infarction, % (n)	10.0(16)	13.2(22)	0.371	13.3(21)	12.7(21)	0.864
Repeat revascularization, % (n)	3.1(5)	1.8(3)	0.437	8.9(14)	4.2(7)	0.09
Need for cardiac or vascular operation,* % (n)	1.3(2)	0.6(1)	0.537	1.3(2)	1.2(2)	0.96
Acute renal dysfunction, % (n)	5.0(8)	4.8(8)	0.93	5.1(8)	4.2(7)	0.717
Cardiopulmonary resuscitation or ventricular arrhythmia requiring cardioversion, % (n)	1.9(3)	2.4(4)	0.745	3.2(5)	2.4(4)	0.679
Aortic valve damage/increase in aortic insufficiency, % (n)	0.0(0)	0.0(0)	---	0.0(0)	0.0(0)	---
Severe hypotension requiring treatment, % (n)	10.6(17)	3.0(5)	0.006	7.6(12)	1.8(3)	0.013
Angiographic failure, % (n)	0.6(1)	0.0(0)	0.306	0.0(0)	0.0(0)	---

*IABP: intra-aortic balloon pump; TIA: transient ischemic attack. * Cardiac, thoracic, or abdominal operation, or vascular operation for limb ischemia.*

Subgroup analyses on 30-day and 90- day MAE are depicted in Figure 4A and 4B. In the population not treated with atherectomy, the Impella patients had better outcomes compared with IABP patients, with a significant relative risk reduction in the MAE incidence of 30% and 31% at 30 and 90 days, respectively (p=0.034). Patients with STS scores <10 had better 90-day outcomes with Impella than with IABP (relative risk 0.70, p=0.014), whereas there was no difference between the 2 groups for patients with STS scores ≥10. Additional evidence of a learning effect in early Impella usage To further investigate the learning curve, an analysis was performed looking at how MAE rates changed over the course of the trial. A clear difference in MAE was observed for Impella patients included in the trial in the year 2008 compared with patients included in 2009 and 2010 (Figure 5). MAE rates for IABP patients did not change over the course of the trial. Discussion This prespecified analysis of the PROTECT II trial reveals a significant learning effect associated with the first versus subsequent enrolled Impella patients, which was not observed in patients treated with IABP. MAE rates at both 30 and 90 days were higher in the first Impella patients versus the remaining Impella patients, whereas such discrepant MAE rates were absent in the IABP arm. This learning curve effect is supported by the observation that MAE rates in patients enrolled in the first year (2008) were higher than those observed in patients enrolled in 2009 and 2010. This learning curve effect in the early use of new technologies should have implications on future cardiovascular device trial methodology. Future randomized controlled trials of new technologies should explicitly state how to handle the learning curve and either exclude these initial patients or prioritize an analysis of endpoint data that evaluates both the total population and specific "roll-in" period cut-points, within the context of the primary outcome measures. Currently there are no consensus guidelines for roll-in approaches in cardiovascular medical device trials. Instead, decisions on whether to include a roll-in phase, and whether to include the results experienced by roll-in patients in endpoint analyses, are based on clinical judgment. Chen et al. studied cardiovascular device premarket applications approved by the US Food and Drug Administration between 2000 and 2007, and found that only 16% of the associated device studies reported the use of a roll-in phase.[5] All of those studies excluded the outcomes of the roll-in patients from efficacy analyses. Specific to circulatory support device studies, a study evaluating the TandemHeart assist device in cardiogenic shock included a roll-in phase consisting of the first implant per site at sites without prior device experience. Outcomes for the roll-in patients were reported but were excluded from the endpoint analyses.[4]

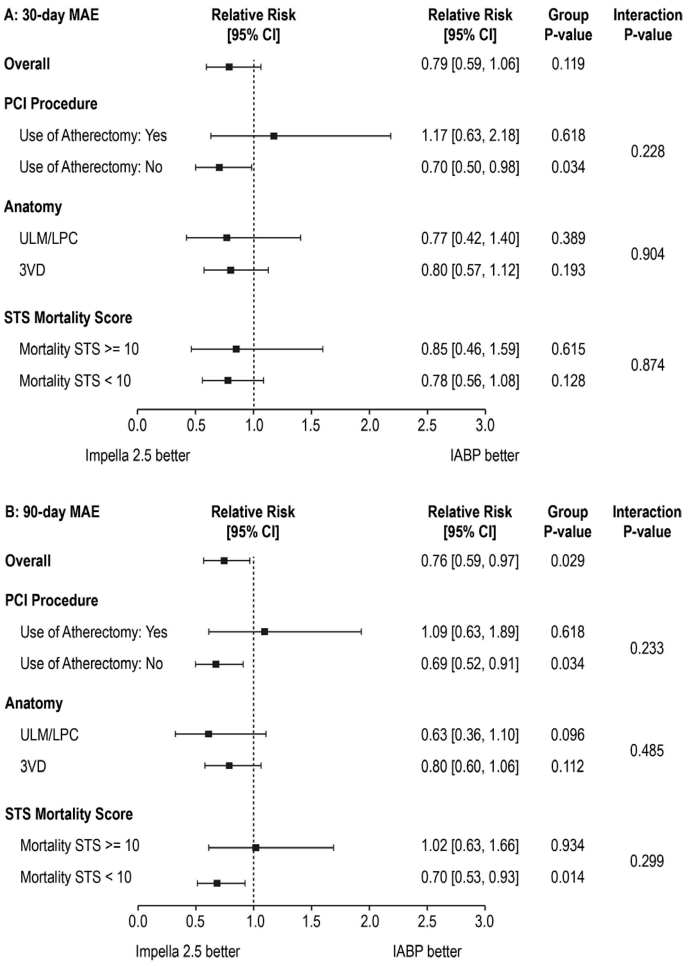

Figure 4 Pre-specified defined subgroup analysis, excluding the first IABP and Impella patients at each site, intent-to-treat population.

A) 30-day MAE. B) 90-day MAE. 3VD, three-vessel disease; CI, confidence interval; LPC, last patent conduit; STS, Society for Thoracic Surgery; ULM, unprotected left main.

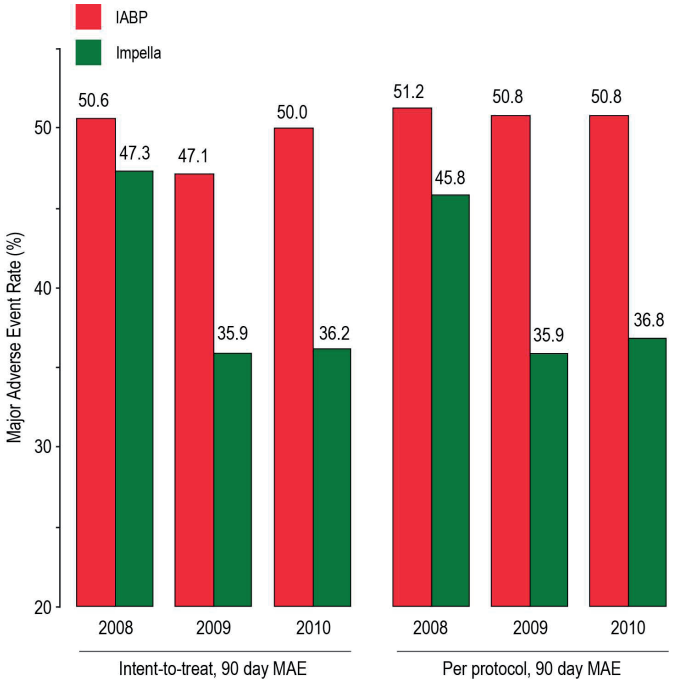

Figure 5 Ninety-day major adverse events rates over the course of the trial. Adapted from O'Neill et al. [6]

Earlier studies shown that familiarity with the IABP has an influence on outcomes.[11] A learning curve was anticipated in the PROTECT II trial since the majority of investigators had no prior experience with Impella, as the PROTECT I had only 7 participating sites. A roll-in phase consisting of the first Impella patients treated at each site was considered yet rejected as it would have caused 18 to 24 months delay due to the large number of participating sites and expected low enrollment rate. With the low expected enrollment it was anticipated that excluding more than one patient per site would have also excluded a significant number of sites from the analysis and perhaps introduced a significant uncontrolled bias. Comparing the first Impella patients to the remaining patients, the composite 30 and 90 day MAE dropped by an absolute 13.1% and 10.3%, respectively (intent to treat), which resulted in a statistically significant lower MAE rate in the Impella group than the IABP group at 90 days when the first patients in each group were excluded. The mortality rates after exclusion of the first patients were consistent with previous reports.[7,12-15]

Comparison of the individual components of the composite MAE for the first and remaining Impella patients showed that the learning curve effect was significantly impacted by incidences of severe hypotension. Hypotension was defined as systolic blood pressure or augmented diastolic pressure (the higher of the two) 90 mmHg for ≥5 min

requiring treatment with intotropic/vasopressor medications or IV fluid. A hypotensive event would trigger an MAE only if the patient was on device support. In a retrospective analysis, there were a total of 10 hypotensive events, 6 of these could have potentially been mitigated representing the only MAE experienced by the first patient at each of these sites. Unlike the IABP, the Impella device is preload dependent, like any other continuous flow pump. The pump performance depends on the right filling pressure. In the early phase of the trial, the physicians learned that the pump would not provide the support expected during transient ischemic times if there were not adequate filling pressure (wedge pressure above 10–12 mmHg). The physicians also had to learn how to manage and titrate the pump flow for different situations during the procedure (eg, long PTCA balloon inflation, stent deployment, runs duration and number of passes during rotablation).

At the time of the interim analysis of the DSMB, the learning curve had a large influence on the analyzed results because all the first Impella patients were included in the first 327 patients analyzed at the interim analysis. Therefore the potential difference between the Impella and IABP group was underestimated.

The lesson learned is that a first usage of a new device is stepping into unknown territory as opposed to relying on a large clinical experience. Each clinical trial assessing the safety and efficacy of new medical devices has to deal with the phenomenon of the learning curve. The effect and duration of the learning curve is different for each device and physician, and is difficult to predict. It is important to take the possible learning curve into account when designing a trial using a new medical device, as it may have affected the results. Manufacturers should be aware of the importance of providing good training programs to minimize the learning curve and obtain the best possible clinical outcomes. Also, the creation of specific regulatory protocols on the learning curve effect in medical device trials as well as how to incorporate its impact on clinical evaluation could help appropriately evaluate and compare new devices.

STUDY LIMITATIONS

Although prespecified, the results of this analysis should be interpreted in the context of a study that was prematurely discontinued and should only be seen as hypothesis generating, as the study did not meet the primary endpoint.

Five of the PROTECT II investigators had prior experience with the Impella 2.5 during the PROTECT I safety and feasibility study. Other investigators may have had experience with the Impella 2.5 prior to the trial due to the 510(k) clearance of the Impella 2.5 (June 2008). This number is likely small since PROTECT II started well before the 510(k)

clearance and because Impella 2.5 sales ramp-up outside the trial occurred over several years.

As also seen in other trials evaluating PCI in severely compromised patients, analysis of the Kaplan-Meier event curves suggests that evaluating the end-point at 30 days is not sufficient and a minimum of 90 days follow-up as an efficacy endpoint should be taken.[6,14,16]

CONCLUSIONS

Significantly lower 90-day rates of MAE were observed with use of the Impella 2.5 compared to the IABP after exclusion of the first patient at each site. This prespecified analysis is suggestive of a learning curve associated with use of the Impella 2.5 during its initial introductory period affecting the outcome of the study. This finding likely applies to other new medical devices. Clinical trials should therefore specifically address the training aspect of new devices.

DISCLOSURES

All authors have either received research grants, speaker honoraria or consultancy fees from Abiomed, with the exception of D.M. Ouweneel and Dr. W.W. O'Neill.

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SUPPLEMENTARY DATA

Protocol/Study Specific Adverse Event Definitions

Acute renal dysfunction	Abnormal kidney function requiring dialysis (including hemofiltration) in patients who did not require this procedure prior to implant, or a rise in serum creatinine of greater than 2 times baseline or greater than 2.5 mg/dL.
Aortic insufficiency	Aortic regurgitation graded by transthoracic echocardiographic measurement as ≥ 2 or an increase in aortic regurgitation by more than one (i.e, 2 grades and higher) assessment level on a 4-point scale as determined by echocardiographic measurement.
Cardiac arrhythmias	Sustained ventricular tachycardia or ventricular fibrillation requiring cardioversion (including ICD discharge) and/or IV amiodarone:
Cardiopulmonary resuscitation (CPR)	Cardiopulmonary resuscitation (CPR) involves a combination of mouth-to-mouth rescue breathing or assisted ventilation and chest compression.
Cardiac or vascular operation	Need for: a) cardiac operation or thoracic or, b) abdominal vascular operation, or c) vascular operation for limb ischemia (limb ischemia =new incidences of hypoperfusion of the leg requiring treatment and marked by such symptoms as decreased skin temperature of the limb or decreased peripheral pulses).
Death – all cause mortality	All deaths occurring at any time during the course of the study. <u>Cardiac Death:</u> Defined as death due to any of the following: – Acute myocardial infarction – Heart failure/CHF/cardiogenic shock or pulmonary edema. All deaths from hypotension (systolic BP <90mmHg) and/or respiratory failure without other clear etiology will be considered as heart failure – Cardiac perforation/Pericardial tamponade – Arrhythmia or conduction abnormality – Cerebrovascular accident within 30 days of procedure or suspected of being related to the procedure – Death due to a complication of the procedure, including bleeding, vascular repair, transfusion reaction or bypass surgery. – Any death in which a cardiac cause cannot be excluded <u>Non-cardiac Death:</u> Defined as any death not attributable to a cardiac cause

Myocardial infarction (MI)

The American College of Cardiology definition will be used for the diagnosis of MI. The diagnosis of MI will be made on the basis of clinical information available from hospitalization (laboratory data, ECG) and will require an appropriate clinical history consistent with acute MI.

A. Criteria for acute, evolving or recent MI

Either one of the following criteria satisfies the diagnosis for an acute, evolving or recent MI:

1. Typical rise and gradual fall (troponin) or more rapid rise and fall (CK-MB) of biochemical markers of myocardial necrosis with at least one of the following:

a. ischemic symptoms;
b. development of pathologic Q waves on the ECG;
c. ECG changes indicative of ischemia (ST segment changes)
d. coronary artery intervention (e.g., coronary angioplasty).

2. Pathologic findings of an acute MI.

B. Criteria for established MI

Any one of the following criteria satisfies the diagnosis for established MI:

1. Development of new pathologic Q waves on serial ECGs. The patient may or may not remember previous symptoms. Biochemical markers of myocardial necrosis may have normalized, depending on the length of time that has passed since the infarct developed.
2. Pathologic findings of a healed or healing MI.

Cardiac Enzymes will be considered abnormal if:

1. The enzyme profile must exhibit a typical rise and fall and result from an ischemic event.
2. For CK-MB or CK, the elevation must be > 2 times the upper limit of normal upper limit for the local laboratory. CK-MB result takes precedence over total CK result.
3. For cTn, the elevation must be > 2 ULN using local laboratory criteria established as diagnostic of MI. cTn takes precedence over CK-MB (i.e. when CK-MB is abnormal but cTn is normal, the enzyme profile will be considered normal)
4. When CK-MB is collected after a coronary revascularization procedure, the threshold for abnormality is increased to > 3 ULN for PCI procedures and >10ULN for CABG procedures. cTn post-procedure will not be used to diagnose post-procedure MI because of the lack of reliable long-term data at the current time, except in the situation where there are no available CK-MB data, in which case cTn will be used to establish a diagnosis. In this case cTn> 3ULN will be used to establish the diagnosis.
5. Isolated cardiac enzyme rise alone does not qualify as an MI event.

Neurological dysfunction	Any new, temporary or permanent, focal or global neurological deficit ascertained by a standard neurological examination (administered by a neurologist or other qualified physician and documented with appropriate diagnostic tests and consultation note). The examining physician will distinguish between a transient ischemic attack (TIA), which is fully reversible within 24 hours (and without evidence of infarction), and a stroke, which lasts longer than 24 hours (or less than 24 hours if there is evidence of infarction). The NIH Stroke Scale must be re-administered at 30 days following the event to document the presence and severity of neurological deficits. Each neurological event must be subcategorized as: 1. Transient Ischemic Attack (acute event that resolves completely within 24 hours with no evidence of infarction) 2. Ischemic or Hemorrhagic Cardiovascular Accident/CVA (event that persists beyond 24 hours or less than 24 hours associated with infarction on an imaging study.
Repeat revascularization	Any repeat revascularization that involves: i) the target lesion (the originally treated segment; for stented lesions this includes an area 5mm proximal or distal to the stented segment), or ii) target vessel (all coronary segments in the same epicardial artery as the treated lesion if that segment may have been involved during passage of the coronary guidewire or any treatment device), or iii) non-target vessels. This intervention could be either percutaneous or surgical bypass.
Severe hypotension	Severe hypotension is defined as systolic blood pressure or augmented diastolic pressure (the higher of the two) <90 mmHg for ≥ 5 min requiring inotropic/pressor medications or IV fluid while on device support. Also considered as severe hypotension, are severe and life-threatening hypotensive events (i.e, sudden hydrodynamic collapse) with systolic blood pressure or augmented diastolic pressure (the higher of the two) <90 mmHg that requires immediate and aggressive treatment such as IV inotropic/pressor medications, resuscitative manoeuvres, etc. to restore hemodynamics when patient is on device support (regardless of the duration of the hypotension). Only those severe hypotensive episodes which occur while the patient is on device support will be considered MAE and will be part of the primary and secondary endpoint analysis

Adverse events in the first Impella 2.5 patients

The subgroup of first Impella 2.5 patients experienced numerically, but not statistically significant, higher rates of death, CPR/ventricular arrhythmia, myocardial infarction, severe hypotension, and angiographic failure compared to the remaining Impella 2.5 patients (Table 3). The first Impella 2.5 patients showed a strong trend toward an increased incidence of severe hypotension during the procedure compared to the remaining Impella 2.5 patients: 17.2% versus 8.4%, p=0.060 at 30 days in the Intent-to-treat population.

Seven deaths occurred through 30 days in the subgroup of first Impella 2.5 patients. One death occurred after two failed Impella 2.5 insertion attempts in a patient with severe PVD, and was adjudicated as 'probably' device related by the independent Clinical Events Committee (CEC). The other 6 deaths were adjudicated as having 'no' or 'remote'

relatedness to use of the Impella 2.5. Two of these 6 deaths were due to complications during PCI: a perforation of a coronary artery by the wire during the PCI, and a right ventricular tear presumably caused by the pacing wire during the PCI. The other 4 deaths included one case of MI due to stent thrombosis at day 4, 2 cases of ventricular arrhythmia post-discharge at day 12 and day 29, and one case of acute respiratory failure post-discharge at day 19. Each death was accompanied by additional MAEs, including a 1-for-1 correspondence with CPR/ventricular arrhythmia requiring cardioversion (the terminal event for the deaths).

Twelve incidences of myocardial infarction occurred through 30 days in the subgroup of first Impella 2.5 patients. Nine incidences involved periprocedural non-Q wave MIs, and rotational atherectomy was used in four of those cases. One of the nine patients suffered a periprocedural complication (perforation by wire during PCI) and died day 0. The other eight patients were successfully discharged from the hospital without further complications. Three spontaneous MIs occurred, all due to restenosis of a target vessel or stent thrombosis. Two of those patients underwent successful repeat revascularization, while the third patient died on day 4 due to acute stent thrombosis.

Ten patients in the subgroup of first Impella 2.5 patients experienced severe hypotension during device support that required treatment (inotropic or vasopressor medications or IV fluid). For 5 of the 10 patients, severe hypotension was the only MAE they experienced during the trial, representing 19.2% of the total MAE observed in the first Impella 2.5 patient group (5/26 MAE's). All cases were resolved with fluids and/or inotropes except one, in which the patient suffered a coronary perforation with a coronary wire during PCI and expired.

Nine incidences of CPR or ventricular arrhythmia requiring cardioversion occurred through 30 days in the subgroup of first Impella 2.5 patients. As discussed previously, 7 of the 9 events were directly associated with the 7 deaths in this subgroup as the terminal event prior to death. One additional event consisted of two episodes of ventricular tachycardia the day after PCI when the amiodarone was changed from intravenous to oral dosing. The second additional event was an episode of ventricular fibrillation during the PCI that was addressed by the patient's implanted defibrillator. This patient was discharged on day 2 with no further complications.

Three cases of angiographic failure occurred through 30 days in the subgroup of first Impella 2.5 patients. One patient had angioplasty with a residual stenosis of 40%. Attempts to cross the lesion with the stent were unsuccessful due to anatomical difficulties. The second patient had a target lesion with 90% stenosis that was stented and the stenosis reduced to 40%. The third patient experienced severe hypotension and the investigator chose not to treat the lesion.

Supplementary Table 1 Patient baseline characteristics.
First patients at each site compared to remaining patients, intent-to-treat population.

	IABP			Impella 2.5		
	First patients (n=62)	Remaining patients (n=161)	*p*	First patients (n=58)	Remaining patients (n=167)	*p*
Age, y	68 ± 11	67 ± 11	0.351	68 ± 10	68 ± 11	0.98
Sex, male, %	83.9	80.1	0.521	77.6	80.2	0.666
Weight, kg	83.5 ± 22.6	83.6 ± 20.7	0.963	82.9 ± 17.3	83.1 ± 19.3	0.931
History of CHF, %	83.9	83.2	0.908	91.4	91	0.934
Current NYHA (class III/IV), %	74.5	60.4	0.09	78.3	63.6	0.068
Cardiomyopathy, %	71	68.3	0.702	81	65.3	0.025
Diabetes mellitus, %	46.8	52.2	0.47	51.7	52.1	0.961
Renal insufficiency, %	32.3	29.4	0.675	25.9	22.2	0.564
Valve disease, %	62.9	66.3	0.638	56.9	65.3	0.255
Peripheral vascular disease, %	29	25.5	0.589	24.1	26.2	0.755
Pacemaker/AICD, %	41	27.3	0.05	39.7	32.9	0.354
Previous CABG, %	33.9	26.7	0.289	39.7	37.7	0.794
LVEF, %	24.2 ± 7.1	24.1 ± 6.1	0.997	24.2 ± 5.5	23.2 ± 6.6	0.321
STS mortality score	6.8 ± 9.3	5.7 ± 5.8	0.367	6.0 ± 5.8	5.8 ± 6.1	0.812
SYNTAX score	31.1 ± 13.6	28.7 ± 13.5	0.334	31.7 ± 13.9	29.8 ± 12.9	0.465
Not surgical candidate, %	74.2	60.9	0.062	72.4	60.5	0.104

AICD: automated implantable cardioverter-defibrillator; CABG: coronary artery bypass graft; CHF: congestive heart failure; IABP: intra-aortic balloon pump; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association; PCI: percutaneous coronary intervention; STS: Society of Thoracic Surgery; SYNTAX: Synergy Between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery trial.

Supplementary Table 2 Procedural characteristics.
First patients at each site compared to remaining patients, intent-to-treat population.

	IABP			Impella 2.5		
	First patients (n=62)	Remaining patients (n=161)	*p*	First patients (n=58)	Remaining patients (n=167)	*p*
No. of lesions attempted	2.9 ± 1.4	2.9 ± 1.5	0.8	2.9 ± 1.7	2.8 ± 1.3	0.759
No. of stents placed	2.8 ± 1.6	3.0 ± 2.0	0.511	3.1 ± 1.9	3.1 ± 1.80	0.928
Total length of all lesion treated, mm	31.0 ± 18.9	37.0 ± 28.8	0.074	33.2 ± 26.6	37.0 ± 26.9	0.35
Use of heparin, %	75.8	86.3	0.061	100	91	0.018
Glycoprotein IIb/IIIa inhibitors, %	27.4	25.5	0.766	17.2	12.6	0.374
Rotational atherectomy, %	9.7	8.7	0.818	13.8	14.4	0.914
Median no. of passes/lesion (IQR)	2 (1-5)	1 (1-2)	0.427	3 (2-3)	4 (2-5)	0.076
Median no. of passes/patient (IQR)	2.0 (1.0–5.0)	2.0 (2.0-3.0)	0.458	6.5 (3.0-10.0)	5.0 (3.5-9.0)	1.000
Median RA time/lesion (IQR), s	20 (15-70)	40 (25-47)	0.612	60 (48-97)	64 (40-134)	0.647
Saphenous vein graft treatment, %	9.7	8.7	0.818	19	9.6	0.06
Total support time, h	9.6 ± 29.2	8.0 ± 18.2	0.679	1.8 ± 1.5	1.9 ± 3.0	0.588
Duration of index procedure, h	1.1 ± 0.6	1.0 ± 0.7	0.547	1.2 ± 0.7	1.0 ± 0.7	0.049
Discharge from cath lab on device, %	35	37	0.749	5.4	6.1	0.839
MAP before procedure, mmHg	88.4 ± 17.2	89.7 ± 16.3	0.617	86.2 ± 14.7	89.0 ± 14.5	0.219
PAP (sys) before procedure, mmHg	46.0 ± 23.2	42.3 ± 15.4	0.293	41.8 ± 19.7	43.1 ± 14.9	0.678
PCWP before procedure, mmHg	17.1 ± 8.0	17.4 ± 8.7	0.818	17.9 ± 9.2	19.7 ± 9.5	0.279
Cardiac index before procedure, mmHg	2.5 ± 1.1	3.4 ± 0.8	0.555	2.3 ± 0.7	2.2 ± 0.6	0.265
Contrast administered during the procedure, mL	237 ± 95	243 ± 121	0.711	266 ± 155	267 ± 137	0.98
IV fluid administered during the procedure, mL	417 ± 345	417 ± 392	1.000	572 ± 561	549 ± 649	0.825
Transfusion required during the procedure or at pump removal, %	1.6	1.9	0.9	8.6	1.8	0.016
Post-procedural NYHA Class III/IV, %	54.5	47.4	0.494	62.5	40.2	0.028
More lesions treated than planned pre-procedurally, %	21	27.5	0.318	17.5	31.1	0.048
Patients with complications during the procedure, %	3.2	6.9	0.299	8.9	10.2	0.786
SYNTAX score post-PCI	16.6 ± 13.3	13.9 ± 12.4	0.235	14.5 ± 13.3	15.0 ± 12.8	0.842
Difference SYNTAX score pre-post PCI	-14.5 ± 9.1	-14.9 ± 9.4	0.806	-17.1 ± 9.9	-14.8 ± 9.5	0.226

Data are expressed as mean ± standard deviation except when mentioned otherwise. When median and interquartile range (IQR) are reported, the Wilcoxon rank-sum test p-values are used. IABP: intra-aortic balloon pump; IV: intravenous; MAP: mean arterial pressure; NYHA: New York Heart Association; PAP: pulmonary artery pressure; PCI: percutaneous coronary intervention; PCWP: pulmonary capillary wedge pressure; SYNTAX: Synergy Between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery trial.

Supplementary Table 3 Major adverse events (hierarchical).
First Impella 2.5 patients at each site compared to remaining Impella 2.5 patients, intent-to-treat population.

	30 Days			90 Days		
	First Impella 2.5 patients (n=58)	Remaining patients (n=167)	*p*	First Impella 2.5 patients (n=58)	Remaining patients (n=166)	*p*
Composite of major adverse events, % (n)	44.8 (26)	31.7 (53)	0.072	48.3 (28)	38.0 (63)	0.168
Death, % (n)	12.1 (7)	6.0 (10)	0.131	15.5 (9)	10.8 (18)	0.347
Stroke/TIA, % (n)	0.0 (0)	0.0 (0)	-	1.7 (1)	0.6 (1)	0.434
Myocardial infarction, % (n)	15.5 (9)	13.2 (22)	0.656	10.3 (6)	12.7 (21)	0.642
Repeat revascularization, % (n)	0.0 (0)	1.8 (3)	0.304	1.7 (1)	4.2 (7)	0.379
Need for cardiac or vascular operation,* % (n)	1.7 (1)	0.6 (1)	0.431	1.7 (1)	1.2 (2)	0.767
Acute renal dysfunction, % (n)	1.7 (1)	4.8 (8)	0.305	3.4 (2)	4.2 (7)	0.797
Cardiopulmonary resuscitation or ventricular arrhythmia requiring cardioversion, % (n)	1.7 (1)	2.4 (4)	0.765	1.7 (1)	2.4 (4)	0.761
Aortic valve damage/increase in aortic insufficiency, % (n)	0.0 (0)	0.0 (0)	-	0.0 (0)	0.0 (0)	-
Severe hypotension requiring treatment, % (n)	10.3 (6)	3.0 (5)	0.025	10.3 (6)	1.8 (3)	0.004
Angiographic failure, % (n)	1.7 (1)	0.0 (0)	0.089	1.7 (1)	0.0 (0)	0.09

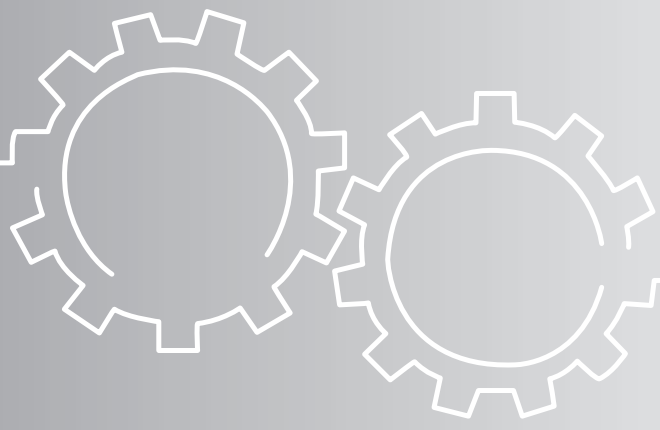
*TIA: transient ischemic attack. * Cardiac, thoracic, or abdominal operation, or vascular operation for limb ischemia.*

Supplementary Table 4 Major adverse events (hierarchical).
First IABP patients at each site compared to remaining IABP patients, intent-to-treat population.

	30 Days			90 Days		
	First IABP patients (n=62)	Remaining patients (n=160)	*p*	First IABP patients (n=61)	Remaining patients (n=158)	*p*
Composite of major adverse events, % (n)	40.3 (25)	40.0 (64)	0.965	47.5 (29)	50.0 (79)	0.744
Death, % (n)	6.5 (4)	5.6 (9)	0.814	9.8 (6)	8.2 (13)	0.705
Stroke/TIA, % (n)	1.6 (1)	1.9 (3)	0.895	3.3 (2)	2.5 (4)	0.761
Myocardial infarction, % (n)	11.3 (7)	10.0 (16)	0.777	16.4 (10)	13.3 (21)	0.555
Repeat revascularization, % (n)	6.5 (4)	3.1 (5)	0.26	4.9 (3)	8.9 (14)	0.328
Need for cardiac or vascular operation,* % (n)	1.6 (1)	1.3 (2)	0.834	3.3 (2)	1.3 (2)	0.319
Acute renal dysfunction, % (n)	3.2 (2)	5.0 (8)	0.567	3.3 (2)	5.1 (8)	0.571
Cardiopulmonary resuscitation or ventricular arrhythmia requiring cardioversion, % (n)	6.5 (4)	1.9 (3)	0.08	6.6 (4)	3.2 (5)	0.257
Aortic valve damage/increase in aortic insufficiency, % (n)	0.0 (0)	0.0 (0)	-	0.0 (0)	0.0 (0)	-
Severe hypotension requiring treatment, % (n)	3.2 (2)	10.6 (17)	0.077	0.0 (0)	7.6 (12)	0.027
Angiographic failure, % (n)	0.0 (0)	0.6 (1)	0.533	0.0 (0)	0.0 (0)	-

*IABP: intra-aortic balloon pump; TIA: transient ischemic attack. * Cardiac, thoracic, or abdominal operation, or vascular operation for limb ischemia.*

CHAPTER 4



ASSESSMENT OF CARDIAC DEVICE POSITION ON SUPINE CHEST RADIOGRAPH IN THE ICU: INTRODUCTION AND APPLICABILITY OF THE AORTIC VALVE LOCATION RATIO

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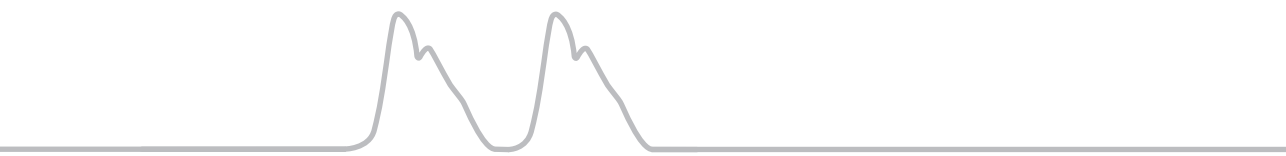

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ABSTRACT

Objectives

The use of intracardiac assist devices is expanding, and correct position of these devices is required for optimal functioning. The aortic valve is an important landmark for positioning of those devices. It would be of great value if the device position could be easily monitored on plain supine chest radiograph in the ICU. We introduce a ratio-based tool for determination of the aortic valve location on plain supine chest radiograph images, which can be used to evaluate intracardiac device position.

Design

Retrospective observational study.

Setting

Large academic medical center.

Patients

Patients admitted to the ICU and supported by an intracardiac assist device.

Interventions

We developed a ratio to determine the aortic valve location on supine chest radiograph images. This ratio is used to assess the position of a cardiac assist device and is compared with echocardiographic findings.

Measurements and main results

Supine anterior-posterior chest radiographs of patients with an aortic valve prosthesis (n = 473) were analyzed to determine the location of the aortic valve. We calculated several ratios with the potential to determine the position of the aortic valve. The aortic valve location ratio, defined as the distance between the carina and the aortic valve, divided by the thoracic width, was found to be the best performing ratio. The aortic valve location ratio determines the location of the aortic valve caudal to the carina, at a distance of 0.25 ± 0.05 times the thoracic width for male patients and 0.28 ± 0.05 times the thoracic width for female patients. The aortic valve location ratio was validated using CT images of patients with angina pectoris without known valvular disease (n = 95). There was a good correlation between cardiac device position (Impella) assessed with the aortic valve location ratio and with echocardiography (n = 53).

Conclusions

The aortic valve location ratio enables accurate and reproducible localization of the aortic valve on supine chest radiograph. This tool is easily applicable and can be used for assessment of cardiac device position in patients on the ICU.

A growing number of patients are being treated with intracardiac assist devices and admitted to the ICU. Correct position of these devices is required for optimal function. Transthoracic echocardiographic (TTE) imaging is frequently used for assessment of device position but may be challenging as patients are frequently intubated and in the supine position. Often, these patients have poor acoustic windows that limit the diagnostic value of TTE, hampering appropriate echocardiographic assessment and decision making. Supine chest radiograph is done on a regular basis in patients admitted to the ICU. It would be of great value if intrathoracic device position could accurately be determined on plain supine chest radiograph. Specific cardiac structures, such as the native aortic valve, are difficult to localize on a supine chest radiograph image. We introduce a validated, easy, and reliable method to determine the aortic valve location (AVL) on standard supine chest radiograph by using anatomical landmarks to calculate ratios to determine the position of the aortic valve. Furthermore, we evaluated the accuracy of this method in patients admitted to the ICU for circulatory support (Impella, Abiomed, Danvers, MA) [1].

MATERIALS AND METHODS

The local institutional review board approved the study protocol. Several steps were taken to identify and evaluate the location of the aortic valve on supine chest radiograph, using both supine radiograph and CT images (Figure 1). First, potential anatomical landmarks were determined, that is, carina, thoracic width, lung apex, and diaphragm position. We measured distances between these landmarks and calculated ratios between these distances, which identify the position of the aortic valve (Figure 1). Several ratios with a possible relation to the AVL on chest radiograph were calculated and subsequently analyzed and are available in the Supplementary data. For the sake of conciseness, this article evaluates the novel AVL ratio, which was found to be the best performing ratio. The AVL ratio was determined by measuring the distance between the carina and the aortic valve divided by the thoracic width, measured at the inside of the thoracic wall, on the level of the medial section of the diaphragm at the level of the spine (Figure 1; and Supplementary Figure 1).

$$\text{Aortic Valve Location Ratio} = \frac{\text{Carina - aortic valve}}{\text{thoracic width}}$$

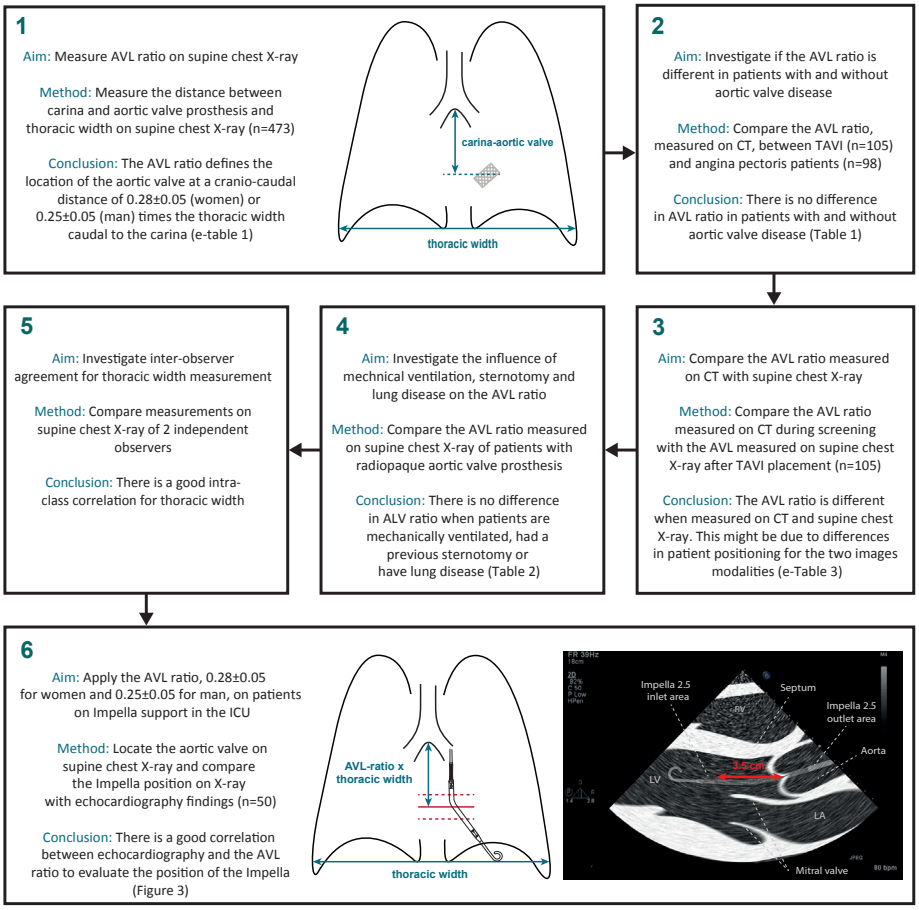

Figure 1 Flowchart of the steps taken to calculate, evaluate, and apply the aortic valve location (AVL) ratio. Chest x-ray = chest radiograph; TAVI = transcatheter aortic valve implantation.

Because the native aortic valve is not visible on chest radiograph, supine chest radiographs of patients with an implanted radiopaque aortic valve prosthesis were analyzed (n = 473) (step 1). Then, the AVL ratio was validated using CT images of patients with angina pectoris without aortic valve disease (n = 98) and patients referred for transaortic valve implantation (n = 105) (steps 2 and 3; Figure 1). The influence of covariables on the AVL ratio was evaluated (step 4), and the interobserver variability was determined (step 5). Last, the AVL ratio was used to evaluate the position of an intracardiac assist device (Impella) in ICU patients. The position of the Impella on supine chest radiograph was compared with the corresponding TTE findings (n = 53) (step 6; Figure 1).

Determination of the AVL Ratio

Chest radiographs of patients who had received an aortic valve prosthesis either by surgical or transcatheter approach were analyzed (Figure 2). Supine chest radiographs of patients after surgical aortic valve replacement (SAVR) were obtained from 294 patients who were operated on between January 2013 and August 2014. Patients were excluded if the aortic valve prosthesis was not visible on radiograph (n = 54), if it was not possible to evaluate the radiograph because of poor quality (n = 4), or if the aortic valve prosthesis was not situated in the appropriate position because of anatomic abnormalities (n = 1). Supine chest radiographs of patients after transcatheter aortic valve implantation (TAVI) were obtained from patients who had received an Edwards Sapien prosthesis (Edwards Lifesciences, Irvine, CA) between October 2007 and December 2014 (n = 477). Patients were excluded if a supine chest radiograph was not available (n = 232) or if the chest radiograph did not allow proper assessment of the AVL (n = 5) or if the patient had previously undergone pneumonectomy (n = 2).

Combining SAVR (n = 235) and TAVI (n = 238) patients resulted in 473 patients; the supine chest radiograph images of those were analyzed, and the AVL ratio was calculated. A total of 401 radiograph images were taken on the same day as the surgical (or TAVI) procedure, 27 were taken on day 1, and 22 on day 2 after the procedure, meaning that 95% of all radiographs were taken within 2 days of the procedure. The remaining 5% were taken within 3 weeks after the procedure.

Validation

In order to validate the AVL ratio, CT scans of consecutive patients without known valvular disease (n = 98), referred for coronary artery calcium scoring, were compared with CT scans carried out during TAVI workup. In addition, CT scans carried out during TAVI workup were analyzed and compared with chest radiograph measurements of the same patient (n = 105). The influence of a sternotomy, intubation, and lung disease (defined as FEV1/FVC ratio [FEV1%] < 75%) on the AVL ratio was assessed using chest radiographs. To evaluate interobserver variability, two observers independently measured the AVL ratio on supine chest radiograph of 122 TAVI patients.

Monitoring Intracardiac Assist Device Position

Supine chest radiographs were subsequently used to assess intracardiac device position (Impella) in ICU patients treated between January 2013 and November 2015 in our institution. The Impella (Abiomed) is a catheter-based axial blood pump, inserted into the left ventricle via the femoral artery. Echocardiography is currently the standard technique used to assess the position of the Impella. TTE evaluation of the position was carried out using the parasternal long-axis three-chamber view, showing both the aortic valve and the inlet area (Figure 3). For optimal positioning of the Impella, the inlet area

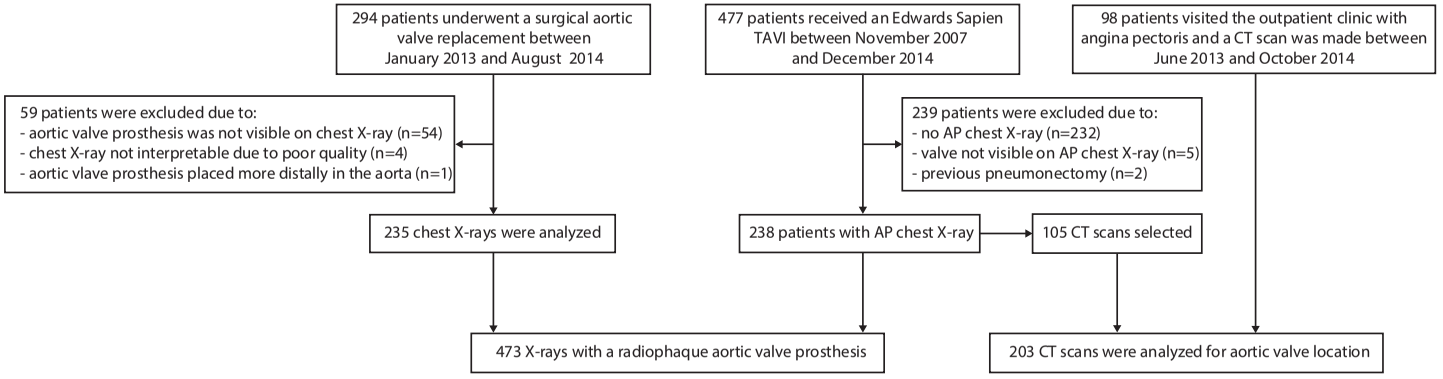

Figure 2 Flowchart of patient selection.
AP = anterior-posterior, chest x-ray = chest radiograph, TAVI = transcatheter aortic valve implantation.

should be about 3.5 cm below the aortic valve annulus and well away from papillary muscle and subannular structures. The outlet area should be well above the aortic valve. The distance between the aortic valve annulus and the inlet area was measured by a cardiologist experienced in echocardiographic assessment of Impella position. A five-point scale was developed to evaluate the position of the Impella on chest radiograph (Figure 3). The position of the Impella on supine chest radiograph was then graded by an interventional cardiologist and a cardiovascular radiologist. If no agreement could be reached, a third cardiologist assessed the grading. Concordance of Impella position on chest radiograph and echocardiographic imaging was evaluated if the radiograph and echocardiographic imaging were performed within a 3-hour time frame.

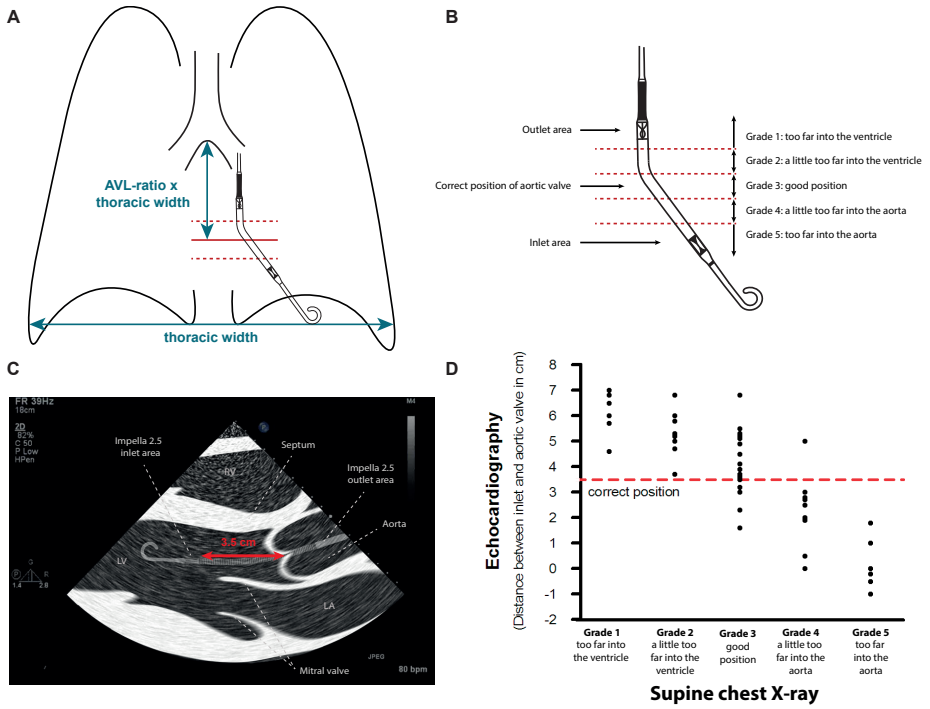

Figure 3 Comparison of the Impella position between supine chest radiograph (chest x-ray) and echocardiography.
A) Schematic image of the method to estimate the aortic valve location (AVL-ratio times the thoracic width). B) Aortic valve position score on supine chest radiograph. If the Impella is correctly positioned, the aortic valve is just proximal to the curvature. C) Schematic image of a transthoracic echocardiogram of the Impella catheter in the correct position (parasternal long-axis view). The Impella is at the correct position when the inlet area is 3.5 cm below the aortic valve annulus, away from the papillary muscle. D) Comparison of Impella position as determined by echocardiography compared with supine chest radiograph.

Data Analysis

The ratios are shown as mean ± sd. Differences between groups were evaluated using the independent samples t test and Levene test. A paired sample t test was used to compare CT and radiograph measurements in the same patients. Interobserver variability was assessed using the intraclass correlation coefficient and by using a Blant-Altman plot.

RESULTS

Location of the Aortic Valve on Supine Chest radiograph

Several ratios with a possible relation to the AVL on chest radiograph were analyzed and are available in the Supplementary data. The AVL ratio, measured on the supine chest radiographs of 473 patients with a radiopaque aortic valve prosthesis, was found to be the best performing ratio. Several confounders of the AVL ratio were assessed in univariate and multivariate models. The model correcting for gender performed the best in estimating the distance between carina and the aortic valve (Supplementary data). The AVL ratio was 0.25 ± 0.05 in male and 0.28 ± 0.05 in female patients, respectively (Figure 1; and Supplementary Table 1). The distance between the carina and the aortic valve was 8.0 ± 1.3 cm for men and 7.8 ± 1.2 for women, respectively. The thoracic width was 31.8 ± 2.3 cm for men and 27.8 ± 1.7 for women, respectively (not corrected for magnification of the chest radiograph). The mean magnification of the chest radiograph, which was variable because of the use of a mobile radiograph device, was calculated using the documented size of the aortic valve prosthesis for calibration. The mean magnification was 1.1 ± 0.1. The AVL ratio was normally distributed (Kolmogorov-Smirnov, $p = 0.100$).

Validation

When measured on CT, the AVL ratio did not differ significantly between patients with and without aortic valve disease (Table 1). The AVL ratio measured on CT was compared with the measurement on a chest radiograph of the same patient ($n = 105$). The distances measured on the supine chest radiograph were corrected for magnification using the size of the aortic valve prosthesis. When assessed on CT scan, the AVL ratio was different than when measured on supine chest radiograph (Supplementary Table 3). The AVL ratio, measured on supine chest radiograph, was similar in patients with and without mechanical ventilation, sternotomy, and lung disease (Table 2). The intraclass correlation coefficient for the thoracic width is 0.979 with a mean difference of 0.1 cm and an sd of 0.6 cm (Supplementary Figure 2).

Table 1 CT measurements comparing transcatheter aortic valve implantation patients with and without aortic valve disease.

	TAVI						Angina Pectoris						
	all		men		women		all		men		women		
	n	mean	n	mean	n	mean	n	mean	n	mean	n	mean	*p* *
Distances measured on CT (cm)													
A: Carina - aortic valve	105	5.4 ± 1.4	46	5.3 ± 1.6	59	5.4 ± 1.3	97	5.3 ± 1.1	46	5.4 ± 1.1	51	5.2 ± 1.1	0.451
B: Thoracic width	95	28.4 ± 2.3	36	30.3 ± 1.8	59	27.3 ± 1.7	94	29.0 ± 3.3	44	31.3 ± 2.8	50	27.0 ± 2.2	0.126
Calculated ratios													
A/B (AVL ratio)	95	0.19 ± 0.05	36	0.17 ± 0.04	59	0.20 ± 0.05	94	0.18 ± 0.04	44	0.17 ± 0.03	50	0.19 ± 0.04	0.413

** measurements are not corrected for magnification; SD=standard deviation;*

Table 2 The influence of intubation, sternotomy, and lung disease on the Aortic Valve Location Ratio.

		AVL ratio		
		n	mean	*p*
Intubation				0.335
	yes	318	0.26 ± 0.05	
	no	132	0.27 ± 0.05	
Sternotomy				0.604
	yes	388	0.27 ± 0.05	
	no	61	0.26 ± 0.05	
Lung disease				0.146
	yes	112	0.27 ± 0.04	
	no	291	0.27 ± 0.04	

Monitoring Intracardiac Assist Device Position

The position of the Impella, determined by the AVL ratio on supine chest radiograph, was compared with the position of the Impella on corresponding echocardiography images (Figure 3). Echocardiographic assessment of Impella position was done in 42 patients in the ICU, resulting in a total of 73 echocardiographic measurements with corresponding supine chest radiograph measurements. Cases were excluded because of 1) non-diagnostic echocardiography image quality with consequently unmeasurable Impella depth (n = 4), 2) more than 3 hours between performing the TTE and the radiograph (n = 17), or 3) repositioning of the Impella between the TTE and the radiograph (n = 2). This resulted in a total of 50 modality comparisons in 28 patients. Figure 3 shows a good correlation between the echocardiographic measurements and the grading of Impella position on supine chest radiograph measurements. Some examples of supine chest radiograph and corresponding echocardiography images are shown in Supplementary Figure 3.

DISCUSSION

This study shows that the location of the native aortic valve can be accurately estimated on supine chest radiograph. With this knowledge, we introduced a novel tool, the AVL ratio, which can be used for evaluation of intracardiac assist device position in patients in the ICU. The use of a supine chest radiograph to evaluate the position of an intracardiac assist device is very useful as supine radiographs are easily and frequently carried out on an ICU, whereas the quality of echocardiography is often impaired. If malposition of a device is suspected on supine chest radiograph, additional echocardiography can be done to further assess and adjust the position of the device. Based on our analyses,

we decided to use the thoracic width and the carina as anatomical markers to locate the aortic valve. The AVL ratio determines the location of the aortic valve using the thoracic width to calculate the distance between the carina and the aortic valve. This ratio seemed to be constant in patients both with and without aortic valve disease, but it is also constant in patients with and without mechanical ventilation and previous sternotomy. The AVL ratio was determined on supine chest radiographs of patients with an aortic valve prosthesis because the native aortic valve is not visible on chest radiograph. This patient population differs from the average population of patients treated with an intracardiac assist device, obviously in having been treated for severe aortic valve disease, but also in age (patients with an aortic valve prosthesis are generally older than patients treated with an intracardiac assist device). To assess generalizability of the AVL ratio derived from the patient population with aortic valve prosthesis, the AVL ratio was validated on CT scans of patients with angina pectoris (comparable with the patient population treated with intracardiac assist devices in mean age [57 ± 10 vs 60 ± 9 yr, respectively]; $p = 0.938$) and the absence of major structural heart disease. The AVL ratio did not differ significantly between the patient populations ($p = 0.413$; Supplementary data). For the sake of generalizability, also the influence of sternotomy (i.e., conventional aortic surgery with sternotomy vs TF-TAVI without sternotomy) and mechanical ventilation on the AVL ratio was assessed (Table 2). In summary, these analyses indicated good generalizability of the AVL ratio derived from the population of patients with an aortic valve prosthesis to the patient population treated with a cardiac assist device and no difference in AVL ratio in patients with and without aortic valve disease, with or without sternotomy, and finally with or without mechanical ventilation. The value of the AVL ratio is different when measured on radiograph or CT images. This discrepancy might be caused by differences in patient positioning during examination. Although patients are in the supine position during both CT and chest radiograph, the position of their arms is different, as the CT is done with the arms elevated above the head of the patient, whereas the arms are alongside the body during the radiograph on the ICU. As the CT was carried out before the procedure and the radiograph was taken after the procedure, the location of the aortic valve is measured using the native valve on the CT images while using the location of the prosthesis on the radiograph, which might be a slightly different location. During CT, patients are requested to take a deep breath, whereas chest radiograph is not always synchronized with respiration as the patients might still be unconscious or intubated. Although the AVL ratio locates the aortic valve horizontally, it should be kept in mind that the aortic valve has an oblique orientation, which means that the distance between the most cranial and caudal location of the aortic valve may be a few centimeters. Using the AVL ratio to locate the aortic valve on a coronal view does not yield an exact location but a narrow range of its location. We evaluated Impella position using supine chest radiograph and compared the findings with echo-

cardiographic images. Maintaining the correct position of the Impella is a key factor in managing these patients. Patients are usually supported for several days, and assessing the position of the Impella needs to be as easy as possible. We have shown a good correlation of device position assessed by either supine chest radiograph images, the AVL ratio, or echocardiography. The sensitivity and specificity are 100% and 45%, respectively, with malposition defined as grade 1,2, 4 or 5 on chest radiograph (Figure 3) and as a distance of greater than 7.0 or less than 1.0 cm between aortic valve and Impella inlet on echocardiography. The 100% sensitivity indicates that if the chest radiograph suggests that the device is well positioned, assessment of device position with echocardiography will suggest the same (i.e., no false negatives). However, the lower specificity indicates that chest radiograph may suggest device malposition, whereas in truth, the device is properly positioned. Therefore, the AVL ratio can be used as a screening tool as it gives a good indication of when echocardiography should be performed. Although we found a good correlation, there might be a slight discrepancy between the exact position of the device determined with both methods. For example, as the Impella device is freely positioned in the ventricle, across the aortic valve, it is able to move along with the contractions and/or filling properties of the left ventricle. The Impella device therefore is not in one fixed position. However, as the distance between the inlet and the outlet of the Impella 2.5 catheter is 6.5 cm, and even longer in the Impella CP (7.8 cm) or Impella 5.0 (8.0 cm), the Impella is in correct position within a certain range around the aortic valve. Another cause of discrepant findings between supine chest radiograph and echocardiography is the difficulty in some cases to visualize both the distal part of the Impella and the aortic valve in a single three-chamber long-axis view, which could result in accidently measuring the Impella pigtail (which is around 3.5 cm in length) instead of measuring the Impella cannula. A limitation of our study that should be addressed is a possible change in Impella device position in the time between the echocardiography and chest radiograph. We therefore limited the time period between imaging modalities to 3 hours. Nevertheless, the position of the Impella could have been altered by the movement of the patient, altered filling properties of the left ventricle, or altered performance level of the Impella. The advantage of echocardiography imaging for evaluation of the position of intracardiac assist devices is the possibility to assess the relative position of the anatomical structures adjacent to the device (i.e., the mitral valve apparatus), instead of only the aortic valve. Also, cardiac function can be evaluated, and as stated above, the position can be adjusted under direct echocardiographic guidance. However, echocardiographic imaging is not always readily available, is time consuming, is operator-dependent, and necessitates the availability of a dedicated echocardiographer. Therefore, we propose a strategy of screening of the position of the intracardiac assist devices with an easily available supine chest radiograph and in the case of a presumed dislocation, further echocardiographic imaging. Previously, a bedside method to moni-

tor the position of an intraaortic balloon pump was proposed by measuring distances between puncture site in the right femoral artery to the sternal angle via the umbilicus, illustrating the need for a bedside measure to monitor device positioning.[2] Chest radiograph is easily available and frequently used for screening and diagnosis of many diseases. In cardiology, chest radiograph is commonly used to calculate the cardiothoracic ratio (CTR), which is the ratio between the transverse diameter of the heart and the transverse diameter of the thorax measured on posterior-anterior chest radiograph. This ratio was first proposed by Danzer in 1919 to screen military recruits for cardiac enlargement.[3] The relationship between cardiac dimensions on plain chest radiograph and cardiac function or cardiac disease is still the subject of debate, as positive as well as negative correlations have been described.[4,5] Nevertheless, CTR is routinely used for initial assessment of the heart and can subsequently be supplemented by echocardiographic assessment of the cardiac function, illustrating the applicability of a ratio based on an easily available imaging modality. In this study, we used the AVL ratio to evaluate the Impella position, but there are many other devices that could benefit from this method, such as HeartMate PHP (Percuteaneous Heart Pump, Thoratec Corporation, Pleasanton, CA).[6] Because the routine use of the intraaortic balloon pump showed no clinical benefit in patients with cardiogenic shock after myocardial infarction[7], and the guidelines allow other mechanical support devices in these patients[8,9], it is to be expected that new mechanical support devices and other types of intracardiac devices will enter the clinical field. For this reason, easy and bedside evaluation of proper device position will be crucial. Evaluation of the position of intracardiac assist devices is a key factor in the management of these critically ill patients to ensure appropriate operation of these devices. It is important that evaluation of the position is easy and can be frequently performed to optimize the treatment of these patients.

CONCLUSIONS

The AVL ratio is a novel method to locate the aortic valve on supine chest radiographs. This new method is highly applicable in current clinical practice to evaluate the position of intracardiac assist devices in patients in the ICU, enabling appropriate operation of these devices. The AVL ratio determines the position of the aortic valve at a caudal distance from the carina of 0.25 times the thoracic width in male patients and 0.28 times the thoracic width in female patients.

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SUPPLEMENTARY DATA

Supplementary Table 1 Measurements on AP chest X-rays of patients with a radiopaque aortic valve prosthesis.

	all		man		women		
	n	mean ± SD	n	mean ± SD	n	mean ± SD	*p*
Distances measured (cm) *							
A: Carina - aortic valve	455	8.0 ± 1.2	239	8.1 ± 1.3	216	7.8 ± 1.2	0.010
B: Thoracic width	460	29.9 ± 2.8	239	31.8 ± 2.2	221	27.9 ± 1.7	<0.001
C: Aortic valve - diaphragm	445	6.2 ± 1.7	233	6.3 ± 1.6	212	6.2 ± 1.8	0.308
D: Carina - diaphragm	432	14.3 ± 1.8	225	14.5 ± 1.6	207	14.1 ± 1.9	0.023
E: Lung apex - diaphragm	442	24.9 ± 2.5	230	25.5 ± 2.4	212	24.2 ± 2.5	<0.001
Calculated ratios							
A/B (AVL ratio)	448	0.27 ± 0.05	232	0.25 ± 0.04	216	0.28 ± 0.05	<0.001
A/D	432	0.56 ± 0.09	225	0.56 ± 0.08	207	0.56 ± 0.09	0.762
A/E	430	0.32 ± 0.05	223	0.32 ± 0.05	207	0.32 ± 0.05	0.130
C/A	432	0.82 ± 0.30	225	0.82 ± 0.27	207	0.82 ± 0.32	0.968
C/B	438	0.21 ± 0.06	226	0.20 ± 0.05	212	0.22 ± 0.06	<0.001
C/D	432	0.43 ± 0.09	225	0.43 ± 0.08	207	0.43 ± 0.09	0.764
C/E	439	0.25 ± 0.05	229	0.25 ± 0.05	210	0.25 ± 0.06	0.613

** measurements are not corrected for magnification; SD=standard deviation; AP=anterior-posterior*

Supplementary Table 2 CT measurements - comparing TAVI and AP patients.

	TAVI		Angina Pectoris		
	n	mean ± SD	n	mean ± SD	*p*
Distances measured on CT (cm)					
A: Carina - aortic valve	105	5.4 ± 1.4	97	5.3 ± 1.1	0.451
B: Thoracic width	95	28.4 ± 2.3	94	29.0 ± 3.3	0.126
C: Aortic valve - diaphragm	105	7.9 ± 1.5	97	7.2 ± 1.3	<0.001
D: Carina - diaphragm	105	13.2 ± 2.0	97	12.4 ± 1.6	0.004
E: Lung apex - diaphragm	67	23.1 ± 2.4	52	21.7 ± 2.6	0.002
Calculated ratios					
A/B (AVL ratio)	95	0.19 ± 0.05	94	0.18 ± 0.04	0.413
A/D	105	0.42 ± 0.24	97	0.42 ± 0.07	0.998
A/E	67	0.23 ± 0.07	52	0.25 ± 0.04	0.128
C/A	105	1.58 ± 0.56	97	1.43 ± 0.41	0.028
C/B	95	0.28 ± 0.06	94	0.25 ± 0.05	0.001
C/D	105	0.61 ± 0.14	97	0.58 ± 0.07	0.070
C/E	67	0.35 ± 0.06	52	0.34 ± 0.05	0.260

CT=Computed tomography; SD=standard deviation, TAVI=transcatheter aortic valve replacement;

Supplementary Table 3 Difference between CT and AP chest X-ray measured of TAVI patients.

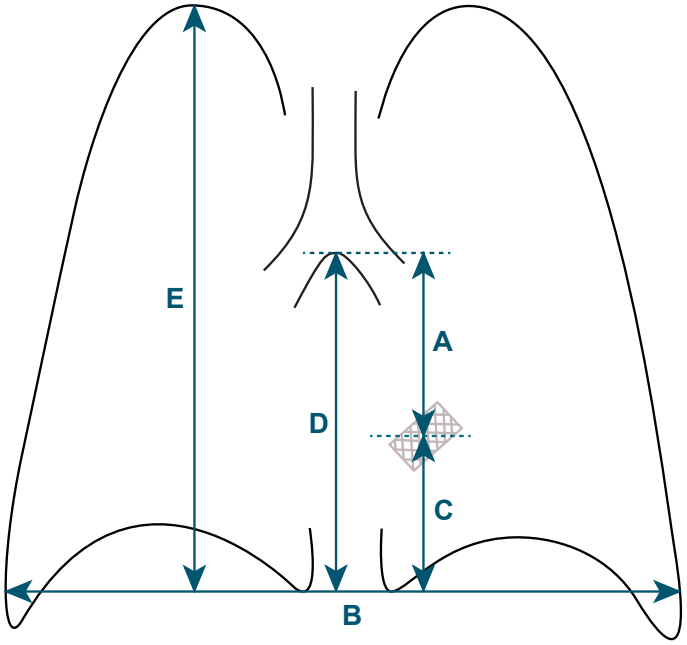
		CT	X-ray *	
	n	mean ± SD	mean ± SD	*p*
Distances measured (cm)				
A: Carina - aortic valve	102	5.4 ± 1.5	4.9 ± 1.3	<0.001
B: Thoracic width	93	28.4 ± 2.3	26.1 ± 2.6	<0.001
C: Aortic valve - diaphragm	99	7.9 ± 1.5	5.8 ± 1.8	<0.001
D: Carina - diaphragm	98	13.2 ± 2.0	13.0 ± 2.0	0.441
E: Lung apex - diaphragm	64	23.0 ± 2.4	22.5 ± 2.8	0.101
Calculated ratios				
A/B (AVL ratio)	94	0.19 ± 0.05	0.28 ± 0.05	<0.001
A/D	100	0.42 ± 0.25	0.56 ± 0.09	<0.001
A/E	65	0.23 ± 0.07	0.32 ± 0.06	<0.001
C/A	100	1.59 ± 0.56	0.83 ± 0.32	<0.001
C/B	93	0.28 ± 0.06	0.22 ± 0.06	<0.001
C/D	100	0.61 ± 0.14	0.44 ± 0.09	<0.001
C/E	65	0.35 ± 0.06	0.26 ± 0.06	<0.001

** corrected for magnification by measuring the size of the aortic valve prosthesis. SD=standard deviation.*

Supplementary Table 4 Different multivariate models for the AVL ratio, with corrections for gender, BMI and age.

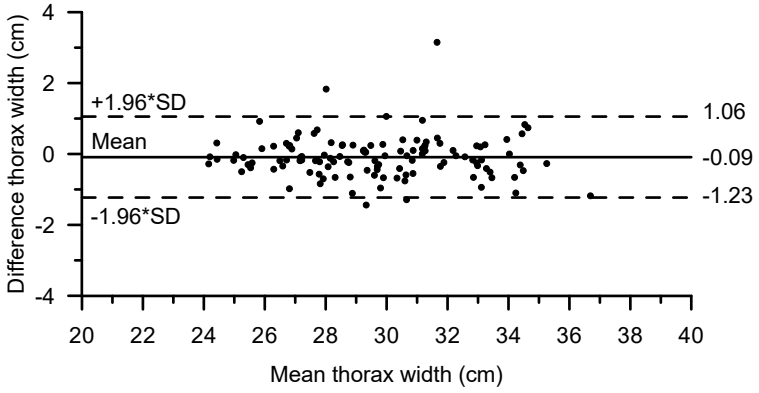
Model	Correcting variables	AVL – ratio =	Carina-aortic valve difference (measured and estimated) Mean difference ± SD (cm)
1	-	0.27	-0.15 ± 1.37
2	Gender	0.28 – 0.027 (if male)	-0.05 ± 1.31
3	Gender, age	0.24 - 0.024 (if male) + 0.001*age	0.93 ± 1.34
4	Gender, BMI	0.35 - 0.028 (if male) - 0.002*BMI	0.31 ± 1.27
5	Age, BMI	0.27 + 0.001*age - 0.002*BMI	0.70 ± 1.35
6	Gender, Age, BMI	0.30 + 0.002*BMI + 0.001*age -0.026 (if male)	1.18 ± 1.29

We tested different models with corrections for gender, BMI and age. The models were designed by using a multivariate model to estimate the AVL ratio. After estimating the AVL ratio, the AVL ratio was used to calculate the distance between the carina and the aortic valve (by multiplying it with the thorax width). This estimated distance was compared with the measured distance on the supine chest X-ray images of patients with an aortic valve prosthesis. The difference between the calculated and measured distance between the carina and the aortic valve was smallest when only correcting the AVL ratio for gender (see table).
The model only correcting for gender performed the best (smallest mean difference in estimating the distance between carina and the aortic valve. Therefore we have chosen to correct the AVL ratio for gender only. We believe it is important for the ratio to be simple and easily applicable, encouraging correction for gender only and not for additional variables.



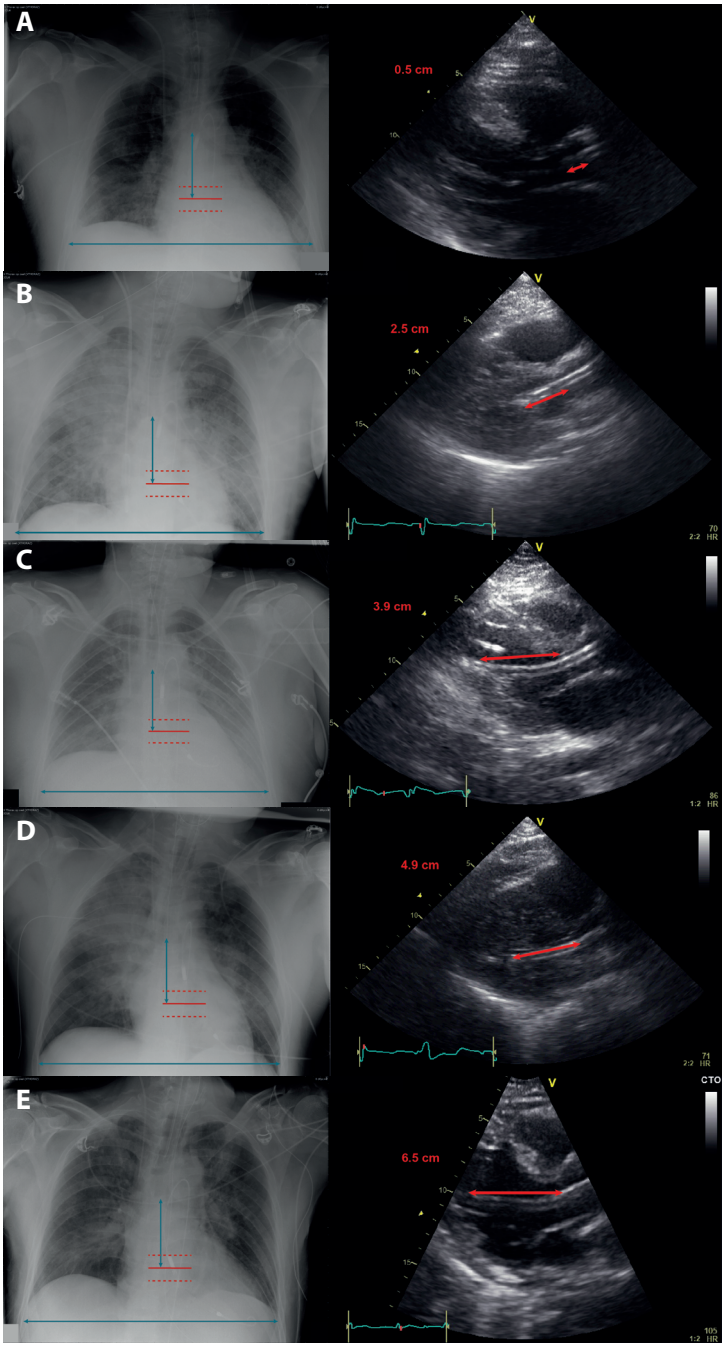
Supplementary Figure 1 Measured ratios

Several distances were measured to define the location of the aortic valve in relation to anatomical landmarks seen on chest X-ray. The anatomical landmarks used to measure the ratios are: (1) the tracheal bifurcation (carina), (2) the medial portion of the diaphragm at the level of the spine, (3) the apex of the lung and (4) the middle of the aortic valve prosthesis. The AVL ratio is defined as A/B in which A is the distance between the carina and the aortic valve and B the internal thoracic width at the level of the medial portion of the diaphragm.



Supplementary Figure 2 Bland-Altman plot thoracic width

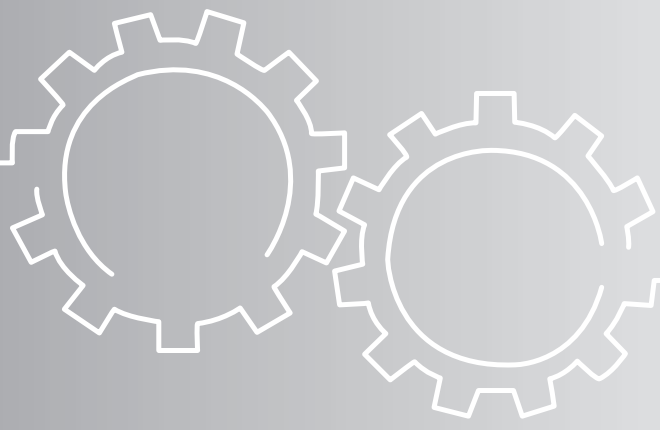
Bland-Altman plot of the thoracic width measured by 2 independent observers on supine chest X-ray of TAVI patients. The solid line represents the mean difference of -0.09 cm. The dashed lines represent the 95% limits of agreement.



Supplementary Figure 3 Examples of Impella position on supine chest X-ray images and corresponding echocardiography

A) The Impella is too far into the aorta; B) The Impella is a little too far into the aorta; C) The Impella is in correct position; D) The Impella is a little too far into the ventricle; E) The Impella is too far into the ventricle.

CHAPTER 5



REAL-LIFE USE OF LEFT VENTRICULAR CIRCULATORY SUPPORT WITH IMPELLA IN CARDIOGENIC SHOCK – 12 YEAR EXPERIENCE

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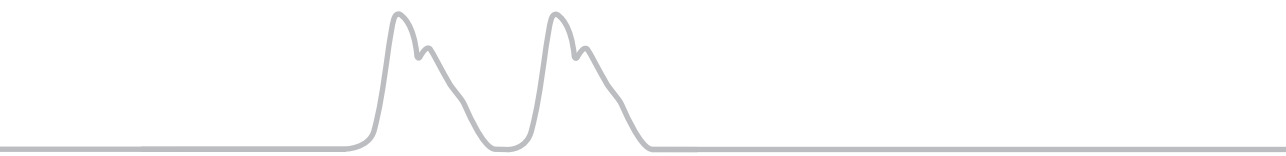

In preparation

ABSTRACT

Introduction

Mortality in cardiogenic shock (CS) patients remains high. Short-term mechanical circulatory support with Impella can be used to support the circulation in these patients. We describe our long standing clinical experience with the Impella system and aim to evaluate predictive factors for outcome.

Methods

We describe a single center registry from October 2004 to December 2016 including all patients treated with Impella. For acute myocardial infarction patients with CS, we performed an in-depth analysis on clinical course, events and predictors for 30-day mortality.

Results

Our overall clinical experience consists of 250 patients treated with Impella 2.5, Impella CP or Impella 5.0. A total of 172 patients received Impella therapy for cardiogenic shock. Etiology for cardiogenic shock was acute myocardial infarction (n=112), post-cardiotomy (n=34), non-ischemic cardiomyopathy (n=12), ischemic cardiomyopathy (n=4), complicated high-risk PCI (n=5) or other causes (n=5). Patients were treated with Impella 2.5, Impella CP or Impella 5.0. In patients with acute myocardial infarction (n=112), overall 30 day mortality was at 30 days was 56.2%. Complications consisted of device related vascular complications (17.0%), non-device related bleeding (12.5%), hemolysis (7.1%) and stroke (3.6%). In a multivariate analysis, Impella placement after the primary PCI was associated with higher 30-day mortality compared with Impella placement before the primary PCI (HR 3.52, 95% CI 1.20-10.3 p=0.022) and higher lactate levels were associated with higher mortality (HR 1.09, 95% CI 1.01-1.16, p=0.021). Cardiac arrest with ROSC time < 20 minutes was associated with lower mortality compared with having no cardiac or cardiac arrest with ROSC time > 20 minutes (HR 0.30, 95% CI 0.11 – 0.80, p=0.016).

Conclusion

In patients with cardiogenic shock after acute myocardial infarction, our registry suggests that higher lactate levels, initiation of Impella therapy after revascularization, absence of cardiac arrest and cardiac arrest with time till return of spontaneous circulation more than 20 min were associated with higher 30-day mortality.

INTRODUCTION

Mechanical circulatory support (MCS) devices provide support to the heart and overall circulation. Several percutaneous support devices (pMCS) are available, including the Impella devices (Abiomed Inc, Massachusetts).[1] The Impella platform allows percutaneous insertion and is placed across the aortic valve. It is an axial pump which pulls blood from the left ventricle and expels it through a cannula into the ascending aorta.
In patients with cardiogenic shock (CS), the aim of Impella treatment is to support the heart and circulation while increasing mean arterial pressure and cardiac output. Moreover, the Impella unloads the left ventricle by volume unloading, reduces left ventricular wall stress which reduces myocardial oxygen consumption and improves myocardial perfusion.[2,3]
The Impella technology is available in several types. The Impella 2.5 and Impella CP, can be placed percutaneously and can provide a maximum support of 2.5 and 3.7 L/min respectively. The larger Impella 5.0 can provide 5.0 L/min but requires surgical cut-down of the femoral or axillary artery.[4] These three Impella types provide hemodynamic support to the left ventricle. The Impella RP provides circulatory support to the right ventricle.
The Impella was first used in our institution in 2004, initially during high-risk percutaneous coronary interventions (PCI) and later we expanded its usage in other conditions, especially in cardiogenic shock. The aim of this study is to report our 12 year clinical experience with the Impella devices, with the focus on patients with cardiogenic shock.

Impella program

The Impella program started with the use of the Impella 2.5 in patients undergoing elective high-risk PCI with the aim to prevent hemodynamic compromise during complex PCI procedures.[5-9] After gaining experience with the Impella in this more controlled elective setting, we expanded Impella usage in the acute setting in patients with large anterior myocardial infarction without major hemodynamic comprise. Only thereafter we initiated usage in patients with cardiogenic shock.[10-13] More Impella devices have become available over the years. Initially only the Impella 2.5 and the Impella 5.0 were available. After our first report on the outcome of Impella 2.5 and 5.0 in cardiogenic shock, we adhered to the strategy to either place an Impella 5.0 immediately or, if not possible, to initially insert an Impella 2.5 and upgrade to an Impella 5.0 before the patient was transferred to the intensive care unit.[12] In 2012, the Impella CP became available and patients were routinely treated with the Impella CP. As we deemed the difference of support between the Impella CP and the Impella 5.0 to be around 1L/min we did not frequently upgrade to an Impella 5.0 device, as it requires a surgical cut-down of the femoral artery.

METHODS

Patient population

All patients who received an Impella in our hospital are prospectively entered in a dedicated database. For the purpose of this study, we analyzed all patients treated with Impella from 2004 until December 2016. For the in-depth analysis on patients in cardiogenic shock after acute myocardial infarction, patients were included when they had an acute myocardial infarction, underwent revascularization by percutaneous coronary intervention (PCI) and were in cardiogenic shock. Cardiogenic shock was defined as a clinical diagnosis made by the treating physician, based on blood pressure criteria from the SHOCK trial, which was systolic blood pressure ≤ 90 mmHg for at least 30 minutes or the need for vasopressors to maintain a systolic blood pressure > 90 mmHg.[14] Patients were excluded when they received Impella for urgent elective or high-risk PCI, acute myocardial infarction without shock, after cardiothoracic surgery or if referred to our hospital while already on Impella support. The study was approved by the Academic Medical Center's Institutional Review Board.

Treatment

Before 2012, only the Impella 2.5 and Impella 5.0 were available. Many CS patients were initially treated with Impella 2.5 and were upgraded to Impella 5.0. After its introduction, the Impella CP became the first choice device, except for post-cardiotomy patients. Duration of Impella support was at discretion of the treating physicians. Also, timing of initiation of Impella therapy (before or after revascularization) was left at the physicians discretion. Impella performance was set to a maximum level without console alarms (suction or position). Weaning was typically started usually 12-24 hours after PCI upon hemodynamic recovery allowing reduction of the inotropes and vasopressors in combination with echocardiographic imaging. Weaning usually occurred in two steps. From maximum possible support (P 7-8) to more or less half support (P 4-5) and if needed patients were observed for a couple of hours, typically overnight, low level Impella support (P 2-3) before device removal. Device removal is typically also two staged. First removal from the left ventricle into descending aorta. Heparin is then stopped while Impella support on P1 (or P2) in order to prevent thrombus formation. After 45-60 minutes of Heparin cessation, the device is removed altogether, followed by around 30 minutes femoral compression. During Impella support, all patients were treated with unfractionated heparin. All patients with ST-segment elevation myocardial infarction (STEMI) were treated with heparin (5000 IU) and aspirin (500mg) pre-PCI. Adjunctive treatment with glycoprotein IIb/IIIa inhibitors was at the discretion of the operator. Dual antiplatelet therapy post PCI was prescribed in all patients according to the guidelines.

Analysis

Patients were divided according to the indication for Impella support. We categorized subgroups of patients with cardiogenic shock according to the initial Impella strategy. Primary outcome was 30 day mortality.

A device related vascular complication was defined as limb ischemia requiring extraction of the device, a thrombotic occlusion of the femoral artery in which the device was placed, the need for vascular surgery to correct a vascular complication at the device access site, or an access site related bleeding. Device related bleeding was subdivided in minor and major bleeding. Major bleeding was defined as a bleeding associated with serum hemoglobin level decrease of 3.1 mmol/L (5 g/dL), a bleeding necessitating a minimum of 2 packed cells of blood product transfusion or the need for surgery to control the bleeding.[13] Hemolysis was defined as clinically relevant hemolysis requiring extraction of the device or requiring blood transfusion. Stroke was confirmed by a neurologists and a concurring CT scan.

Normally distributed continuous variables are reported as mean ± standard deviation (SD) and compared with ANOVA corrected for multiple testing by Bonferroni. Skewed distributed variables are presented as median [25^{th} – 75^{th} percentile] and compared with the Wilcoxon rank sum test. Categorical variables are presented as proportions and compared with Chi-square test. Kaplan Meier analyses were calculated and a log-rank test was used to compare the clinical outcomes between groups.

Univariate Cox-proportional hazard analyses and Kaplan-Meier analyses were performed to identify with established parameters as well as with Impella device and moment of Impella placement were performed to identify predictors for 30-day mortality. For this analysis, we only included patients receiving an Impella in the same procedure as the primary PCI in order avoid bias from delayed Impella therapy (placement in a separate procedure) into account. Age was dichotomized above and below the age of 75 years. Cardiac arrest was dichotomized in 3 categories: no cardiac arrest, ROSC time below 20 minutes and above 20 minutes. Creatinin was dichotomized with the use of the clinical threshold for impaired renal function (>95 µmol/L for women and >110 for men). Hemoglobin was dichotomized using the clinical threshold for anemia (7.5 mmol/L for woman and 8.5 mmol/L for man). Arterial pH, lactate, glucose and peak CKMB are dichotomized according to the median value. Blood pressure on moment of Impella placement was dichotomized using the clinical threshold of 90 mmHg for systolic blood pressure and mean arterial pressure of 70 mmHg.

To evaluate the association between timing of Impella placement and 30-day mortality, a Cox proportional-hazards regression model was used to calculate multi-variable adjusted hazard ratios. Established parameters for 30-day mortality in cardiogenic shock (lactate, glucose and creatinine levels (all continuous), cardiac arrest with ROSC < 20 minutes, cardiac arrest with ROSC > 20 minutes and timing of Impella placement were entered into the model. Not all univariate significant variables were added to the model

because of the limited number of patients and consequent loss of power of the model. A covariate was removed from the model if its significance level exceeded p=0.10. Analyses were performed with SPSS (version 23.0, Chicago, Illinois).

RESULTS

Cardiogenic shock etiology

Between October2004 and December 2016 a total of 250 patients received Impella in our institution (Figure 1). A total of 172 patients were in cardiogenic shock. The etiology of the cardiogenic shock was acute myocardial infarction (n=112), post-cardiotomy (34), non-ischemic and ischemic cardiomyopathy (n=12, n=4), complicated high-risk PCI (n=5), or other reasons (n=5; myocarditis, contusio cordis and cardiogenic shock after renal transplantation). Patients who underwent emergency coronary artery bypass grafting as primary revascularization strategy were analyzed in the post-cardiotomy group. In Table 1 and Figure 3 mortality per cardiogenic shock etiology is shown.

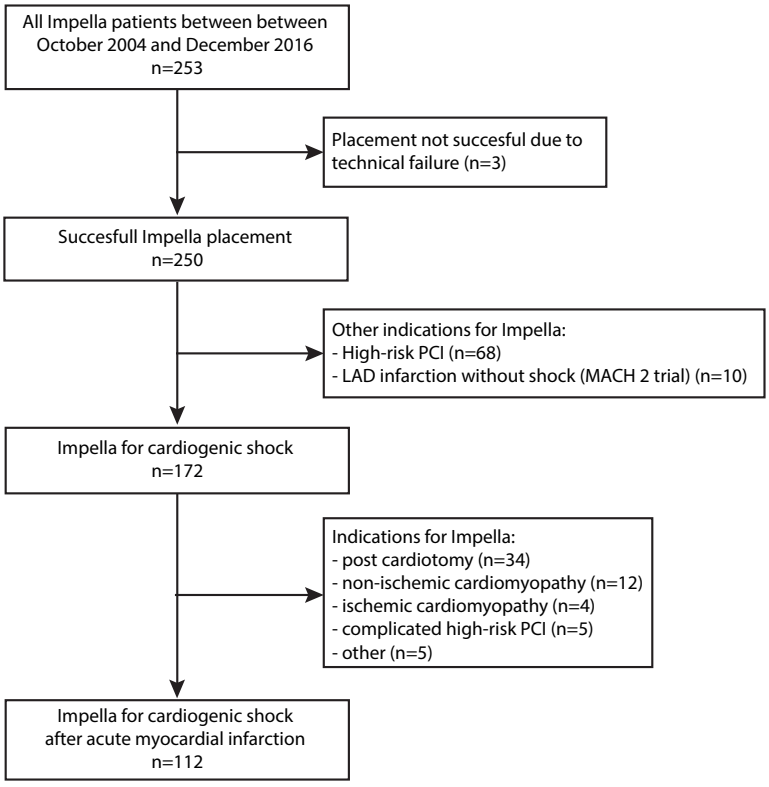

Figure 1 Flow-diagram of the patients treated with Impella in the Academic Medical Center, Amsterdam.

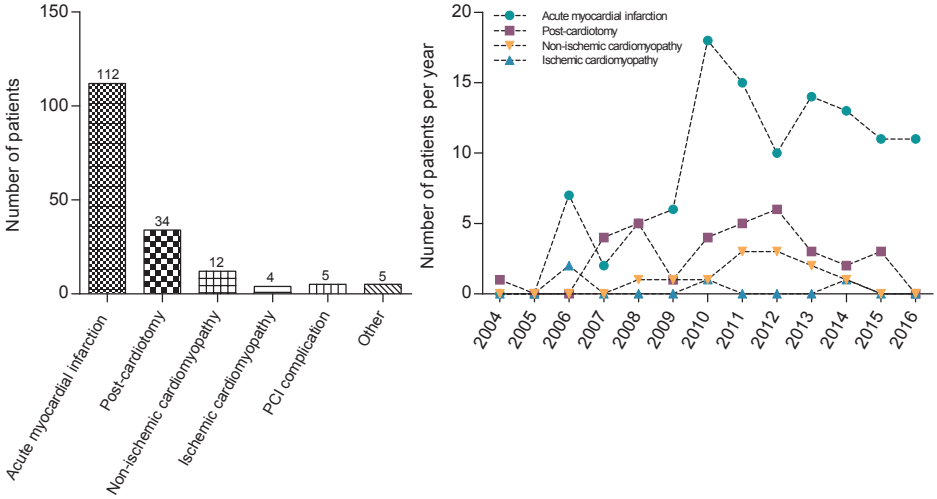

Figure 2 Cardiogenic shock etiology and number of patients treated with Impella.

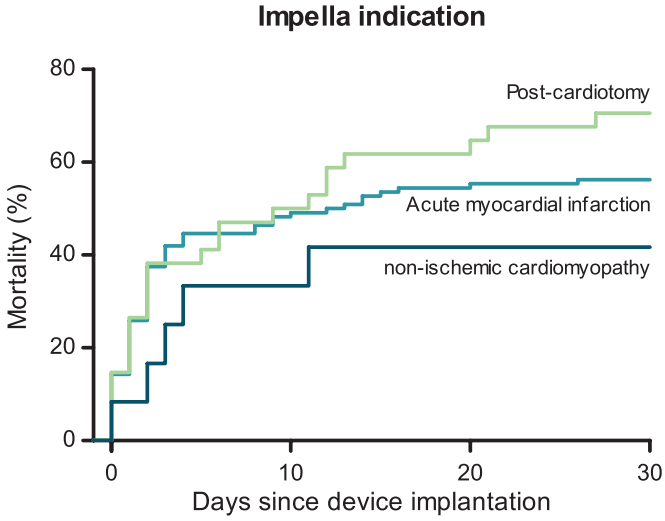

Figure 3 Kaplan Meier curves for different cardiogenic shock etiologies.

Table 1 Mortality by Kaplan-Meier estimates for cardiogenic shock etiology.

	n	30-day mortality (%)	6 month mortality (%)	1-year mortality (%)
Cardiogenic shock	172	59.3	62.8	63.5
Cardiogenic shock etiology				
Acute myocardial infarction	112	56.2	60.8	60.8
Post-cardiotomy	34	66.7	70.6	70.6
Non-ischemic cardiomyopathy	12	41.7	50.0	58.3
Ischemic cardiomyopathy	4	75.0	75.0	75.0
Complicated high-risk PCI	5	40.0	40.0	40.0
Other	5	100	100	100

PCI = percutaneous coronary intervention.

Acute myocardial infarction

Patient population

A total of 112 patients with cardiogenic shock received Impella therapy in the setting of acute myocardial infarction. Patients were 60 ± 10 years old and 80% was male (Table 2). A total of 60% of the patients experienced cardiac arrest before Impella placement. All patients underwent primary percutaneous coronary intervention (PCI), 89% of patients were mechanically ventilated and 87% were treated with catecholamines or inotropes during primary PCI. Median ischemic time was 153 minutes and 81% had an anterior located myocardial infarction. Angiographic success was achieved in 98% of the patients, defined as TIMI flow post-PCI of 2/3.

Clinical course

The initial Impella strategy consisted of Impella 2.5 in 40 patients (35.7%), Impella CP in 52 patients (46.4%) and Impella 5.0 in 20 patients (17.9%), Table 2. The Impella was placed before primary PCI in 18.8% of the patients. In 58% the Impella was placed directly after the primary PCI (in the same procedure), and in 23.2% of the patients the Impella was placed in a separate procedure (after having left the catheterization laboratory). Median Impella support time was 53 hours. A total of 12 patients (10.7%) underwent an upgrade to a higher flow support device (Impella 5.0 or veno-arterial extra-corporeal membrane oxygenation (ECMO)) (Table 3). One patient received a surgical left ventricular assist device (LVAD) after Impella and ECMO treatment.

Table 2 Baseline characteristics of patients with Impella support for acute myocardial infarction.

	all patients (n=112)	Impella 2.5 (n=40)	Impella CP (n=52)	Impella 5.0 (n=20)	*p*
Clinical characteristics and risk factors					
Age (years)	60.1 ± 10.6	59.8 ± 11.0	60.2 ± 10.4	60.6 ± 10.6	0.957
Male sex, n (%)	90 (80.4)	36 (90.0)	40 (76.9)	14 (70.0)	0.128
Body mass index (kg/m2)	26.1 [24.2-27.7]	26.2 [24.5 - 27.9]	25.4 [24.2 - 27.7]	26.4 [23.2-27.5]	0.567
Cardiovascular risk factors, n (%)					
Current smoking	41 (42.7)	16 (41.0)	23 (56.1)	2 (12.5)	0.011
Hypertension	38 (35.2)	13 (33.3)	19 (38.0)	6 (31.6)	0.843
Hypercholesterolemia	15 (14.2)	4 (10.3)	8 (16.7)	3 (15.8)	0.677
Diabetes mellitus	17 (15.3)	6 (15.4)	8 (15.4)	3 (15.0)	0.999
Prior myocardial infarction, n (%)	17 (15.7)	8 (20.5)	6 (12.2)	3 (15.0)	0.569
Prior TIA or stroke, n (%)	4 (3.7)	-	3 (5.9)	1 (5.3)	0.312
Known peripheral arterial disease, n (%)	5 (4.8)	1 (2.6)	4 (8.5)	-	0.244
Prior PCI or CABG, n (%)	15 (13.6)	6 (15.4)	6 (11.8)	3 (15.0)	0.867
Clinical characteristics on admission					
Cardiac arrest, n (%)	67 (59.8)	19 (47.5)	36 (69.2)	12 (60.0)	0.062
Out of hospital cardiac arrest, n (%)	49 (74.2)	9 (50.0)	31 (86.1)	9 (75.0)	0.017
Witnessed arrest, n (%)	58 (90.6)	17 (94.4)	32 (91.4)	9 (81.8)	0.512
First rhythm VT/VF/AED, n (%)	56 (86.2)	13 (72.2)	32 (88.9)	11 (100)	0.085
Time till return of spontaneous circulation (min)	21 [11-50]	20 [6-55]	24 [15-50]	20 [10-45]	0.662
Traumatic injuries at admission, n/n (%)	7 (6.3)	2 (5.0)	4 (7.7)	1 (5.0)	0.842
Laboratory values on admission					
Lactate (mmol/L)	6.3 [3.7 - 9.6]	4.2 [2.0-8.4]	7.7 [5.2-10.9]	4.0 [2.3-7.3]	0.013
Hemoglobin (mmol/L)	8.4 [7.5 - 9.3]	8.6 [7.4-9.3]	8.4 [7.8-9.0]	8.6 [6.7-9.3]	0.867
Creatinine (mg/dL)	119 [91 - 130]	119 [89-129]	105 [90-127]	121 [90-146]	0.442
Glucose (mmol/L)	13.6 [10.2-18.8]	13.4 [10.1-18.7]	15.5 [11.6-20.7]	12.1 [8.5-16.2]	0.057
Arterial pH	7.20 [7.07-7.31]	7.21 [6.94-7.35]	7.18 [7.07-7.25]	7.27 [7.16-7.33]	0.117

Table 2 Baseline characteristics of patients with Impella support for acute myocardial infarction. (continued)

	all patients (n=112)	Impella 2.5 (n=40)	Impella CP (n=52)	Impella 5.0 (n=20)	*p*
Primary percutaneous coronary intervention					
Ischemic time (min)	153 [107 - 240]	172 [112-305]	153 [96-210]	143 [109-297]	0.708
Infarct-related artery, n (%)					0.316
Left main	29 (25.9)	14 (35.0)	11 (21.2)	4 (20.0)	
Left anterior descending	62 (55.4)	21 (52.5)	29 (55.8)	12 (60.0)	
Left circumflex	13 (11.6)	3 (7.5)	9 (17.3)	1 (5.0)	
Right coronary artery	8 (7.1)	2 (5.0)	3 (5.8)	3 (15.0)	
Multi-vessel disease, n (%)*	74 (66.1)	31 (77.5)	32 (61.5)	11 (55.0)	0.142
Mechanical complications, n (%)	3 (2.7)	2 (5.0)	1 (1.9)	-	0.474
TIMI flow 0/1 pre-PCI, n (%)	90 (81.8)	35 (87.5)	40 (78.4)	15 (78.9)	0.505
TIMI flow 2/3 post-PCI, n (%)	101 (91.0)	37 (92.5)	47 (92.2)	17 (85.0)	0.585
Cardiogenic shock during primary PCI	103 (92.0)	37 (92.5)	49 (94.2)	17 (85.0)	0.430
Catecholamines or inotropes, n (%)	94 (83.9)	31 (77.5)	48 (92.3)	15 (75.0)	0.078
Mechanical ventilation, n (%)	98 (87.5)	32 (80.0)	47 (90.4)	19 (95)	0.175
Primary PCI in other hospital	9 (8.0)	-	5 (9.6)	4 (20.0)	0.023
Before device placement					
Catecholamines or inotropes, n (%)	102 (91.1)	33 (82.5)	50 (96.2)	19 (95.0)	0.059
Mechanical ventilation, n (%)	100 (89.3)	33 (82.5)	47 (90.4)	10 (100)	0.111
Intra-aortic balloon pump before Impella placement, n (%)	22 (19.6)	8 (20.0)	6 (11.5)	8 (40.0)	0.025
Blood pressure values					
Mean arterial pressure	67 [56-77]	69 [59-82]	67 [53-76]	66 [52-76]	0.311
Systolic blood pressure (mmHg)	86 [73-102]	86 [74-101]	84 [74-101]	91 [65-106]	0.671
Diastolic blood pressure (mmHg)	58 [44-65]	61 [50-75]	56 [40-63]	52 [45-62]	0.097
Heart rate (beats per minute)	96 [78-113]	107 [81-118]	91 [70-105]	100 [81-103]	0.041

Table 2 Baseline characteristics of patients with Impella support for acute myocardial infarction. (continued)

	all patients (n=112)	**Impella 2.5** (n=40)	**Impella CP** (n=52)	**Impella 5.0** (n=20)	*p*
Blood values					
Lactate (mmol/L)	6.2 [3.6-9.7]	4.2 [2.0-8.4]	7.65 [5.3-10.7]	3.8 [2.2-8.0]	0.009
Hemoglobin (mmol/L)	8.4 [7.5-9.4]	8.6 [7.5-9.3]	8.5 [7.9-9.4]	8.2 [6.6-9.7]	0.709
Creatinine (mg/dL)	114 [90-136]	119 [91-129]	104 [89-128]	129 [95-170]	0.102
Glucose (mmol/L)	13.4 [9.8-18.3]	13.4 [10.1-18.7]	15.7 [12.5-20.5]	9.5 [8.1-13.0]	0.001
Arterial pH	7.21 [7.07-7.31]	7.21 [6.94-7.35]	7.18 [7.07-7.25]	7.27 [7.19-7.31]	0.023
Mechanical circulatory support					
Moment of device placement					< 0.001
Impella placement before primary PCI, n (%)	21 (18.8)	8 (20.0)	11 (21.2)	2 (10.0)	
Impella placement directly after primary PCI, n (%)	67 (59.8)	27 (67.5)	34 (65.4)	6 (30.0)	
Impella placement in separate procedure after primary PCI, n (%)	24 (21.4)	5 (12.5)	7 (13.5)	12 (60.0)	
Time between revascularization and Impella placement (hours)	13 [8-23]	8 [3- 32]	13 [9-97]	14 [9 - 17]	0.604
IABP between primary PCI and Impella placement, n (%)	10 (41.7)	1 (20.0)	2 (28.6)	7 (58.3)	0.243

*Data are displayed as percentile (frequency), mean ± standard deviation or median [25th percentile - 75th percentile]. p-value for the comparison between the Impella devices. VF: ventricular fibrillation; VT: ventricular tachycardia; PCI: percutaneous coronary intervention; CABG: coronary artery bypass grafting; AED: Automated External Defibrilator. * > 50% stenosis in non-culprit vessel*

Table 3 Clinical course.

	all patients (n=112)	Impella 2.5 (n=40)	Impella CP (n=52)	Impella 5.0 (n=20)	*p*
Mechanical circulatory support					
Duration of Impella support (hours) *	52 [22 - 122]	49 [12-122]	49 [25-89]	104 [41-148]	0.105
Change of mechanical support device, n (%)	12 (10.7)	8 (20.0)	3 (5.8)	1 (5.0)	0.060
Upgrade to Impella 5.0	9 (75)	8 (100)	1 (33.3)	-	
Upgrade to ECMO	3 (25)	-	2 (66.7)	1 (100)	
Device replacement by similar device, n (%)	2 (1.8)	-	-	2 (10)	0.009
Device failure requiring extraction of the device, n (%)	1 (0.9)	1 (2.5)	-	-	0.403
During admission					
Inotropic or vasopressor therapy, n (%)	106 (94.6)	35 (87.5)	51 (98.1)	20 (100)	0.041
Renal replacement therapy, n (%)	43 (38.4)	14 (35.0)	21 (40.4)	8 (40.0)	0.859
Mechanical ventilation, n (%)	106 (94.6)	37 (92.5)	49 (94.2)	20 (100)	0.470
Peak CKMB, µmol/L	457 [184-934]	401 [198-779]	539 [178-1104]	499 [181-824]	0.404
Blood products, n (%)	68 (60.7)	27 (67.5)	25 (48.1)	16 (80.0)	0.025
Number of patients in the intensive care unit, n (%)	100 (89.3)	31 (77.5)	49 (94.2)	20 (100)	0.008
Days on the intensive care unit	5 [3-15]	5 [2-15]	4 [2-16]	7 [4-13]	0.570

*p-value for the comparison between the Impella devices. * sum of support duration of all given support devices, including upgrades. PCI = percutaneous coronary intervention. ECLS = extra-corporeal life support.*

The majority of the patients were treated with inotropic or vasopressor agents (95%), mechanical ventilation (95%) and were admitted to the intensive care unit (89%), Table 4. Renal replacement therapy was necessary in 38% of the patients and 59% required blood products.

Outcome

The overall in-hospital mortality was 58.0%. The cause of death was refractory cardiogenic shock (67.7%), post-anoxic brain injury (20.0%) or other reasons (12.3%). Four patients were diagnosed with stroke during admission (3.6%). Device related vascular complications occurred in 19 patients (17%) of which 14 patients had an access site related bleeding (11 major and 3 minor bleeding), 4 patients experienced limb ischemia requiring surgery and 1 patient had an access site infection requiring surgery. Clinically relevant hemolysis occurred in 7.1% of the patients. Non-device related bleeding occurred in 14 patients (12.5%).

Difference between Impella devices

There were some differences in the baseline characteristics of patients with Impella 2.5, CP and 5.0. Patients treated with Impella 2.5 experienced OHCA less frequently. In the Impella 5.0 group, biochemical values at admission were compatible with a less severe state of cardiogenic shock, although there was no difference in mean arterial blood pressure. Also, patients with primary PCI at another center more often received an (initial) Impella 5.0 upon arrival at our institution. Impella 5.0 was placed more often during a separate procedure than the primary PCI. There were differences in the number of patients who were upgraded to another support device, the number of patients receiving blood products, and the number of days on the intensive care. There was no difference in stroke, device related vascular complications or hemolysis between patients treated with Impella 2.5, CP or 5.0.

Moment of device placement

Baseline characteristics between patients treated with Impella before the primary PCI, directly after the primary PCI and in a separate procedure are shown in the supplementary Table 1. Patients who received the Impella in a separate procedure, had higher systolic blood pressure, lower glucose levels and higher pH on the moment of Impella placement, more often underwent PCI in another hospital and were less often in cardiogenic shock during the primary PCI.

Table 4 Clinical outcome.

	all patients (n=112)	Impella 2.5 (n=40)	Impella CP (n=52)	Impella 5.0 (n=20)	*p*
In-hospital outcome					
Mortality					
In-hospital mortality, n (%)	65 (58.0)	27 (67.5)	31 (59.6)	7 (35.0)	0.053
Refractory cardiogenic shock	44 (67.7)	20 (74.1)	18 (58.1)	6 (85.7)	
Post-anoxic brain injury	13 (20.0)	4 (14.8)	8 (25.8)	1 (14.3)	
Other reason	8 (12.3)	3 (11.1)	5 (16.1)	-	
Stroke, n (%)	4 (3.6)	2 (5.0)	1 (1.9)	1 (5.0)	0.682
Hemorrhagic stroke	1 (25.0)	1 (50.0)	-	-	
Ischemic stroke	3 (75.0)	1 (50.0)	1 (100)	1 (100)	
Device related vascular complication, n (%)	19 (17.0)	6 (15.0)	10 (19.2)	3 (15.0)	0.838
Limb ischemia	4 (21.1)	3 (50.0)	1 (10.0)	-	
Access site related bleeding	14 (73.7)	3 (50.0)	9 (90.0)	2 (66.7)	
Major bleeding	11 (78.6)	1 (33.3)	8 (88.9)	2 (100)	
Minor bleeding	3 (21.4)	2 (66.7)	1 (11.1)	-	
Access site infection	1 (5.3)	-	-	1 (33.3)	
Non-device related bleeding	14 (12.5)	6 (15.0)	5 (9.6)	3 (15.0)	0.691
Gastro-intestinal bleeding	6 (42.9)	3 (50.0)	1 (20.0)	2 (66.7)	
Other location	8 (57.1)	3 (50.0)	4 (80.0)	1 (33.3)	
Clinically relevant hemolysis, n (%)	8 (7.1)	2 (5.0)	5 (9.6)	1 (5.0)	0.639
Surgical LVAD placement, n)%)	1 (0.9)	-	-	1 (5.0)	0.098
Heart transplantation, n (%)	-	-	-	-	-

Table 4 Clinical outcome. (continued)

	all patients (n=112)	Impella 2.5 (n=40)	Impella CP (n=52)	Impella 5.0 (n=20)	*p*
Follow-up outcome					
30-day all-cause mortality, n (%) *	63 (56.2)	26 (65.0)	30 (57.1)	7 (35.0)	0.126
6 months all-cause mortality, n (%) *	68 (60.8)	28 (70.0)	32 (61.6)	8 (40.0)	0.110
1 year all-cause mortality n (%) *	68 (60.8)	28 (70.0)	32 (61.6)	8 (40.0)	0.110

*p-value for the comparison between the Impella devices. LVAD = left ventricular assist device; * Kaplan-Meier estimates.*

30-day mortality

In patients who received Impella during the same procedure as the primary PCI, we evaluated factors that were associated with 30-day mortality (Table 5 and Supplementary Figure 1). Patients with renal impairment before Impella placement had a higher mortality than patients with normal renal function (68.3 versus 42.2%, p=0.048). Also, patients with arterial pH lower than 7.2 had a higher mortality than patients with higher pH levels (67.4% versus 43.7%, p=0.05). Patients who received therapy before revascularization had numerical lower mortality than patients who received the Impella after revascularization (42.9 versus 59.7%, p=0.184). Although not significantly different, patients with cardiac arrest and ROSC times lower than 20 minutes have a lower mortality than patient without cardiac arrest (37.5% versus 57.1%) or patients with cardiac arrest and ROSC time higher than 20 minutes (67.9%).

Table 5 Univariate risk factors for 30-day mortality.

	n	30-day mortality by KM estimates (%)	Hazard ratio (95% CI)	*p*
Impella				0.546
Impella 2.5	35	60	reference	-
Impella CP	45	55.6	0.91 (0.51 - 1.62)	0.735
Impella 5.0	8	37.5	0.51 (0.15 - 1.70)	0.507
Timing of device placement				
Before the primary PCI	21	42.9	reference	-
After the primary PCI	67	59.7	1.63 (0.79 - 3.37)	0.184
Age				
≤ 75 years old	81	54.3	reference	-
> 75 years old	7	71.4	1.76 (0.70 - 4.44)	0.234
Sex				
Male	72	52.8	reference	-
Female	16	68.7	1.52 (0.77 - 2.97)	0.225
Cardiac arrest				0.117
no cardiac arrest	35	57.1	reference	-
ROSC time ≤ 20 min	24	37.5	0.63 (0.286 - 1.38)	0.247
ROSC time > 20 min	28	67.9	1.44 (0.77 - 2.71)	0.256
Traumatic injuries before admission				
Absent	82	54.9	reference	-
Present	6	66.7	1.21 (0.43 - 3.36)	0.717
Infarct related artery				
LM/LAD	72	54.2	reference	-
RCX/RCA	16	62.5	1.21 (0.61 - 2.43)	0.590

Table 5 Univariate risk factors for 30-day mortality. (continued)

	n	30-day mortality by KM estimates (%)	Hazard ratio (95% CI)	*p*
Pre-PCI TIMI flow				
TIMI flow 0/1	70	57.1	reference	-
TIMI flow 2/3	18	50.0	0.82 (0.40 - 1.71)	0.61
Post-PCI TIMI flow				
TIMI flow 0/1	5	60.0	1.30 (0.41-4.20)	0.656
TIMI flow 2/3	83	55.4	reference	-
Lactate level				
≤ 6.7 mmol/L	30	40.0	reference	-
> 6.7 mmol/L	29	58.6	1.75 (0.83 - 3.66)	0.141
Glucose level				
≤ 15.5 mmol/L	40	50.0	reference	-
> 15.5 mmol/L	36	55.6	1.25 (0.67 - 2.32)	0.486
Renal impairment				
lower than normal reference value	38	42.1	reference	-
higher than normal reference value	41	68.3	1.86 (1.01 - 3.45)	0.048
pH				
≤ 7.2	43	67.4	reference	-
> 7.2	32	43.7	0.53 (0.28 - 1.00)	0.05
Hb				
lower than normal reference value	35	60	reference	-
higher than normal reference value	44	52.3	0.80 (0.44 - 1.44)	0.453
Infarct size				
Peak CKMB ≤ 450 µmol/L	40	45.0	reference	-
Peak CKMB > 450 µmol/L	41	58.5	1.41 (0.76 - 2.59)	0.276
Systolic blood pressure before Impella placement				
≤ 90 mmHg	52	59.6	reference	-
> 90 mmHg	32	53.1	0.88 (0.49 - 1.59)	0.675
Mean arterial blood pressure before Impella placement				
≤ 70 mmHg	53	60.4	reference	-
> 70 mmHg	30	53.3	0.83 (0.46 - 1.52)	0.551

In a multivariate analysis, Impella placement after the primary PCI was associated with higher 30-day mortality compared with Impella placement before the primary PCI (HR 3.52, 95% CI 1.20-10.3 p=0.022), Table 6. Also, higher lactate levels were associated with higher mortality (HR 1.09, 95% CI 1.01–1.16, p=0.021). Cardiac arrest with ROSC time < 20 minutes was associated with lower mortality compared with having no cardiac or cardiac arrest with ROSC time > 20 minutes (HR 0.30, 95% CI 0.11–0.80, p=0.016).

Table 6 Multivariate model for 30-day mortality.

	Hazard ratio (95% CI)	*p*
Moment of device placement		
Before the primary PCI	reference	-
After the primary PCI	3.52 (1.20 - 10.3)	0.022
Cardiac arrest		
ROSC time ≤ 20 min	0.30 (0.11-0.80)	0.016
no cardiac arrest or ROCS time > 20 min	reference	-
Lactate (mmol/L) *	1.09 (1.01 - 1.16)	0.021

** continuous variable. hazard ratio per increase of mmol/L. PCI = primary coronary intervention; ROSC = return of spontaneous circulation.*

DISCUSSION

This analysis describes the largest single-center experience with Impella technology over many years. It provides an insight into the treatment strategy, management, outcomes and events of patients treated with Impella in an experienced center. In our experience, initiation of Impella therapy is feasible in the elective setting, as well as the emergent setting, and even before primary PCI.

The key finding of this registry is that hat placement of the Impella prior to revascularization may significantly improve survival. These findings are in accordance with other registries which also report that initiation of Impella therapy before the revascularization is associated with lower mortality.[15,16] Impella placement before primary PCI may enable stable hemodynamics during the intervention. It may prevent deterioration during the time of the procedure and when opening the occluding vessel. Several animal studies have shown that unloading the left ventricle before reperfusion reduces infarct size despites the longer ischemic time.[17-19] These studies demonstrated that the use of Impella before revascularization activates the neuro-hormonal cascade associated with reperfusion injury. This results in a cardio-protective signaling cascade which limits the myocardial damage. In our registry, the Impella was placed before the primary PCI in 19% of patients and this decision to place the Impella before the revascularization might be biased by the severity of the patients´ condition. A randomized trials are needed to evaluate whether Impella placement before the primary PCI reduces mortality.

Although Impella has been on the market since 2004, there is still little randomized evidence on the effectiveness of the Impella in cardiogenic shock. Although Impella can provide more hemodynamic support than IABP, this was not translated in reduced mortality in randomized trials.[13,20-22] There are 3 small randomized trials comparing Impella with IABP in cardiogenic shock, but all without enough power to show a difference in mortality. A meta-analysis combining all randomized trials comparing Impella with IABP, did not show an effect on mortality. However, a large percentage of the randomized

patients experienced cardiac arrest before admission, resulting in a high percentage of neurological damage, which might underestimated the treatment effect of Impella support. In the randomized Impress in Severe Shock trial (n=48), comparing IABP with Impella CP, the timing of device placement was left to the treating physician. A numerical difference in 30-day mortality was observed in patients receiving the mechanical support device before the primary PCI (25% versus 53%; HR 2.42, p=0.16).[13]

Mortality rates in real-life cohorts are higher than in randomized controlled trials with mechanical circulatory support in cardiogenic shock patients.[13,21,23,24]. Registries who describe real-life usage of devices are describe an unselected patient cohort.[12,15,16,25-31] Especially in critically ill patients in an emergency situation, randomized controlled trials are difficult to conduct. Also, severely ill patients with very poor prognosis are often excluded from randomized studies. This is why registries are of interest in these severely ill patients and they provide important hypothesis generating which can be evaluated in future clinical trials.

We describe an 30-day mortality of 56.2%, with a high percentage of patients having experienced cardiac arrest before Impella treatment (59.8%). Comparable mortality rates are found by other registries: Basir et al. describe a 56% in-hospital mortality in patients with acute myocardial infarction but with 40% of patient with cardiac arrest, and Lackermair et al. describes a 30 day mortality of 64% in a mixed patient cohort.

The Impella strategy in our hospital has changed over time. Improvements of the console allows for a much quicker initiation of the device, and it has become more user friendly. Also, the devices itself has undergone various improvements and the Impella CP has become available. The Impella 2.5 was initially the standard therapy, until the Impella CP became available in 2012. The Impella CP requires a slightly larger insertion sheath (14 F versus the 13 F), but can provide more flow (3.7 L/min versus 2.5). From comparing baseline characteristics between patients treated with both devices, a much more liberal use of Impella CP is evident, resulting in treatment of more severely ill patients, with possibly more severe neurological damage on admission. Despite the treatment of more severely ill patients, the mortality rates of the are numerically lower in the Impella CP group (57.1% versus 65%).

Hemodynamic support of 2.5 L/min (Impella 2.5) or 3.7L/min (Impella CP) may not be enough for patients in severe hemodynamic shock. Univariate analysis shows a numerically lower 30-day mortality in the Impella 5.0 group than in the Impella CP and Impella 2.5 group (65%, 57.1%, 35% respectively, p=0.126), supplementary figure 1. However, because of the need for surgical cut-down of the femoral or axillary artery in order to place the 21 F catheter, the Impella 5.0 is frequently placed during a separate procedure. This delayed Impella placement induces selection bias of the patients, as the most severely ill patients will be treated with a percutaneous Impella during the primary PCI because they may have been deemed too ill to wait for surgical cut-down. Patients

admitted to the ICU without Impella may deemed to be less ill, and may either recover or deteriorate and require delayed mechanical support. Unfortunately, our sample size is too small to take all possible confounders into account is a multivariate analysis and therefore we cannot evaluate our hypothesis properly.

The Impella 2.5 and CP require 13F and 14F sheaths and therefore some vascular complications may be expected. In our cohort, device related vascular complications occurred in 19 patients (17%), of which the majority had access site related bleeding (n=14). Limb ischemia occurred in 4 patients (3.6%). The largest Impella cohort reporting complications (n=154) describes 9.7% vascular complications requiring surgery, 3.9% limb ischemia and 17.5% bleeding requiring transfusion.[7] Other smaller cohorts report limb ischemia of 12% [25,29], 3% [27] and 25% [28].

Access site related bleeding occurred in 14 patients (12.5%) of which 11 patients had a major bleeding. Non-device related bleeding occurred in 14 patients (12.5%). During mechanical support, patients receive heparin in addition to standard dual antiplatelet therapy after PCI (aspirin and a P2Y12 receptor blocker), which facilitates bleeding in combination with larger bore sheaths. In a registry of post-cardiac arrest patients (n=78), the bleeding rated was 26% and 3 cardiogenic shock registries (n=120, n=154, n=66) describe rates of 24%, 18% and 35%). [15,26,27,29] Hemolysis occurred in 7.1% of the treated patients. Hemolysis is numerically higher in the Impella CP treated patients, which might be related to the difference in size of the inlet and outlet and rotator speed. Earlier reports describe hemolysis in 6.0%, 7.5% and 10.3% of patients treated with Impella 2.5. [15,26,27] The stroke rate is relatively low in these severely ill patients (3.6%). Other cohorts describes 4 strokes (3.6%), which is comparable with other cohorts (5% [29], 1.9% [15] , 0% [27] , 1.7%[26]).

Analysis of the PROTECT II trail, comparing IABP with Impella 2.5 in the setting of high-risk PCI, suggests a learning curve associated with introduction of the Impella. Our experience describes a stepwise introduction of the Impella in the setting of elective high-risk PCI followed by the use of Impella in the emergent setting of cardiogenic shock and placement of Impella prior to emergent revascularization. A stepwise introduction is important to allow for a successful introduction of a new technology into the clinical setting.

There are several limitations to consider. This is an observation study with its known limitations. Only 19% of patients are treated with Impella before the revascularization. The timing of the Impella placement might have been influenced by the patients´ condition. A randomized trial is needed to evaluate if initiation of Impella therapy before revascularization reduces mortality. In addition, there are many factors who might have influenced the results, such as experience with the device, change of therapy over time, improvement of general therapy of cardiogenic shock and STEMI patients over time, change in patient selection over time. Also, we performed two randomized controlled

trials comparing Impella with IABP[13,20]. During the inclusion period of these trials, half of the patients were randomized to IABP and the type of Impella therapy was defined by the study protocol.

In patients with cardiogenic shock after acute myocardial infarction, our registry shows a lower mortality in patients in whom Impella therapy was initiated before revascularization compared with patients in whom Impella therapy was initiated after revascularization. Future prospective randomized studies need to evaluate this finding.

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Supplementary table 1 Baseline characteristics according to moment of device placement.

	All patients	Impella before revascularisation	Impella directly after revascularisation	Delayed Impella placement	
	n=112	n=21	n=67	n=24	*p*
Clinical characteristics and risk factors					
Age (years)	60.1 ± 10.6	60,0 ± 11,7	61.2 ± 10.0	57.1 ± 10.8	0.262
Male sex, n (%)	90 (80.4)	18 (85.7)	54 (80.6)	18 (75.0)	0.663
Body mass index (kg/m2)	26.1 [24.2-27.7]	25.7 [23.6 - 27.4]	26.0 [24.5 - 27.6]	26.6 [23.3 - 29.3]	0.540
Cardiovascular risk factors, n (%)					
Current smoking	41 (42.7)	8 (40.0)	23 (44.2)	10 (41.7)	0.942
Hypertension	38 (35.2)	8 (40.0)	23 (35.9)	7 (29.2)	0.741
Hypercholesterolemia	15 (14.2)	-	12 (19.4)	3 (12.5)	0.094
Diabetes mellitus	17 (15.3)	5 (25.0)	9 (13.4)	3 (12.5)	0.411
Prior myocardial infarction, n (%)	17 (15.7)	3 (16.7)	13 (19.7)	1 (4.2)	0.200
Prior TIA or stroke, n (%)	4 (3.7)	1 (5.0)	1 (1.5)	2 (8.3)	0.299
Known peripheral arterial disease, n (%)	5 (4.8)	1 (5.6)	4 (6.3)	-	0.475
Prior PCI or CABG, n (%)	15 (13.6)	5 (23.8)	10 (15.4)	-	0.055
Clinical characteristics on admission					
Cardiac arrest, n (%)	67 (59.8)	11 (52.4)	42 (62.7)	14 (58.3)	0.883
Out of hospital cardiac arrest, n (%)	49 (74.2)	10 (90.9)	29 (70.7)	10 (71.4)	0.383
Witnessed arrest, n (%)	58 (90.6)	10 (100)	36 (90.0)	12 (85.7)	0.484
First rhythm VT/VF/AED, n (%)	56 (86.2)	8 (72.7)	35 (87.5)	13 (92.9)	0.325
Time till return of spontaneous circulation (min)	21 [11-50]	25 [18-50]	20 [11-53]	18 [10-27]	0.416
Traumatic injuries at admission, n/n (%)	7 (6.3)	2 (9.5)	4 (6.0)	1 (4.2)	0.752
Laboratory values on admission					
Lactate (mmol/L)	6.3 [3.7 - 9.6]	7.7 [4.2-9.6]	6.5 [3.8-10.4]	4.2 [2.8-7.6]	0.305
Hemoglobin (mmol/L)	8.4 [7.5 - 9.3]	8.4 [7.4-9.0]	8.7 [7.6-9.4]	8.3 [7.2-9.3]	0.562
Creatinine (mg/dL)	119 [91 - 130]	111 [98-134]	112 [89-128]	124 [90-163]	0.428
Glucose (mmol/L)	13.6 [10.2-18.8]	13.8 [11.0-18.0]	15.7 [11.1-20.4]	11.6 [8.5-13.8]	0.055
Arterial pH	7.20 [7.07-7.31]	7.22 [6.94 - 7.34]	7.18 [7.05-7.28]	7.29 [7.13-7.36]	0.063

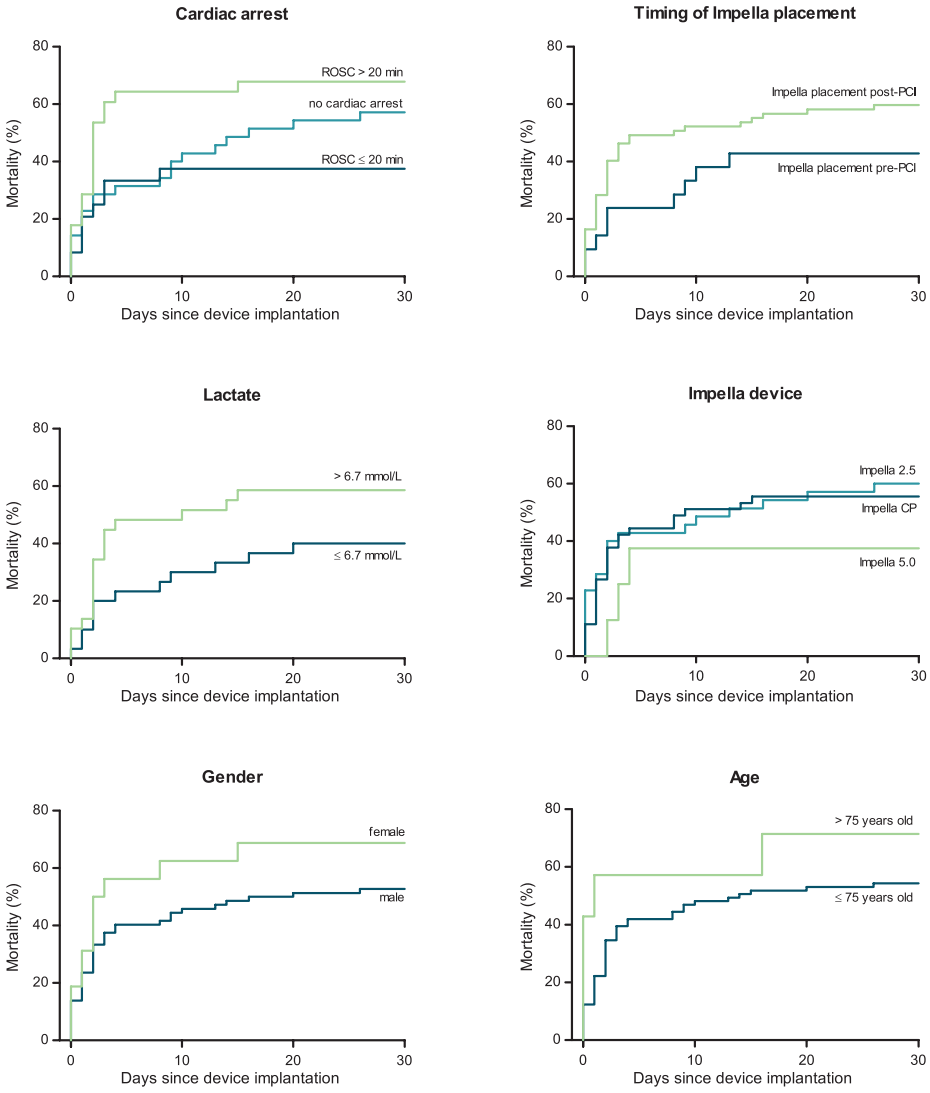
Supplementary table 1 Baseline characteristics according to moment of device placement. (continued)

	All patients	Impella before revascularisation	Impella directly after revascularisation	Delayed Impella placement	
	n=112	n=21	n=67	n=24	*p*
Primary percutaneous coronary intervention					
Ischemic time (min)	153 [107 - 240]	198 [118-414]	150 [96-219]	145 [120-303]	0.324
Infarct-related artery, n (%)					0.546
Left main	29 (25.9)	7 (33.3)	18 (26.9)	4 (16.7)	
Left anterior descending	62 (55.4)	10 (47.6)	37 (55.2)	15 (62.5)	
Left circumflex	13 (11.6)	1 (4.8)	9 (13.4)	3 (12.5)	
Right coronary artery	8 (7.1)	3 (14.3)	3 (4.5)	2 (8.3)	
Multi-vessel disease, n (%)*	74 (66.1)	17 (81.0)	44 (65.7)	13 (54.2)	0.166
Mechanical complications, n (%)	3 (2.7)	-	2 (3.0)	1 (4.2)	0.668
TIMI flow 0/1 pre-PCI, n (%)	90 (81.8)	35 (87.5)	40 (78.4)	15 (78.9)	0.505
TIMI flow 2/3 post-PCI, n (%)	101 (91.0)	37 (92.5)	47 (92.2)	17 (85.0)	0.585
Cardiogenic shock during primary PCI	103 (92.0)	21 (100)	67 (100)	15 (62.5)	<0.001
Catecholamines or inotropes, n (%)	94 (83.9)	31 (77.5)	48 (92.3)	15 (75.0)	0.078
Mechanical ventilation, n (%)	98 (87.5)	32 (80)	47 (90.4)	19 (95.0)	0.175
Primary PCI in other hospital	9 (8.0)	-	-	9 (8.0)	<0.001
Before device placement					
Catecholamines or inotropes, n (%)	102 (91.1)	19 (90.5)	59 (88.1)	24 (100)	0.211
Mechanical ventilation, n (%)	100 (89.3)	18 (87.7)	60 (89.6)	22 (91.7)	0.808
Intra-aortic balloon pump before Impella placement, n (%)	22 (19.6)	-	12 (17.9)	10 (41.7)	0.002
Blood pressure values					
Mean arterial pressure (mmHg)	67 [56-77]	58 [49-66]	68 [56-77]	74 [61-82]	0.031
Systolic blood pressure (mmHg)	86 [73-102]	80 [68-95]	85 [71-101]	96 [81-116]	0.049
Diastolic blood pressure (mmHg)	58 [44-65]	49 [40-58]	60 [45-67]	61 [47-69]	0.053
Heart rate (beats per minute)	96 [78-113]	83 [61-108]	97 [80-112]	100 [85-115]	0.099

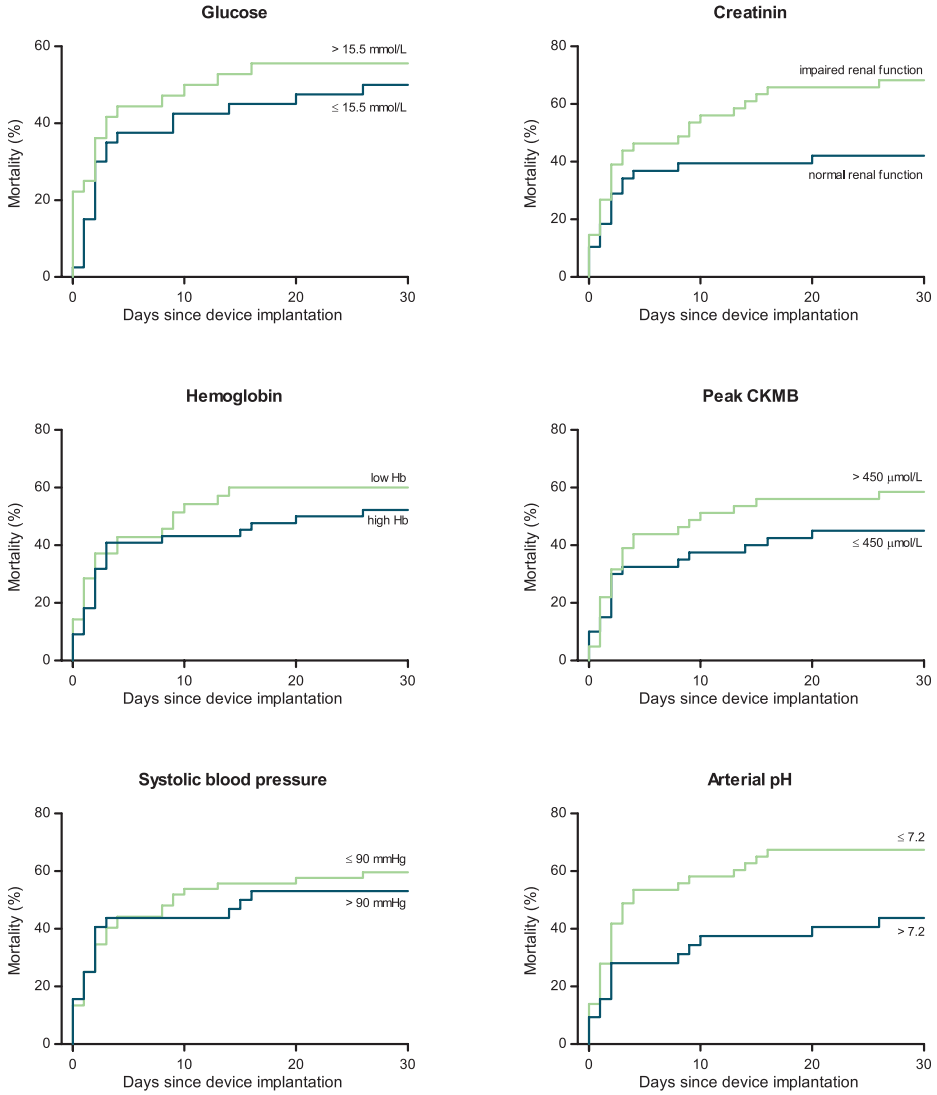
Supplementary table 1 Baseline characteristics according to moment of device placement. (continued)

	All patients n=112	**Impella before revascularisation** n=21	**Impella directly after revascularisation** n=67	**Delayed Impella placement** n=24	*p*
Blood values					
Lactate (mmol/L)	6.2 [3.6-9.7]	7.7 [4.2-9.6]	6.4 [3.8-10.4]	4.1 [2.8-8.6]	0.338
Hemoglobin (mmol/L)	8.4 [7.5-9.4]	8.4 [7.4-9.0]	8.7 [7.6-9.4]	7.9 [6.9 - 9.7]	0.526
Creatinine (mg/dL)	114 [90-136]	111 [98-134]	110 [89-128]	131 [94 - 169]	0.123
Glucose (mmol/L)	13.4 [9.8-18.3]	13.8 [11.0-18.0]	15.4 [11.1-20.3]	10.5 [8.4-13.0]	0.006
Arterial pH	7.21 [7.07-7.31]	7.22 [6.94 - 7.34]	7.18 [7.05-7.28]	7.28 [7.21-7.41]	0.002
Mechanical circulatory support					
Impella device					<0.001
Impella 2.5	40 (37.5)	8 (38.1)	27 (40.3)	5 (20.8)	
Impella CP	52 (46.4)	11 (52.4)	34 (50.7)	7 (29.2)	
Impella 5.0	20 (17.9)	2 (9.5)	6 (9.0)	12 (50.0)	
IABP between primary PCI and Impella placement, n (%)	22 (19.6)	-	12 (17.9)	10 (41.7)	0.002

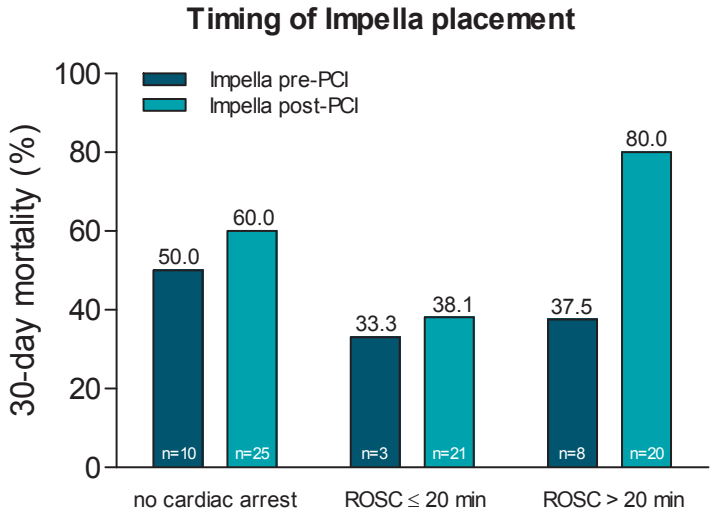
*p-value for the comparison between the moment of Impella placemen. Data are displayed as percentile (frequency), mean ± standard deviation or median [25th percentile - 75th percentile]. VF: ventricular fibrillation; VT: ventricular tachycardia; PCI: percutaneous coronary intervention; CABG: coronary artery bypass grafting; AED: Automated External Defibrilator. * > 50% stenosis in non-culprit vessel*



Supplementary Figure 1 Kaplan Meier curves for different variables.
Univariate factors in patients in whom Impella therapy was initiated during the same procedure as the primary PCI.

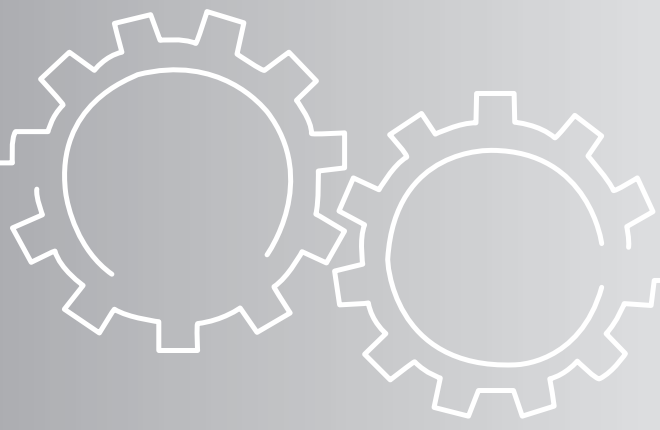


Supplementary Figure 1 (continued) Kaplan Meier curves for different variables.
Univariate factors in patients in whom Impella therapy was initiated during the same procedure as the primary PCI.



Supplementary Figure 2 Timing of initiation of Impella therapy grouped by cardiac arrest duration.

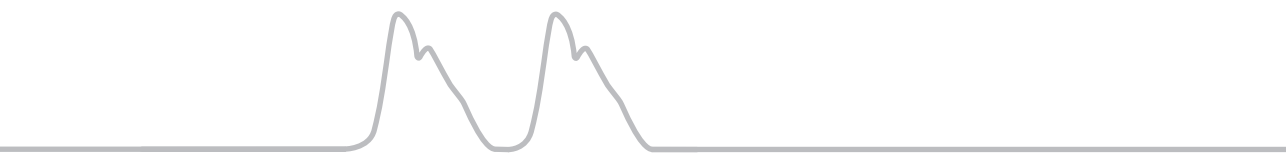
CHAPTER 6



HET BESCHADIGDE HART:

ONDERSTEUNING EN HERSTEL MET HET IMPELLA-SYSTEEM 5 JAAR LATER

Dagmar M. Ouweneel, Wim K. Lagrand, Bas A.J.M. de Mol, José P.S. Henriques



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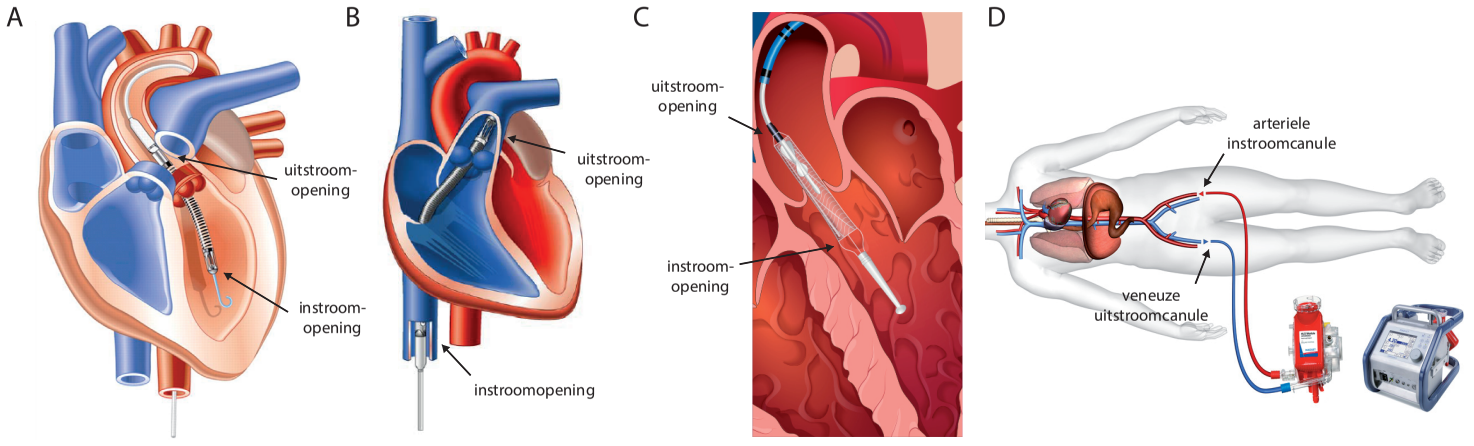
SAMENVATTING

Tijdelijke mechanische ondersteuning van het hart wordt steeds vaker toegepast, met name bij patiënten met cardiogene shock of tijdens een hoog-risico dotterprocedure. In de afgelopen 5 jaar zijn er veel ontwikkelingen geweest op dit gebied. Er is steeds meer ervaring opgedaan in het gebruik van deze tijdelijke hartpompen en daarnaast zijn er meer nieuwe pompen op de markt gekomen. De intra-aortale ballonpomp was tot voor kort de standaardbehandeling bij cardiogene shock, maar door nieuwe onderzoeksresultaten naar de effectiviteit van de ballonpomp wordt deze pomp steeds minder gebruikt. In de afgelopen jaren heeft de Amerikaanse FDA toestemming gegeven voor het gebruik van Impella in cardiogene shock. In Nederland wordt behandeling met een Impella bij cardiogene shock sinds 2012 door de zorgverzekering vergoed.

TECHNIEK

De Impella is een hartpomp die de functie van het hart tijdelijk kan ondersteunen. Het is een kleine pomp (ongeveer zo groot als een balpen), vastgemaakt op een katheter en kan via de lies naar het hart worden opgevoerd[1]. Buiten het lichaam wordt de katheter aangesloten op een console, waarmee de instellingen van de pomp geregeld worden.
In de afgelopen jaren is de Impella pomp verder ontwikkeld en zijn er nu verschillende versies beschikbaar gekomen. Voor het ondersteunen van de linker harthelft zijn er 3 versies. De Impella 2,5 en de Impella CP kunnen respectievelijk 2,5 en 3,7 liter per minuut pompen. De Impella 5,0 kan 5 liter per minuut pompen maar moet, door de grotere diameter van de pomp, door de chirurg in de liesarterie worden ingebracht. Om de rechterkamer te ondersteunen kan de rechterkamer Impella worden gebruikt (Figuur 1). Deze pomp wordt veneus in de lies ingebracht en kan het bloed met 4 liter per minuut van de vena cava inferior naar de arteria pulmonalis pompen.



Figuur 1 Voorbeelden van tijdelijke hartpompen die via de lies kunnen worden ingebracht
A) de linker kamer Impella (Abiomed Inc), B) de rechter kamer Impella (Abiomed Inc), C) de Heartmate PHP (St. Jude Medical), D) ECMO (CardioHelp, Maquet).

WAT IS ER VERANDERD?

Cardiogene shock

Mechanische ondersteuning van het hart wordt voornamelijk gebruikt bij patiënten in cardiogene shock, bijvoorbeeld na een hartinfarct of bij een gecompliceerd beloop na hartchirurgie. De intra-aortale ballonpomp was de standaard behandeling op het gebied van mechanische hartondersteuning. In de afgelopen jaren zijn er grote veranderingen geweest in het gebruik van de ballonpomp nadat er in een grote gerandomiseerde studie met 600 patiënten met cardiogene shock na een STEMI werd aangetoond dat het gebruik van de ballonpomp niet resulteerde in een verbetering van de overleving.[2] Mede door deze resultaten wordt het routine gebruik van de ballonpomp bij cardiogene shock na een hartinfarct niet meer aanbevolen in de Europese richtlijnen. Door de veronderstelde verbetering van coronaire circulatie wordt de ballonpomp voor andere indicaties nog steeds gebruikt.

De Europese richtlijnen geven aan dat ondersteuning met een hartpomp kan worden overwogen. Het Impella platform biedt een krachtigere circulatie ondersteuning ten opzichte van de ballonpomp. Echter, recent liet een kleine gerandomiseerde studie uit het AMC zien, dat er geen verschil is in overleving tussen ballonpomp en Impella in beademde patiënten met cardiogene shock. In deze studie was de overleving op 30 dagen 50%. Er waren weinig complicaties Een grotere gerandomiseerde wordt op dit moment nog uitgevoerd. Een grote registratie studie heeft aangetoond dat het vroeg plaatsen van de Impella, al voor de dotterprocedure of zo snel mogelijk erna, resulteert in een betere overleving. Onlangs heeft de Amerikaanse FDA toestemming gegeven voor het gebruik van Impella bij cardiogene shock.

Hoog risico procedures

Tijdens hoog-risico procedures kan mechanische ondersteuning worden toegepast om te voorkomen dat er hemodynamische instabiliteit ontstaat tijdens de behandeling, bijvoorbeeld bij dotterbehandelingen of ablaties. In een gerandomiseerde studie waarin de ballonpomp werd vergeleken met de Impella 2.5 tijdens dotterprocedures werd er geen verschil aangetoond. Wanneer de eerste patiënt van elke ziekenhuis niet werd meegenomen in de analyse, was het gebruik van Impella geassocieerd met betere klinische uitkomsten. Dit laat zien dat er ook voor het gebruik van de Impella een leercurve bestaat. Ervaring en patiënten-selectie is een essentieel voor een succesvol programma voor gebruik van alle tijdelijke hartpompen.[3]

GEBRUIK VAN HARTPOMPEN

De richtlijnen geven aan dat het gebruik van een tijdelijke hartpomp kan worden overwogen bij cardiogene shock. Er komen daarom steeds meer soorten hartpompen op de markt en er is steeds meer ervaring met het gebruik van deze pompen[4]. De nieuwere Heartmate PHP pomp (St Jude Medical) lijkt op de Impella pomp en ook geschikt is voor tijdelijk ondersteunen van de linker ventrikel. Daarnaast wordt ECMO (een verkleinde hart-long machine die via de lies kan worden geplaatst) ook steeds vaker gebruikt bij linkerventrikel- en rechterventrikelfalen. De pompen worden vooral gebruikt bij cardiogene shock, maar er komt ook steeds meer ervaring met het gebruik bij andere indicaties, zoals bijvoorbeeld tijdens reanimatie[5]. Bij (vaak gereanimeerde en) diepe cardiogene shock patiënten blijft de mortaliteit rond de 50%. De complicaties die voorkomen zijn vooral het gevolg van de grootte van de pompen en de plaats waar ze worden ingebracht, zoals vasculaire complicaties (9.7%), ischemie van het been (3.9%) en hemolyse (10.3%).[6]

IMPELLA IN NEDERLAND

In Nederland wordt de Impella in meerdere ziekenhuizen gebruikt. In het AMC zijn er van 2004 tot en met 2015 in totaal 246 patiënten met Impella behandeld (tabel 1). In Nederland wordt vooral de Impella 2,5 gebruikt voor hoog-risico dotterprocedures en de Impella CP en Impella 5.0 voor cardiogene shock. Sinds 2012 wordt het percutaan inbrengen van een hartpomp door de zorgverzekering vergoed. Het gebeurt steeds vaker dat patiënten naar een Impella ziekenhuis worden verwezen voor het plaatsen van een Impella bij cardiogene shock of bij hoog-risico dotterprocedures. Daarbij is het belangrijk, in het geval van cardiogene shock, dat de Impella behandeling zo vroeg mogelijk wordt gestart en dat de patiënten tijdig worden overgeplaatst.

Table 1 Toepassing van de Impella hartpomp in het AMC.
Toegespitst op de indicaties voor behandeling (periode: 1-jan 2004 – 1 jan 2015)

Indicatie	Aantal behandelde patiënten
Hoogrisico dotterbehandeling	68
Cardiogene shock na hartinfarct	116
Cardiogene shock na hartchirurgie	27
Overige	35

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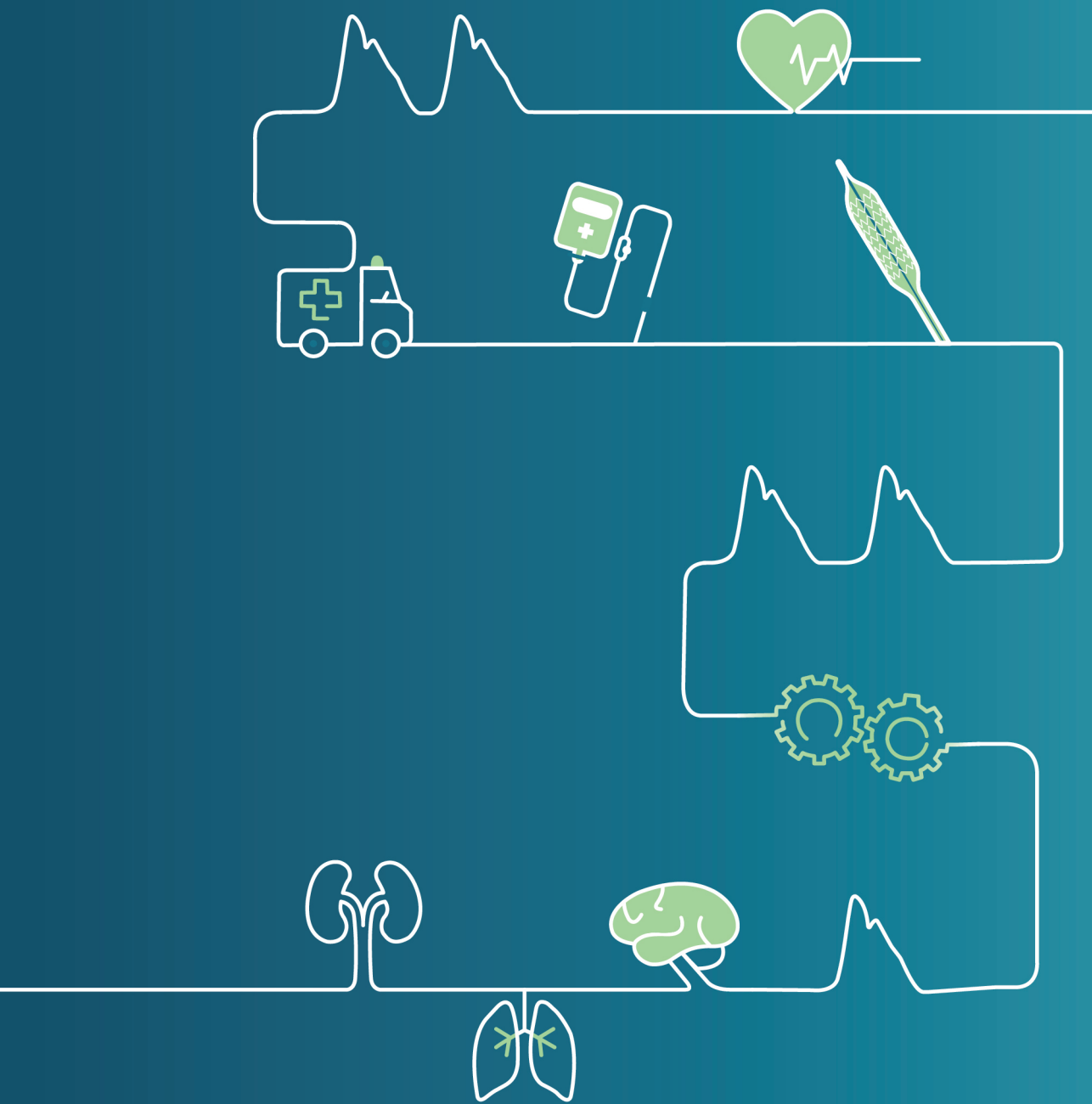
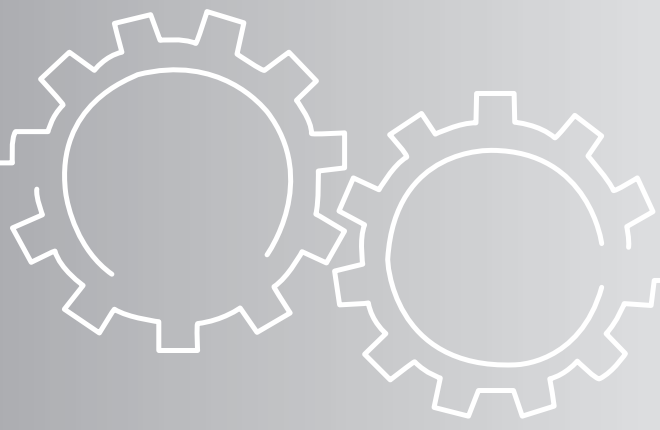


PART II

HEMODYNAMIC SUPPORT WITH IMPELLA: RANDOMISED DATA

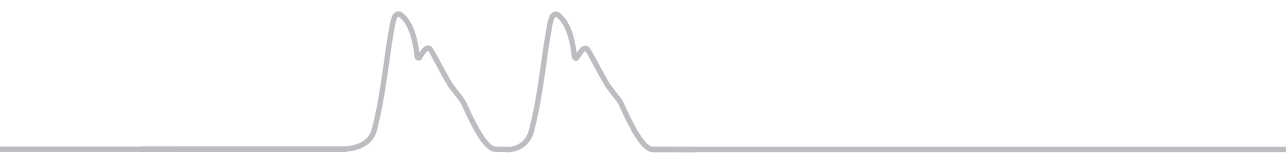
CHAPTER 7



EXPERIENCE FROM A RANDOMISED CONTROLLED TRIAL WITH IMPELLA 2.5 VERSUS IABP IN STEMI PATIENTS WITH CARDIOGENIC PRE-SHOCK.

LESSONS LEARNED FROM THE IMPRESS IN STEMI TRIAL

Dagmar M. Ouweneel, Annemarie E. Engström, Krischan D. Sjauw, Alexander Hirsch, Jonathan M. Hill, Bernard Gockel, Vegard Tuseth, René van der Schaaf, José P.S. Henriques



International Journal of Cardiology. 2016 Jan 1;202:894-6

TO THE EDITOR

Cardiogenic shock occurs in approximately 6-10% of patients with acute ST-segment elevation myocardial infarction (STEMI).[1] Anterior STEMI patients with high heart rate or low systolic blood pressure may qualify as pre-shock patients and until recently these patients were frequently supported with an intra-aortic balloon pump (IABP). However, routine usage of the IABP patients with anterior STEMI and cardiogenic shock is not associated with clinical benefit and is no longer recommended.[2-4] Therefore, research is currently directed at potentially more powerful devices for percutaneous mechanical circulatory support.[5] However, evidence from randomized controlled trials is scarce, as this patient population is difficult to identify and study.

The purpose of the "IMPella versus IABP REduceS infarct Size IN STEMI patients treated with primary PCI" (IMPRESS in STEMI) trial was to study the impact of support with Impella 2.5 compared with IABP after primary PCI in pre-shock anterior STEMI patients on left ventricular ejection fraction after 4 months. In this multi-center, international, randomized controlled trial we aimed to include 130 primary PCI patients with anterior wall STEMI and clinical signs of cardiogenic pre-shock. However, this trial was stopped prematurely due to insufficient inclusion of this difficult patient category. Between January 2008 and July 2011, a total of 21 patients were randomized to either Impella (n=12) or IABP (n=9) in 5 centers. The small number of patients enrolled does not render an appropriate assessment of the clinical results The data are presented in the supplementary file. However, we would like to share our experience and difficulties in performing a randomized trial in pre-shock patients using a relative new device. We therefore summarized a few lessons learned from the Impress in STEMI trial.

The Impella 2.5 device is a micro-axial rotary pump that is placed across the aortic valve expelling aspirated blood from the left ventricle into the ascending aorta and delivers up to 2.5 L/min of antegrade flow.[6] It previously demonstrated safety and feasibility and directly unloads the left ventricle to improve coronary circulation and provides superior hemodynamic support compared with the IABP.[6-9]

Cardiogenic pre-shock was defined as a heart rate >100/min and/or systolic blood pressure <100 mmHg with clinical signs of shock (cold extremities, cyanosis, oliguria, decreased mental status). Main exclusion criteria were full blown cardiogenic shock, left ventricular thrombus and primary PCI more than 12 hours after onset of symptoms. Patients were randomized to IABP or Impella 2.5 therapy after primary PCI.

After oral informed consent was obtained, the patient was randomized to either treatment with the Impella device or IABP in a 1:1 ratio. Eligible patients were randomly assigned to one of the hemodynamic assist devices. The targeted support time with either IABP or Impella 2.5 was at least 96 hours, with additional support time if required

by clinical condition and at the discretion of the treating physician. Investigators were strongly discouraged to cross-over and/or to combine both treatment modalities.

LESSONS LEARNED

Training

At the start of this study in January 2008, there was limited experience with the Impella 2.5, which had recently received CE mark, especially in the acute setting. The protocol required pre-trial experience of at least 10 high-risk PCI procedures with Impella 2.5 and at least 3 acute patients who had been supported for at least 3 days, before a center could participate in this trial. Due to slow enrolment, this pre-trial experience was reduced up to just a few elective cases and a single acute case at some sites. For trials involving new devices in critical conditions, the need of training is crucial. Training with the device can initially be virtual and followed by hands-on during a more stable condition, such as during elective high-risk PCI. The need for training is important and a learning effect of the Impella device has been described before during the PROTECT 2 study which enrolled only elective high-risk PCI patients.[10] This training aspect is especially needed during long-term Impella support on the ICU. Managing hemodynamics under mechanical support requires a different clinical approach, incorporating frequent evaluation of the correct operation and position of the Impella. A recently published collaborative viewpoint from a European Impella expert user group underscores the need for training.[11]

Clinical criteria in cardiogenic shock

As cardiogenic shock is a range between early signs of heart failure or pre-shock and more severe shock, it is important to distinguish between patients and to appropriately adapt treatment options to the severity of shock. In this trial, we attempted to select only the less severe shock patients, in which Impella 2.5 could provide sufficient support.[8] The main reason for discontinuation of this study was related to difficulties in applying the inclusion criteria. Although heart rate and blood pressure are objective and easily available measures, it is less easy to define the clinical pre-shock condition within the continuum from pre-shock to severe shock. In retrospect, the design should not have included the subjectively assessed clinical sign requirement, but use objective and readily available indices.

Broadening inclusion criteria in pre-shock patients

During the trial, the inclusion criteria were broadened (Table 1), which resulted in a higher inclusion rate, but also in inclusion of more elderly patients and patients with

a more severe degree of shock resulting in higher mortality and therefore with more patients not being able to complete the 4 month MRI, which was the primary endpoint. It is worth mentioning that the collaborative European Expert viewpoint also discourages usage of Impella devices in patients over 75 years.[11]

Table 1 Lessons learned from IMPRESS in STEMI.

Training	Take the learning curve into consideration when starting a clinical trial with a relatively new device or technique. A learning curve may influence the inclusion rate and trial results.
Clinical criteria cardiogenic shock	Use clearly defined inclusion criteria that can easily be used to select patients in an emergency clinical setting
Broadening inclusion criteria	Broadening inclusion criteria may increase the inclusion rate, but on the risk of less specific patient category enrollment. The inclusion criteria should be specific for targeted patient population.
Speed of enrollment	Inclusion rates of trials on mechanical assist devices in cardiogenic shock are generally low, partly due to low incidence but also due to complexity of these cases.

Table 2 Inclusion rates in randomized controlled trials of mechanical support devices in patients with acute myocardial infarction.

Trial [¥]	Year of publication	Patients	Randomization	Number of included patients	Number of centers	Duration of trial (months)	Mean number of inclusions per center per month
Thiele	2005	Cardiogenic shock after AMI	IABP - TandemHeart	41	1	40	1.0
Burkhoff	2006	Cardiogenic shock after AMI or decompensated heart failure	IABP - TandemHeart	42	12	24	0.1
ISAR-SHOCK	2008	Cardiogenic shock after AMI	IABP - Impella 2.5	26	2	28	0.5
CRISP-AMI	2011	Acute anterior STEMI without cardiogenic shock	IABP - no IABP	337	30	20	0.6
IABP-SHOCK II trial	2012	Cardiogenic shock after AMI	IABP - medical therapy	600	37	33	0.5
University Hospital Caen Study	-	Cardiogenic shock after AMI	Standard treatment - ECLS/Impella 2.5ǂ	19	13	40 *	0.0
IMPRESS in STEMI	2015	Cardiogenic pre-shock after AMI	Impella 2.5 - IABP	21	5	42 *	0.1
IMPRESS in Severe Shock	-	Cardiogenic shock after AMI	Impella CP - IABP	47	2	30 [#, $]	1.1
Danish Cardiogenic Shock Trial (DanShock)	-	Cardiogenic shock after AMI	Impella CP - standard treatment	40	2	24 [#]	1.7

** The study was stopped prematurely due to insufficient recruitment; # Trial is ongoing;ǂ This study started with ECLS as the intervention, but switched to Impella 2.5.; $ Corrected for one center being open for 9 months;*

Table 3 Changed in- and exclusion criteria during the trial.

	Initial criteria	Renewed criteria
Inclusion criteria		
Moment of eligibility assessment and randomization	After PCI procedure and before transfer from the catheterization laboratory	Immediately before PCI (but after assessment of iliac trajectory) OR immediately after PCI OR within 12 hours after PCI
Delay between offset of chest pain and primary PCI	≤ 12 hours	≤ 36 hours
Myocardial infarction	Anterior ST-elevation MI	Suspected left coronary artery (LAD or CX) related acute MI
Definition of Cardiogenic pre-shock	Clinical signs of pre-shock (cold extremities, cyanosis, oliguria, decreased mental status)	Clinical signs of pre-shock (cold extremities, cyanosis, oliguria, decreased mental status)
	AND	*AND*
	Heart rate > 100/min AND/OR systolic blood pressure < 100 mmHg	Heart rate > 90/min AND/OR systolic blood pressure < 110 mmHg
Exclusion criteria		
Age	< 30 and > 75 years of age	< 18 years of age
Severity	Full blown cardiogenic shock , defined hemodynamically as sustained systolic blood pressure ≤ 90 mmHg despite fluid hydration with ≥ 2 low dose or 1 high dose vasopressor(s) or inotrope(s) within the last 1 hour	Mechanical ventilation at randomization

Speed of enrolment

Slow inclusion in trials including cardiogenic shock patients is very common in randomized controlled trials regarding mechanical assist devices (Table 1). This is partly due to low incidence rate. The incidence of cardiogenic shock after AMI is reported around 7% of STEMI patients.[1] The incidence of more severe shock requiring a mechanical assist device is much lower. Moreover, many cases are complex as a result of trauma or comorbidities and are usually excluded from clinical trials. Obtaining informed consent from the patient or family might also be a limited factor as the family might not be present in the hospital yet and placement of a mechanical assist device is preferred not to be delayed.

RECENT INSIGHTS

Since the start of this trial, the Impella technology itself has undergone further development not only on the 2.5 LP device itself but also with the arrival of the Impella CP enabling even better hemodynamic support (3.7 L/min) with minimal increase of size (12 vs 14 Fr). Also, improvements on the Impella console has shortened set-up, further enabling placement before primary PCI. Experimental data show that left ventricular unloading prior to PCI is associated with infarct size reduction and clinical data from the USpella registry even suggest a mortality reduction in patients supported with Impella prior to primary PCI.[12,13] For comparison, in our study protocol, only two patients received Impella support before PCI.

CONCLUSIONS

This is the first study to compare IABP and Impella 2.5 in the setting of cardiogenic preshock after acute myocardial infarction. Because the study was stopped prematurely, the small number of patients enrolled in the study preclude an appropriate interpretation of the results. However, this study shows, again, that randomized controlled trials in the emergency setting of acute MI complicated by cardiogenic shock are exceptionally difficult to conduct, especially when clinical assessment is part of the inclusion criteria. Appropriately sized randomized controlled trails are needed but difficult to execute. Lessons learned from our and previous studies should be taken into consideration when designing these studies.

FUNDING AND CONFLICTS OF INTEREST

This trial was supported by Abiomed Europe GmbH. The authors report no relationships that could be construed as a conflict of interest.

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SUPPLEMENTARY DATA

Study results

Due to insufficient inclusion of this difficult patient category the study was stopped prematurely. Due to the small number of inclusions, there was unfortunate skewness in the baseline characteristics and clinical conditions in both groups (Supplementary Table 1). More diabetic and female patients were assigned to Impella compared with IABP. Duration of mechanical support was longer when using IABP than Impella (Supplementary Table 2). Of the 21 patients, 1 patient was lost to follow-up (Impella arm) and 4 patients deceased within 4 months (3 in Impella arm, 1 in IABP arm). There was no difference in LVEF between the IABP (41.4±14%) and Impella patients (39.5±7.7%) (p=0.76) at 4 months. There was no difference in MACCE rate at 4 months and 1 year.

Supplementary Table 1 Patient characteristics.

	IABP (n=9)	**Impella** (n=12)	*p*
Clinical characteriscs and risk factors			
Age (yrs)	63 ± 13	57 ± 13	0.36
Male gender	9/9 (100)	9/12 (75)	0.23
Current smoker	4/9 (44)	7/11 (64)	0.65
Hypertension	4/9 (44)	23/12 (5)	0.40
Hypercholesterolemia	2/9 (22)	2/10 (20)	1.00
Diabetes mellitus	0/9 (0)	3/12 (25)	0.23
Family history of CAD	2/7 (29)	4/9 (44)	0.63
Medical history on admission			
Previous MI	2/9 (22)	1/12 (8)	0.55
Previous stroke	0/9 (0)	2/11 (18)	0.48
Previous TIA	0/9 (0)	1/11 (9)	1.00
Previous PCI	1/9 (11)	1/11 (9)	1.00
History of angina	1/9 (11)	1/10 (10)	1.00
History of congestive heart failure with known LVEF <30%	1/9 (11)	0/11 (0)	0.45
History of PVD	2/8 (25)	1/11 (9)	0.55
History of COPD	1/8 (13)	0/11 (0)	0.42
Hemodynamic parameters			
On admission			
Heart rate (beats/min)	85 ± 16	100 ± 21	0.12
Systolic blood pressure (mm Hg)	119 ± 22	114 ± 26	0.60
Diastolic blood pressure (mm Hg)	79 ± 17	76 ± 13	0.61

Supplementary Table 1 Patient characteristics. (continued)

	IABP (n=9)	Impella (n=12)	*p*
Before pump implantation			
Heart rate	105 ± 19	98 ± 19	0.40
Systolic blood pressure	91 ± 11	103 ± 23	0.16
Diastolic blood pressure	63 ± 9	65 ± 7	0.70
Admission laboratory values			
Glucose (mmol/L)	8.2 [7.8;9.9]	8.2 [7.3;11.2]	0.86
Creatinin (µmol/L)	84 [71;95]	81 [63;121]	1.00
Lactate (mmol/L)	1.8 [1.7;3.0]	1.5 [1.1;2.5]	0.09
Hemoglobin (mmol/L)	9.3 [8.4;9.9]	9.2 [7.7;12.4]	0.89
Treatment related characteristics			
VF before procedure	0/9 (0)	0/12 (0)	-
Ischemic time (min)	158 [113;381]	210 [163;359]	0.48
Infarct related vessel			0.53
LM	0/9 (0)	1/12 (8)	
LAD	8/9 (89)	11/12 (92)	
RCX	1/9 (11)	0/12 (0)	
Multi vessel disease	4/9 (44)	6/11 (55)	1.00
TIMI 0 flow pre-PCI	9/9 (100)	10/12 (83)	0.49
TIMI 3 flow post-PCI	7/9 (78)	10/11 (91)	0.57
Moment of device placement			0.27
Before PCI	0/9 (100)	2/12 (17)	
Directly after PCI	9/9 (0)	9/12 (75)	
Within 12 hours after PCI	0/9 (0)	1/12 (8)	

Values are depicted as n (%), n/n (%), mean ± standard deviation or median [Q1-Q3]. CAD: coronary artery disease; COPD: chronic obstructive pulmonary disease; IABP: intra-aortic balloon pump; LAD: left anterior descending artery; LM: left main artery; LVEF: left ventricular ejection fraction; MI: myocardial infarction; PCI: percutaneous coronary intervention; PVD: peripheral vascular disease; RCX: ramus circumflexus; TIA: transient ischemic attack; TIMI: thrombolysis in myocardial infarction; VF: ventricular fibrillation.

Supplementary Table 2 Clinical course and outcome.

	IABP (n=9)	Impella (n=12)	*p*
Mechanical circulatory support			
Duration of mechanical support (hours)	81 ± 18	49 ± 37	0.03
Upgrade to other device	0 (0)	1 (8)	1.00
Clinical course			
Number of patients on ICU	2 (22)	5 (46)	0.37
Days of hospitalisation	8.0 ± 3.1	8.9 ± 6.8	0.70
Number of patients on mechanical ventilation	0 (0)	4 (36)	0.10
Duration of mechanical ventilation (days)	-	1.5 [1;16.3]	-
Need for inotropic therapy	2 (22)	4 (33)	0.66
Duration of inotropic therapy (days)	0 [0;2]	0 [0;1.75]	0.75
Peak CKMB (µmol/L)	419 ± 136	428 ± 283	0.93
Need for renal replacement therapy	0 (0)	2 (18)	0.48
Severe vascular events during hospitalisation	0 (0)	3 (25)	0.23
Hemolysis during hospitalisation	0 (0)	1 (8)	1.00
Ventricular arrhythmias during hospitalisation	1 (11)	1 (8)	1.00
Refractory cardiogenic shock	0 (0)	3 (25)	0.23
Severe bleeding during hospitalisation	0 (0)	1 (8)	1.00
Stroke (hemorrhagic)	0 (0)	1 (8)	1.00
Transient Ischemic Attack (TIA)	1 (11)	0 (0)	1.00
MRI outcome*			
LV ejection fraction (%)	41.4 ± 14	39.5 ± 7.7	0.76
LV end-diastolic volume (ml)	196 ± 51	232 ± 30	0.12
LV end-systolic volume (ml)	121 ± 66	142 ± 34	0.45
LV stroke volume (ml)	75 ± 19	90 ± 10	0.08
LV stroke volume index (ml/m^2)	38 ± 10	47 ± 8	0.07
LV cardiac output (l/min)	5.4 ± 1.4	6.4 ± 1.6	0.26
LV cardiac index (l/min/m^2)	2.8 ± 0.7	3.4 ± 1.1	0.24
Infarct mass (% of LV mass) **	24.4 ± 4.8	24.4 ± 8.1	1.00
Composite of death, myocardial infarction, target vessel revascularization and stroke (MACCE) by Kaplan-Meier estimates			
4 months	3 (33)	3 (26)	0.74
1 year	4 (47)	4 (37)	0.72
3 years	4 (47)	4 (37)	0.72
Mortality by Kaplan-Meier estimates			
4 months	1 (11)	3 (26)	0.37
1 year	1 (11)	3 (26)	0.37
3 years	2 (22)	3 (26)	0.73
NYHA class I			
4 months	6/7 (86)	2/6 (33)	0.10
1 year	5/7 (71)	3/5 (60)	1.00

*All values are depicted as n (%), mean ± standard deviation or median [Q1-Q3]. * measured in 15 patients (7 Impella and 8 IABP), ** measured in 12 patients (6 Impella and 6 IABP patients). CKMB: creatinine kinase myocardial band; IABP: intra-aortic balloon pump; ICU: intensive care unit; LV: left ventricular; NYHA: New York Heart Association;*

Complications

There were 3 patients in the Impella group who had a severe vascular event, 2 patients due to blood oozing along the femoral sheet requiring blood transfusion and 1 patient developed leg ischemia requiring extraction of the device (Supplementary Table 2). One IABP patient experienced leg ischemia after the IABP having been already removed. Refractory cardiogenic shock developed in 3 patients in the Impella group, of which 1 patient recovered and 2 patient deceased (despite the upgrade to an Impella 5.0 in one patient). An unexpected device failure occurred in the first patient of the study, which was reported to the ethical committee. After thorough investigation, the device was revised and the study was continued.

Inclusion rate

Randomized controlled trials of mechanical support devices in acute myocardial infarction mentioned in table 1.

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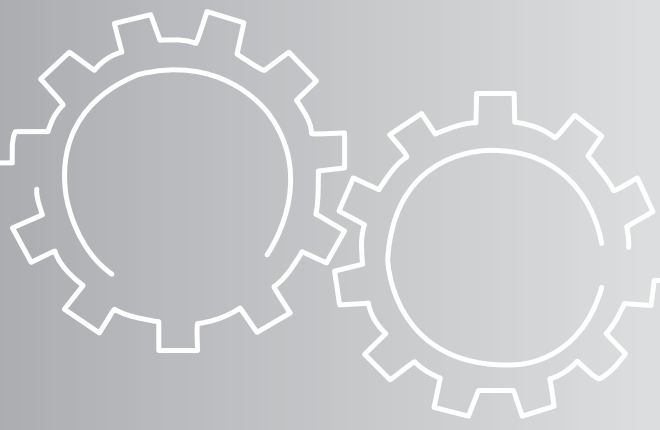
CHAPTER 8



PERCUTANEOUS MECHANICAL CIRCULATORY SUPPORT VERSUS INTRA-AORTIC BALLOON PUMP IN CARDIOGENIC SHOCK AFTER ACUTE MYOCARDIAL INFARCTION

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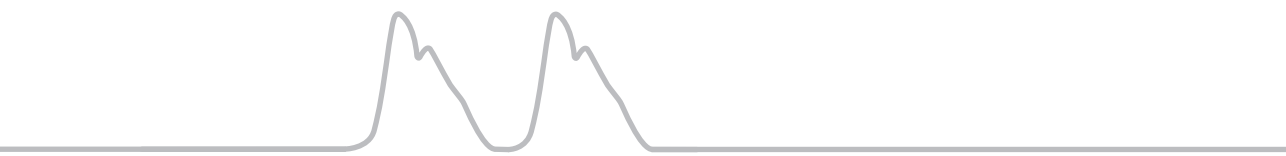

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ABSTRACT

Background

Despite advances in treatment, mortality in acute myocardial infarction (AMI) complicated by cardiogenic shock (CS) remains high. Short-term mechanical circulatory support devices acutely improve hemodynamic conditions.

Objectives

The aim of this study was to determine whether a new percutaneous mechanical circulatory support (pMCS) device (Impella CP, Abiomed, Danvers, Massachusetts) decreases 30-day mortality when compared with an intraaortic balloon pump (IABP) in patients with severe shock complicating AMI.

Methods

In a randomized, prospective, open-label, multicenter trial, 48 patients with severe CS complicating AMI were assigned to pMCS (n = 24) or IABP (n = 24). Severe CS was defined as systolic blood pressure <90 mm Hg or the need for inotropic or vasoactive medication and the requirement for mechanical ventilation. The primary endpoint was 30-day all-cause mortality.

Results

At 30 days, mortality in patients treated with either IABP or pMCS was similar (50% and 46%, respectively; hazard ratio with pMCS: 0.96; 95% confidence interval: 0.42 to 2.18; p = 0.92). At 6 months, mortality rates for both pMCS and IABP were 50% (hazard ratio: 1.04; 95% confidence interval: 0.47 to 2.32; p = 0.923).

Conclusions

In this explorative randomized controlled trial involving mechanically ventilated patients with CS after AMI, routine treatment with pMCS was not associated with reduced 30-day mortality compared with IABP.

Despite advances in treatment, mortality in acute myocardial infarction (AMI) complicated by cardiogenic shock (CS) remains high.[1-4] Short-term mechanical circulatory support devices can be deployed to support the endangered circulation. Intra-aortic balloon counterpulsation (IABP) has been the most widely used mechanical circulatory support device for decades. [5] A meta-analysis of smaller-sized studies and a large randomized controlled trial did not show a beneficial effect of IABP in the setting of CS after AMI.[4,6,7] Today, IABP usage has a Class IIb recommendation in American guidelines and a Class III recommendation in European guidelines. [8-11] The lack of efficacy of the IABP is likely to be, at least partly, the reason for the observed increased usage of more potent mechanical circulatory devices. [5,12]

The percutaneous Impella platform (Abiomed, Danvers, Massachusetts) consists of the Impella 2.5 (maximum output 2.5 l/min) and Impella CP (maximum output around 3.7 l/min). It has been shown that Impella support in the acute situation is feasible and provides greater hemodynamic support when compared with IABP. [13-16] However, neither of the 2 small randomized trials in patients with AMI had enough power to show differences in clinical outcomes, and 1 was prematurely stopped.[15,16] The IMPRESS in Severe Shock (IMPella versus IABP Reduces mortality in STEMI patients treated with primary PCI in Severe cardiogenic SHOCK) trial is an exploratory assessment of mortality and other safety outcomes comparing percutaneous mechanical circulatory support (pMCS) by the Impella CP with IABP in mechanically ventilated patients with CS in AMI.

METHODS

Study design

The Academic Medical Center in Amsterdam designed and sponsored this multicenter, open-label, and randomized trial. Trial administration, data management, and statistical analysis were performed by the sponsor. The executive committee had unrestricted access to the data, and the authors analyzed the data and prepared the paper. The trial design was approved by the ethics committee at each participating center. The ethics committee waived the requirements for written informed consent before randomization to prevent treatment delay in patients who were in imminent danger of death. The requirement for obtaining informed consent to use the data varied depending on local ethical requirements. Informed consent was obtained from the legal representative without any undue delay. Alternatively, informed consent was obtained after recovery (and therefore, no informed consent was obtained in patients who died). An independent data and safety monitoring board and the ethics committees reviewed the interim results after each 10 included patients. During the inclusion period of the trial, the European Society of Cardiology guidelines for routine use of the IABP changed

from Class II (may be considered) to Class III (not recommended)[10]. The ethics committees were notified of this change and approved continuation of the trial. The study was conducted in accordance with the provisions of the Declaration of Helsinki as amended in Edinburgh, Scotland.[17]

Patients

Patients were eligible for the trial if they presented with an AMI with ST-segment elevation complicated by severe CS in the setting of immediate percutaneous coronary intervention (PCI). Severe CS was defined as a systolic blood pressure <90 mmHg for longer than 30 min or the need for inotropes or vasopressors to maintain a systolic blood pressure >90 mm Hg. To select a patient population in even worse condition, patients only qualified if they were mechanically ventilated before randomization. Exclusion criteria were: severe aorto-iliac arterial disease impeding placement of either IABP or pMCS, known severe cardiac aortic valvular disease, serious known concomitant disease with a life expectancy of <1 year, known participation in this study or any other trial within the previous 30 days, or coronary artery bypass grafting within the preceding week.

Treatment

Eligible patients were assigned to treatment with pMCS by Impella CP with IABP (control group). Randomization was performed in a 1:1 ratio using an internet-based application. The moment of initiation of pMCS or IABP (before, during, or immediately after the PCI) was at the discretion of the treating physician. To achieve equal initiation of therapy for both groups, timing of randomization was equal to pMCS or IABP placement: immediately before, during, or after PCI. All patients underwent primary PCI. In multivessel disease, the mode of revascularization (immediate or staged PCI of the nonculprit lesions) was left to the discretion of the operator. Duration of mechanical support was left to the discretion of the treating physician, and IABP or the pMCS device was extracted in accordance with daily clinical routine. Weaning was achieved by reduction of the trigger ratio (IABP) or amount of support (pMCS). Per protocol, crossover was not allowed; however, it did occur.

Outcomes

The primary study endpoint was 30-day all-cause mortality. The secondary endpoint was 6-month mortality. Descriptive endpoints included duration of mechanical ventilation; the need for and duration of inotropic and vasopressor therapy; renal replacement therapy; length of hospital stay; the amount of blood products needed; additional treatments, such as ICD placement and the need for surgical left ventricular assist device (LVAD) placement or heart transplantation; the occurrence of stroke, myocardial reinfarction, repeat PCI, coronary artery bypass grafting, major vascular complications,

major bleeding, or hemolysis requiring extraction of the IABP or pMCS; device failure requiring extraction of the pMCS or IABP; and rehospitalization. Definitions can be found in the supplementary file. An independent clinical event committee adjudicated the events. Imaging parameters were assessed by independent local core laboratories that were blinded to the other trial data and randomization outcome (Supplementary data).

Statistical analysis

On the basis of previous studies and our experience that survival is <10% in patients with severe shock, we assumed that treatment with pMCS would decrease the absolute 30-day mortality rate from 95% to 60%. On the basis of this assumption, a trial with 24 patients in each group would achieve 80% power, with a 2-sided alpha of 5%. The protocol allowed for a sample-size re-estimation after inclusion of 32 patients. At the interim analysis, mortality in the control group was much lower than anticipated, and there was no difference in mortality between the treatment groups. Therefore, adaptation of the sample size was not meaningful, and the Executive Committee decided to complete the study with 48 patients as an exploratory safety study.

All data were analyzed according to the intention-to- treat principle. In addition, a per-protocol analysis of the primary endpoint was performed. Cumulative mortality throughout the first 6 months following randomization was characterized with the use of Kaplan-Meier plots, with the log-rank test used for the comparison between the 2 groups. Descriptive endpoints and clinical course variables were not statistically tested because they are highly influenced by the number of deceased patients in both groups. Additional comparisons were made according to vital status at 30 days. Differences were assessed with the Fisher exact test or the chi-square test for binary endpoints and a Mann-Whitney U test for quantitative endpoints.

A post hoc subgroup analysis was performed in subgroups defined according to age (<75 or >75 years), sex, time to return of spontaneous circulation (ROSC) (>20 or <20 min), lactate level >7.5 or <7.5 mmol/l, TIMI (Thrombolysis In Myocardial Infarction) flow post-PCI, systolic blood pressure before IABP or pMCS placement (>80 or <80 mm Hg), and the presence or absence of traumatic injuries on admission.

RESULTS

Patients

Between June 1, 2012, and September 15, 2015, a total of 48 patients were randomly assigned to either pMCS therapy (n ¼ 24) or IABP (n ¼ 24) (Figure 1). The baseline characteristics of the 2 groups were well balanced (Table 1). The mean age was 58 years,

79% were male, all patients were mechanically ventilated, 96% of the patients received catecholamines, and 92% had had a cardiac arrest before randomization.

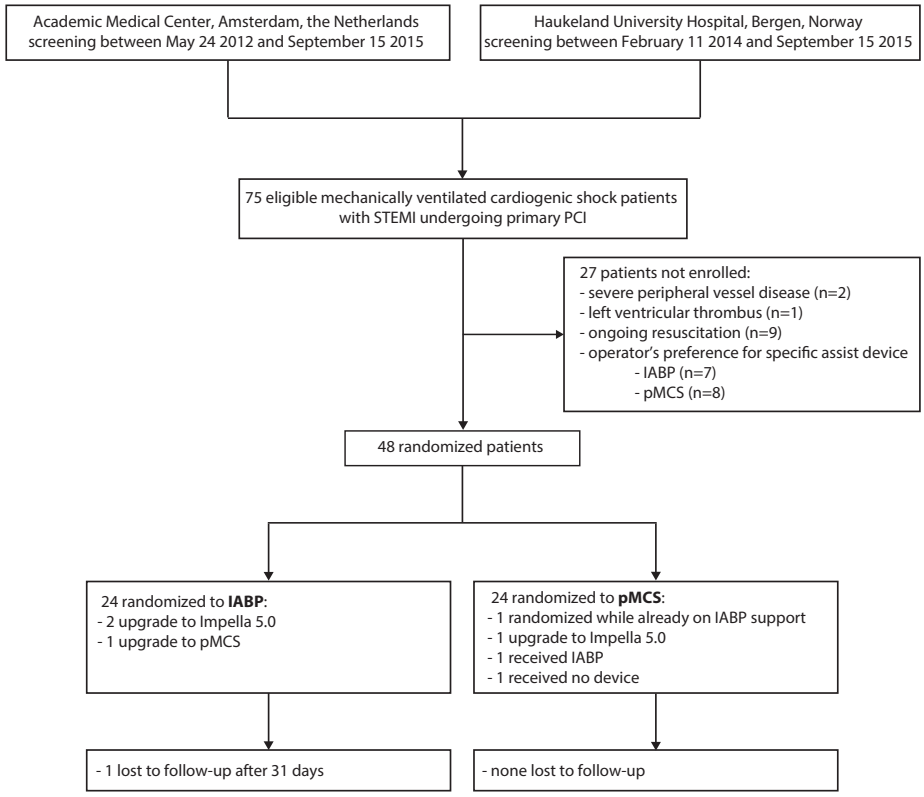

Figure 1 Flowdiagram

Table 1 Baseline characteristics.

	Impella CP (n=24)	IABP (n=24)
Age (years)	58 ± 9	59 ± 11
Male sex, n/n (%)	18/24 (75)	20/24 (83)
Body mass index (kg/m2)	25 [23-26	26 [25-27]
Cardiovascular risk factors, n/n (%)		
Current smoking	11/18 (61)	6/19 (32)
Hypertension	4/20 (20)	6/21 (29)
Hypercholesterolemia	4/20 (20)	5/21 (24)
Diabetes mellitus	2/22 (9)	3/23 (13)
Prior myocardial infarction, n/n (%)	1/22 (5)	1/23 (4)
Prior stroke, n/n (%)	0/22 (0)	1/23 (4)
Known peripheral arterial disease, n/n (%)	2/23 (9)	0/23 (0)
Prior PCI or CABG, n/n (%)	1/22 (5)	0/23 (0)
Hemodynamic variables before randomization		
Heart rate (beats/min)	81 ± 21	83 ± 28
Mean arterial pressure (mm Hg)	66 ± 15	66 ± 15
Systolic blood pressure (mm Hg)	81 ± 17	84 ± 19
Diastolic blood pressure (mm Hg)	58 ± 22	57 ± 13
Medical therapy before randomization		
Catecholamines or inotropes, n/n (%)	24/24 (100)	22/24 (92)
Mechanical ventilation, n/n (%)	24/24 (100)	24/24 (100)
Cardiac arrest before randomization, n/n (%)	24/24 (100)	20/24 (83)
Witnessed arrest, n/n (%)	22/24 (92)	17/20 (85)
First rhythm VT/VF, n/n (%)	22/24 (92)	17/20 (85)
Time till return of spontaneous circulation (min)	21 [15-46]	27 [15-52]
Traumatic injuries at admission, n/n (%)	5/24 (21)	2/24 (8)
Blood values on admission [$]		
Lactate (mmol/L)	7.5 ± 3.2	8.9 ± 6.6
Hemoglobin (mmol/L)	8.6 ± 1.2	8.6 ± 1.2
Creatinine (mg/dL)	96 ± 29	102 ± 22
Glucose (mmol/L)	16.2 ± 4.7	14.1 ± 5.3
Arterial pH	7.14 ± 0.14	7.17 ± 0.17
Baseline echocardiography *		
Estimated left ventricular ejection fraction, n/n (%)		
< 20%	5/22 (23)	8/18 (44)
20-40%	10/22 (46)	6/18 (33)
> 40%	7/22 (32)	4/18 (22)

** First echo made during admission during the first day. In 20 patients the echocardiography was done before device placement and in 21 patients after device placement (within 24 hours). [$] Values are present for the following number of patients: lactate (21 IABP and 20 Impella), Hemoglobin (22 IABP and 21 Impella), Creatinine (23 IABP and 23 Impella), Glucose (23 IABP and 20 Impella), pH (16 IABP and 20 Impella). VF: ventricular fibrillation; VT: ventricular tachycardia. Numbers are presented as mean (± standard deviation), median [25th – 75th percentile] or frequency (percentile).*

Treatment

Randomization and placement of the pMCS or IABP took place after revascularization except for 8 patients in whom IABP or the pMCS was initiated before revascularization (3 in the IABP group and 5 in the pMCS group) (Table 2). The infarct related artery was the left anterior descending (LAD) in the majority of the patients (65%) and 98% of the patients were treated with stent placement. The median duration of circulatory support was 48 h (IABP) and 49 h (pMCS). All patients were treated with catecholamines during admission to the intensive care unit, 31% received renal replacement therapy, and 75% were treated with therapeutic hypothermia (Table 3).

Table 2 Procedural characteristics.

	Impella CP (n=24)	**IABP** (n=24)
Moment of device placement		
Device placement before revascularization, n/n (%)	5/24 (21)	3/24 (13)
Device placement after revascularization, n/n (%)	19/24 (80)	21/24 (88)
Infarct-related artery, n/n (%)		
Left main	1/24 (4)	2/24 (8)
Left anterior descending	16/24 (67)	15/24 (63)
Left circumflex	6/24 (25)	3/24 (13)
Right coronary artery	1/24 (4)	4/24 (17)
Multi-vessel disease *	15/24 (63)	21/24 (88)
Immediate PCI of non-culprit lesion, n/n (%)	3/15 (20)	4/21 (19)
Stent placement	23/24 (96)	24/24 (100)
Drug-eluting stent, n/n (%)	22/23(96)	22/24 (92)
Bare Metal Stent, n/n (%)	1/23 (4)	2/24 (8)
TIMI flow pre-PCI, n/n (%)		
0 or 1	20/24 (83)	20/24 (83)
2 or 3	4/24 (17)	4/24 (17)
TIMI flow post-PCI, n/n (%)		
0 or 1	1/24 (4)	0/24 (0)
2 or 3	23/24 (96)	24/24 (100)
Syntax score pre-PCI	23.2 ± 8.7	28.2 ± 10.6

** > 50% stenosis in non-culprit vessel. Numbers are presented as frequencies (percentages) or mean (± standard deviation).*

Table 3 Clinical course during admission.

	Impella CP (n=24)	**IABP** (n=24)
Mechanical circulatory support		
Duration of support (hours) *	49 [28-76]	48 [24-77]
Crossover or upgrading to device with more support, n/n (%) †	1/24 (4.2)	3/24 (12.5)
Other support before randomization, n/n (%) ‡	1/24 (4.2)	0/24 (0)
Mechanical ventilation		
Patients treated, n/n (%)	24/24 (100)	24/24 (100)
Duration (days since device placement)	4 [3-9]	4 [3-10]
Catecholamines		
Patients treated, n/n (%)	24/24 (100)	24/24 (100)
Number of days (days)	3 [2-6]	3 [2-5]
Inotropic therapy (dobutamine)		
Patients treated, n/n (%)	6/24 (25)	9/24 (38)
Number of days (days)	0 [0-1]	0 [0-2]
Renal replacement therapy		
Patients treated, n/n (%)	8/24 (33)	7/24 (29)
Duration (days)	17 [5-29]	7 [2-9]
Therapeutic hypothermia		
Patients treated, n/n (%)	19/24 (79)	17/24 (71)
Premature ending of therapeutic hypothermia, n/n (%)	3/19 (16)	1/17 (6)
Blood products during admission §		
Any blood products during admission, n/n (%)	11/24 (46)	8/24 (33)
Packed red blood cells		
Patients treated, n/n (%)	11/24 (46)	8/24 (33)
Number of units administered	6 [3-13]	3 [1-5]
Fresh frozen plasma, n/n (%)	3/24 (13)	0/24 (0)
Platelets, n/n (%)	4/24 (17)	1/24 (4)
Placement of implantable cardioverter defibrillator (ICD), n/n (%)	2/24 (8)	1/24 (4)
Length of stay		
Intensive care unit (days)	7 [3-16]	7 [4-10]
Hospital (days)	16 [3-26]	10 [6-24]

** sum of support duration of all given support devices, including upgrades. † One patient was upgraded from IABP to Impella CP and transferred to another hospital to receive extracorporeal life support; One patient received Impella CP and was upgraded to Impella 5.0. One patient was upgraded from IABP to Impella 5.0; One patient was upgraded from IABP to Impella 5.0 and transferred to another hospital to receive extracorporeal life support and surgical LVAD; ‡ One patient was already on IABP support before randomization and was randomized to Impella CP support. § Only blood products in the hospital of randomization are taken into account; Numbers are presented as frequencies (percentages) or median [25th – 75th percentile].*

Of the patients in the IABP group, 1 patient subsequently received pMCS and was transferred to another hospital for treatment with extracorporeal life support oxygenation. Two patients received an alternative device, the Impella 5.0 (Abiomed, Aachen, Germany), after the IABP treatment, and 1 of them received subsequent extracorporeal life support and an LVAD at another hospital. Of the patients treated with the pMCS, 1 patient subsequently received the Impella 5.0. One patient was already on IABP support before randomization (inserted before the start of the primary PCI) and was randomized after the PCI to pMCS treatment. Formally, this patient constitutes a protocol violation, as IABP therapy before randomization was an exclusion criterion. One patient did not receive pMCS as the patient showed signs of recovery after randomization to receive device therapy.

Outcomes

At 30 days, mortality was similar in patients treated with IABP and pMCS therapy: 50% and 46%, respectively (hazard ratio [HR] with pMCS therapy: 0.96; 95% confidence interval [CI]: 0.42 to 2.18; p = 0.92) (Table 4). At 6 months, the mortality rate was 50% in both groups (HR: 1.04; 95% CI: 0.47 to 2.32; p = 0.92). Only minor differences were found in an analysis restricted to the per-protocol population from which 3 patients treated with pMCS were excluded (Supplementary data). The Kaplan-Meier estimates for 6-month mortality in the per-protocol population were 52% in the IABP group and 48% in the pMCS group (HR with pMCS: 0.95; 95% CI: 0.41 to 2.21; p = 0.91).

The primary cause of death at 6 months was brain damage (46% of the deceased patients; 6 of 12 in the IABP group and 5 of 12 in the pMCS group). Death due to refractory CS occurred in 29% of the deceased patients (3 of 12 in the IABP vs. 4 of 12 in the pMCS therapy group).

In each group, 1 patient experienced an ischemic stroke during support. There was 1 major vascular complication in the pMCS group, a retroperitoneal bleeding after pMCS insertion (the patient had a calcified and stented vascular trajectory, but femoroiliac angiography seemed compatible with pMCS insertion, see Supplementary data for event specifications). There were more bleeding events during admission in the pMCS therapy group than in the IABP group (8 vs. 2, of which 3 and 1, respectively, were adjudicated as IABP or pMCS related). There were 2 patients in whom the presence of hemolysis influenced the decision to stop the pMCS support (in one patient, the pMCS support was stopped due to hemolysis in combination with an improved ejection fraction; and in the other patient, the pMCS was removed after the decision to withhold further therapy due to multiorgan failure, recurrent ventricular arrhythmia, hemolysis, and hemodynamic instability).

Table 4 Clinical and functional outcomes.

	Impella CP (n=24)	IABP (n=24)	*p*	Hazard Ratio with Impella CP (95% CI)
Mortality *				
30-day all-cause mortality	11 (46)	12 (50)	0.92	0.96 (0.42 - 2.18)
6 months all-cause mortality	12 (50)	12 (50)	0.92	1.04 (0.47 - 2.32)
Clinical outcomes at 6 months				
Cause of death				
Refractory cardiogenic shock	4 (17)	3 (13)		
Post-anoxic neurological death	5 (21)	6 (25)		
Other reason	3 (13)	3 (13)		
Stroke	1 (4)	1 (4)		
Hemorrhagic stroke	0 (0)	0 (0)		
Ischemic stroke	1 (4)	1 (4)		
Major vascular complication	1 (4)	0 (0)		
Major bleeding	8 (33)	2 (8)		
Device related bleeding	3 (13)	1 (4)		
Retroperitoneal	1 (4)	0 (0)		
IABP/Impella puncture site	2 (8)	1 (4)		
Non-device related bleeding	5 (21)	1 (4)		
Gastro-intestinal bleeding	0 (0)	1 (4)		
Bleeding at other puncture site	1 (4)	0 (0)		
Other location	4 (17)	0 (0)		
Hemolysis requiring extraction of the device	2 (8)	0 (0)		
Device failure requiring extraction	0 (0)	0 (0)		
Surgical LVAD placement	0 (0)	1 (4)		
Heart transplantation	0 (0)	0 (0)		
Other surgery	2 (8)	0 (0)		
Myocardial (re)infarction	1 (4)	2 (8)		
Repeat PCI	0 (0)	3 (13)		
CABG	0 (0)	1 (4)		
Re-hospitalization	5 (21)	1 (4)		
Cardiac	2 (8)	0 (0)		
Non-cardiac	3 (13)	1 (4)		
Echocardiography at 6 months $				
Left ventricular dimensions and systolic function	n=12	n=9 ^		
Ejection fraction (%)	46 ± 11	49 ± 9		
End-diastolic volume (ml)	122 ± 41	120 ± 33		
End-systolic volume (ml)	65 ± 31	61 ± 21		

** Mortality is shown as KM-estimates; $ First available echo after 2 months. Median FU time is 191 [176-297] days. ^ 1 patient wilt surgical LVAD, 1 patient lost to follow-up, 1 patient bedbound due to multiple sclerosis. Numbers are presented as frequencies (percentages). Additional information in events can be found in the supplementary data.*

Follow-up echocardiography was performed and collected in all survivors except for 3 patients: 1 received a surgical LVAD, 1 was lost to follow-up after 31 days, and 1 was bedbound due to multiple sclerosis. Left ventricular ejection fraction after 2.5 months (median 191 days) was 46 ± 11% in the pMCS group and 49 ± 9% in the IABP group.

Subgroup analysis showed no significant interaction in 30-day mortality between the IABP and pMCStreated patients with respect to age, sex, ROSC times, lactate levels on admission, moment of IABP or pMCS placement, systolic blood pressure before device placement, and traumatic injuries on admission (Supplementary data, Table 1).

When analyzing the combined study population, lower 30-day mortality rates were seen in patients who had ROSC in <20 min (19% vs. 70%; HR: 5.50; 95% CI: 1.82 to 16.58; p = 0.001) and patients with lactate level on admission lower than 7.5 mmol/l (29% vs. 60%; HR: 3.09; 95% CI: 1.09 to 8.74; p = 0.04) (Supplementary data, Table 2). A trend toward lower 30-day mortality was observed if therapy with pMCS or IABP was initiated before the primary PCI (25% vs. 53%; p = 0.16) and in patients who did not have traumatic injuries (44% vs. 71%; HR: 1.88; 95% CI: 0.70 to 5.07; p = 0.18) (Supplementary data). Trends in lactate and creatinine levels and inotrope and vasopressors usage can be seen in Figures 1 to 4. Also, characteristics of the survivors versus the nonsurvivors and more extensive cardiac function parameters are described in Supplementary Tables 3 and 4.

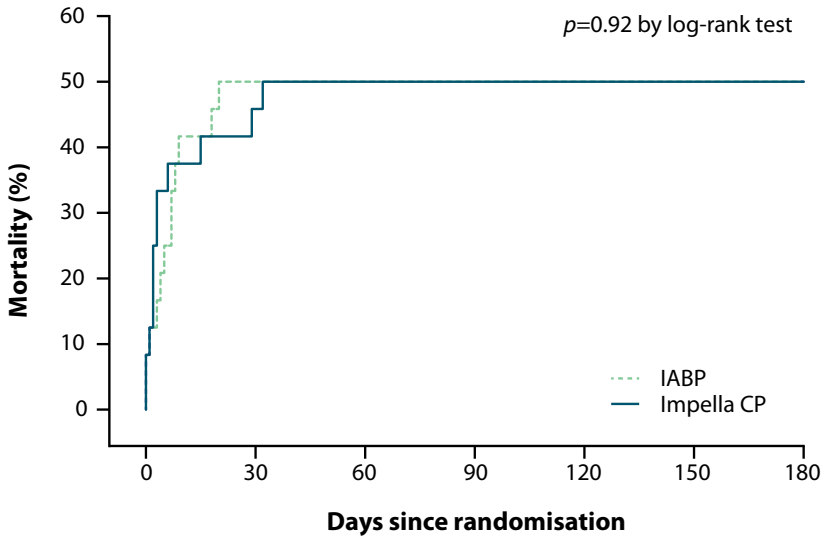

Figure 2 Kaplan-Meier curves for all-cause mortality up to 6 months

DISCUSSION

This is the first randomized trial to compare Impella CP with the IABP in mechanically ventilated patients with CS complicating AMI. pMCS support was not associated with lower 30-day or 6-month mortality when compared with IABP support. Although this trial included only 48 patients, it is thus far the largest trial to randomly compare pMCS and IABP, and it is the only trial to use the Impella CP device.

To date, only a few randomized controlled trials have studied mechanical circulatory support in CS, highlighting the logistical and ethical challenges in conducting trials in these patients. In the setting of CS, 2 small trials have been performed with the Impella 2.5 pMCS, both using IABP therapy as the control therapy. The ISAR-SHOCK (Efficacy Study of LV Assist Device to Treat Patients With Cardiogenic Shock) trial randomized 26 patients between IABP and the Impella 2.5 in the setting of CS complicating AMI. The primary endpoint was the difference in cardiac index after 30 min of support, and the trial showed a higher cardiac index in patients treated with Impella than with IABP. Overall mortality was 46% in both groups.[15] The IMPRESS in STEMI trial randomized between the IABP and Impella 2.5 in patients with cardiogenic pre-shock. This study was powered for a difference in left ventricular function. However, this trial was stopped prematurely due to a lack of enrollment after 21 patients had been enrolled.[16]

In the present trial, we included mechanically ventilated patients with CS. Although the decision to start mechanical ventilation may be arbitrary and the moment of initiation may differ between physicians, it is a marker for worse clinical condition. We have chosen to use this criterion because it is easy to apply, is readily available, and does not require blood sample analysis or additional Swan-Ganz cardiac output measurements. Those inclusion criteria resulted in inclusion of patients with high lactate and low pH levels on admission, and all patients received catecholamines before randomization. Although we did not aim to include resuscitated patients, the inclusion criteria resulted in 92% of enrolled patients having a cardiac arrest prior to randomization. In addition, almost one-half (48%) of the patients had time to ROSC longer than 20 min. Traumatic injuries due to cardiac arrest were frequently present (15%). These criteria identified a unique patient population that is usually excluded from randomized CS clinical trials and resulted in a patient population with a high 30- day mortality rate of 48%. This is higher than in the most recently reported randomized trial on CS (IABPSHOCK II [Intra-Aortic Balloon Counterpulsation in Acute Myocardial Infarction Complicated by Cardiogenic Shock] trial), which reports a mortality of 40% in patients randomized between IABP support and conventional therapy (n = 598).[4] Two previous studies compared IABP and TandemHeart (CardiacAssist Inc., Pittsburgh, Pennsylvania) in CS, with 30-day mortality rates of 44% (n = 41)[18] and 42% (n = 33)[19]. Neither trial observed any difference in mortality between the patients treated with TandemHeart or IABP. A registry reporting

on Impella 2.5 versus IABP in the setting of post-cardiac arrest shock reports mortality rates of 77% in patients treated with the device and 79% in patients treated with IABP.[20] Two multicenter registries including patients with CS complicating AMI supported with a pMCS showed mortality at discharge of 49.3% (n = 154) and 30-day mortality of 64.2% (n = 120).[21,22]

A recent USpella registry analysis submitted to the U.S. Food and Drug Administration for the Impella pre-market approval for use in CS demonstrated a marked difference between patients who were likely to be included in randomized shock trials versus those who were not—the latter of whom resemble the population studied in the present trial.[23] A considerable proportion of patients died due to anoxic brain damage (46%), compared with refractory CS or multiorgan failure (29%), or for other reasons (25%). This high rate of neurologically deceased patients is likely to be the result of the high percentage of resuscitated patients and longer times to ROSC. Nevertheless, our study resembles a real-life cohort in daily clinical practice of patients with CS complicating ST-segment elevation myocardial infarction.

In our study, bleeding occurred more often in the pMCS-treated patients than in the IABP-treated patients. During mechanical support, patients receive heparin in addition to standard dual antiplatelet therapy after PCI (aspirin and a $P2Y_{12}$ receptor blocker), which makes the occurrence of bleeding more likely, especially in patients with additional traumatic injuries on admission. Higher rates of bleeding in pMCS-treated patients compared with IABP-treated patients were also described in a registry comparing Impella 2.5 and IABP in a post cardiac arrest population (n = 78), which found severe bleeding in 26% of the device patients versus 6% of IABP patients.20 Two large multicenter Impella 2.5 registries describe the rates of bleeding requiring transfusion of 24.2% and 17.5% and the rates of hemolysis as 7.5% and 10.3%. [21,22] These complication rates are comparable to the pMCS in our study (33.3% bleeding and 8.3% hemolysis). The IABP-SHOCK II trial reports 20.7% bleeding in the IABP patients (and 20.8% in the control group). This is higher than the 8.2% bleeding in our IABP group. Although discouraged, some crossovers and upgrades to other mechanical support therapy did take place: 3 in the IABP group and 1 in the pMCS group. Crossover or upgrading was solely at the discretion of the investigator. There was a trend toward more upgrading/crossover in the IABP group.

Upon initiation of our study, IABP therapy was still recommended in the guidelines for CS, but was downgraded to a Class III recommendation in the European guidelines and Class II in the American guidelines during the inclusion period of the study. After consultation with the institutional review board and in the light of the severity of clinical condition with higher mortality rates than in the IABP-SHOCK II study, the control therapy remained unchanged. In addition, after the interim analysis it was clear the

study was underpowered to show a difference in mortality at 30 days, and the executive committee allowed it to proceed for exploratory purposes.

Although not adequately powered, our trial suggests that in patients with CS without selection on age, ROSC times, and pre-procedural traumatic injuries, no clear signal of superior outcome was observed in patients with pMCS support when compared with the IABP.

There may be several reasons why the pMCS treated patients did not show improved mortality rates. A possible explanation is the unselective nature of the patients included in the study. In our study, 92% of patients had resuscitated cardiac arrest, which implies a prevalence of post-anoxic neurological damage present at the moment of randomization. Any kind of mechanical circulatory support may be of limited clinical utility in these patients. Another explanation might be that CS after AMI is not only a matter of low cardiac output. The shock syndrome also comprises an irreversible damage due to diminished organ perfusion and inflammatory responses. Hence, providing mechanical hemodynamic support may not be enough to reverse the damage that has already occurred. Although the Impella CP can provide up to 3.5 l/min of forward flow, it might still be insufficient to reverse severe CS with advanced end organ failure, especially as in clinical practice, long-term Impella CP support achieves <3.5 l/min hemodynamic support. In this trial, the main rationale for using Impella CP instead of a device that can provide even more hemodynamic support (e.g., Impella 5.0), was the need for a surgical cut-down for implantation. The Impella CP can be inserted percutaneously, which enables quick insertion even before performing primary PCI. Earlier reports have demonstrated a better survival in patients who received a pMCS before primary PCI than in implantation post-PCI.[22] Our data also shows a trend toward lower mortality rates in patients in whom either the device or IABP was initiated before the primary PCI (25.0% vs. 52.5% overall).

Study limitations

A major limitation of this trial is its small number of patients. Adequately powered randomized clinical trials are needed to ascertain the value of pMCS in patients with CS after AMI.

CONCLUSIONS

In this explorative study, routine treatment with pMCS was not associated with lower 30-day mortality in patients with CS complicating AMI.

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SUPPLEMENTARY DATA

Supplement A: Trial organization

Steering committee
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Angiographic Clinical Event Committee/Angiographic Corelab
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Nuclear Medicine Corelab

H.J. Verberne, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands

Echocardiography and MRI Corelab

A. Hirsch, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands

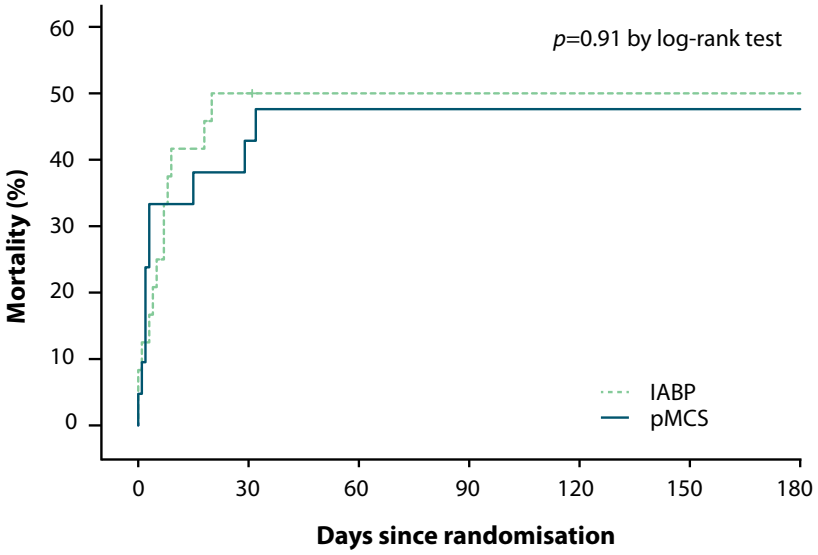
Supplement B: Definitions

Event	Definition
Post-anoxic neurological death	Severe brain injuring preventing recovery despite dissolving cardiogenic shock (low or decrescendo infusion rates of vasoactive agents).
Device failure	Any device failure requiring extraction or replacement of the device. Only randomized device.
Hemolysis requiring extraction of the device	Evidence of clinically relevant hemolysis requiring extraction of the device.
Hospitalization	Re-admission to the hospital for at least one night after discharge from the initial hospitalization.
Major Bleeding	Any of the following: Bleeding with associated serum hemoglobin level decrease of at least 5 g/dL (=3.1 mmol/L). The decrease in hemoglobin will be calculated as the last recorded Hb measurement preceding the onset of the bleeding, subtracted by the nadir Hb measurement (associated with the bleeding). Bleeding necessitating a minimum of 2 packed cells of blood product transfusion (only blood transfusions that are explicitly related to the bleeding are taken into account) The need for surgery to control the bleeding
Major vascular complications	Any of the following: A major bleed arising at the arterial access site (for major bleeding definition see above) requiring extraction of the device A thrombotic occlusion of the femoral artery Limb ischemia requiring extraction of either of the study devices The need for vascular surgery to correct a vascular complication.
Myocardial infarction	Defined by 3rd definition MI [1]
Refractory cardiogenic shock	Cardiac and circulatory failure resulting in organ hypo-perfusion unresponsive to medical therapies.
ROSC time	Time from cardiac arrest until return of sustained spontaneous circulation (first sustained ROSC longer than 5 minutes). Estimated if not available.
Stroke	Any stroke confirmed by a neurologist and a concurring CT scan.
Traumatic injuries	Life threatening traumatic injuries acquired before hospitalization.

[1] *Thygesen K, Alpert JS, Jaffe AS et al. Third universal definition of myocardial infarction. Journal of American College of Cardiology 2012;60:1581-98.*

Supplement C: Per-protocol analysis

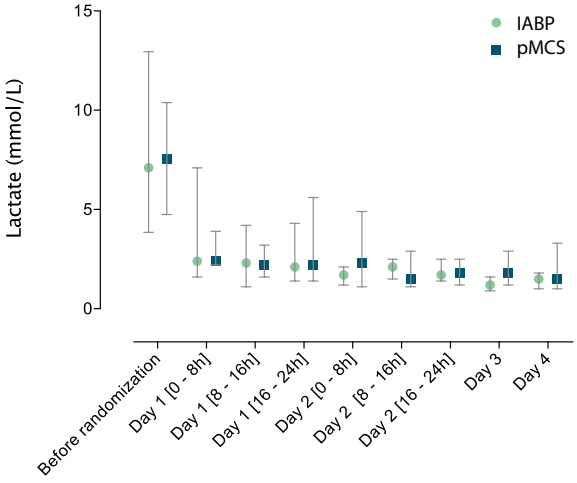
A total of 3 patients were excluded from the pMCS group in the per-protocol analysis. One patient did not receive any mechanical assist devices due to signs of recovery after randomization (pMCS group). Another patient was randomized to pMCS but erroneously an IABP was placed. In a third patient, an IABP was placed during a primary PCI of the left main artery during ongoing CPR. After the primary PCI the patient was randomized to pMCS and received pMCS. However, the patient deceased in the catheterization lab. This was a protocol violation as the patient was already on mechanical support before randomization.



Number at risk							
IABP	24	12	11	11	11	11	11
pMCS	21	12	11	11	11	11	11

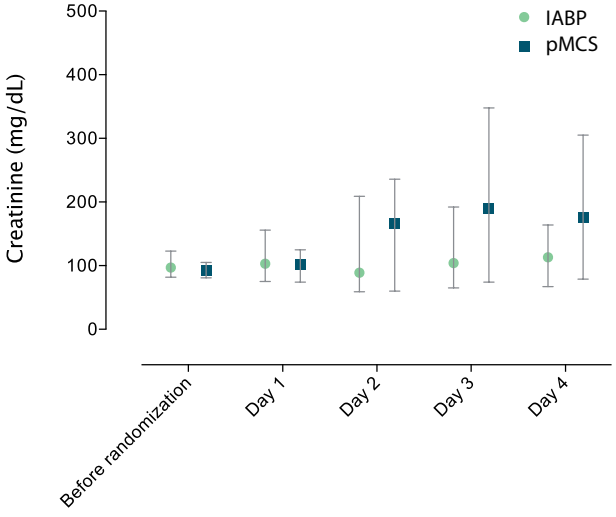
Kaplan-Meier curves for all-cause mortality up to 6 months, per protocol analyses.

Supplement D: Supplementary figures



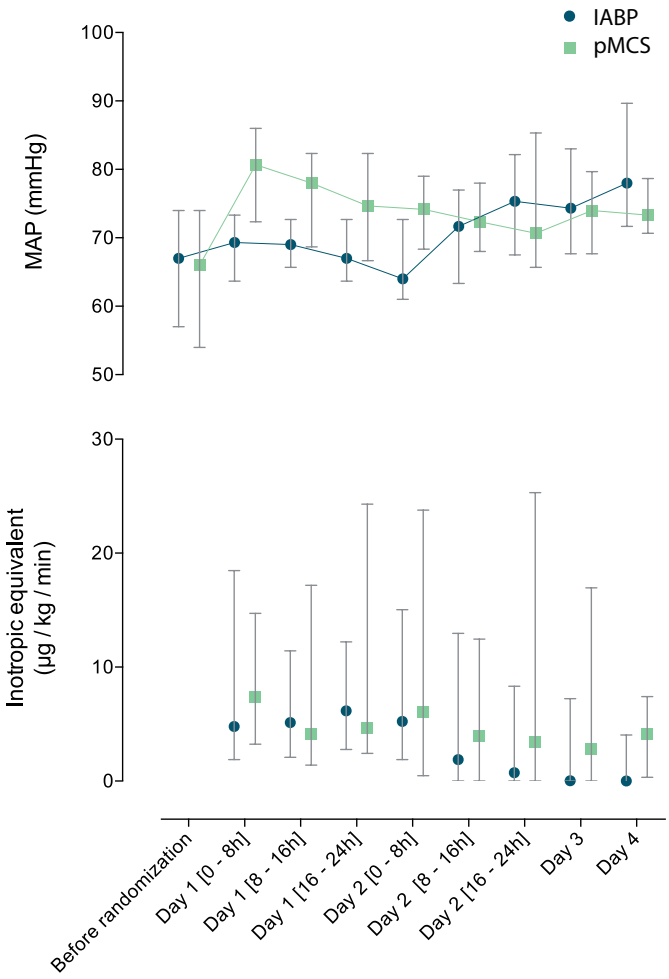
Supplementary Figure 1 Lactate

Lactate measurements during the first 4 days presented as median [25th – 75th percentile]. Not significantly different. When more measurements were done within the period, the mean value was calculated.

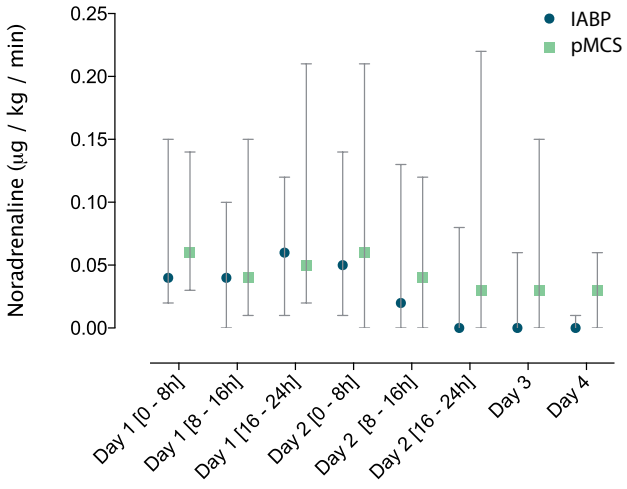


Supplementary Figure 2 Creatinine

Creatinine measurements during the first 4 days presented as median [25th – 75th percentile]. Not significantly different. When more measurements were done within the period, the mean value was calculated. Not significantly different.



Supplementary Figure 3 Mean arterial pressure and catecholamine usage at the intensive care unit. Data presented as median with 25th and 75th percentile. MAP = Mean arterial pressure. Catecholamine dose was evaluated by the inotrope equivalent method (ug/kg/min) = dopamine + dobutamine + 100*epinephrine + 100*norepinephrine + 100*isoproterenol + 15*milrinone [Lin YH et al. Crit Care 2014;18:548]. Not significantly different.

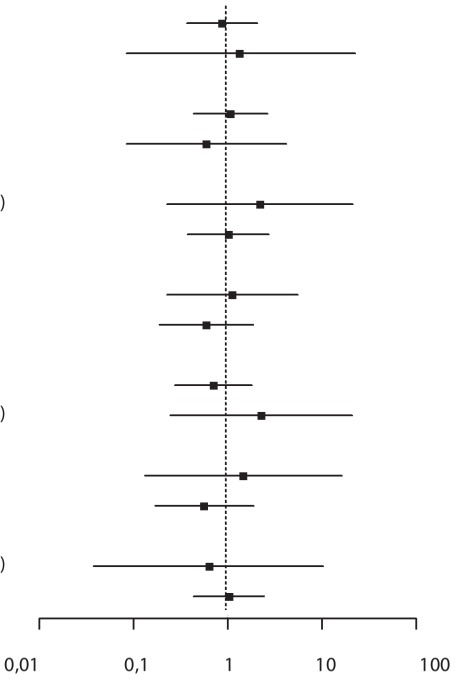


Supplementary Figure 4 Cumulative Noradrenalin dose usage at the intensive care unit. Data presented as median with 25 % and 75% interquartile range. Not significantly different.

Supplement E: Supplementary tables

Supplementary Table 1 Subgroup analysis.

		30 day all-cause mortality				
	n	pMCS n=24	IABP n=24	Hazard ratio with pMCS (95% CI)	Hazard ratio with pMCS (95% CI)	p-value for interaction
Age						
≤ 75 years old, n/n (%)	45	10/23 (44)	11/22 (50)	0.92 (0.39-2.17)		0.61
> 75 years old, n/n (%)	3	1/1 (100)	1/2 (50)	1.41 (0.09-23.6)		
Sex						
Male	38	9/18 (50.0)	10/20 (50)	1.13 (0.46-2.79)		0.57
Female	10	2/6 (33)	2/4 (50)	0.62 (0.09-4.44)		
Time till return of spontaneous circulation						
≤ 20 min	21	3/12 (25)	1/9 (11)	2.32 (0.24-22.32)		0.17
> 20 min	23	8/12 (67)	8/11 (73)	1.08 (0.40-2.89)		
Lactate level on admission						
≤ 7.5 mmol/L	21	3/10 (30)	3/11 (27)	1.17 (0.24-5.82)		0.47
> 7.5 mmol/L	20	5/10 (50)	7/10 (70)	0.62 (0.20-1.96)		
Traumatic injuries before admission						
Absent	41	7/19 (37)	11/22 (50)	0.74 (0.29-1.90)		0.34
Present	7	4/5 (80)	1/2 (50)	2.40 (0.26-21.87)		
Systolic blood pressure before device placement						
≤ 80 mmHg	19	3/9 (33)	4/10 (40)	0.80 (0.18-3.58)		0.79
> 80 mmHg	29	8/15 (53)	8/14 (57)	1.04 (0.39-2.78)		
Moment of device placement						
Before the primary PCI, n/n (%)	8	1/5 (20)	1/3 (33)	0.67 (0.04-10.78)		0.66
After the primary PCI, n/n (%)	40	10/19 (53)	11/21 (52)	1.09 (0.46-2.56)		



Supplementary Table 2 Prognostic factors for 30-day mortality in the overall study cohort.

Subgroups	n	30 day mortality (%)	Hazard ratio (95% CI)	*p*
Age				
≤ 70 years old	43	47	reference	
> 70 years old	5	60	0.98 (0.29 – 3.30)	0.57
Moment of device placement				
Before the primary PCI	8	25	reference	
After the primary PCI	40	53	2.42 (0.60 - 10.36)	0.16
Time till return of spontaneous circulation				
≤ 20 min	21	19	reference	
> 20 min	23	70	5.50 (1.82 - 16.58)	0.001
Lactate level on admission				
≤ 7.5 mmol/L	21	29	reference	
> 7.5 mmol/L	20	60	3.09 (1.09 - 8.74)	0.04
Traumatic injuries before admission				
Absent	41	44	reference	
Present	7	71	1.88 (0.70 - 5.07)	0.18

Supplementary Table 3 30-day survivors versus non-survivors.

	Survivor	Non-survivor	
	n = 25	n = 23	*p*
Baseline characteristics			
Age (yrs)	55 ± 9	62 ± 10	0.02
Male sex, n/n (%)	19/25 (76)	19/23 (83)	0.57
Cardiovascular risk factors, n/n (%)			
Current smoking	12/23 (57)	4/14 (29)	0.10
Hypertension	6/24 (25)	4/19 (21)	0.76
Hypercholesterolemia	4/23 (17)	5/19 (26)	0.48
Diabetes mellitus	2/24 (8)	3/21 (14)	0.53
Prior myocardial infarction, n/n (%)	1/24 (4)	1/21 (5)	0.92
Prior stroke, n/n (%)	0/24 (0)	1/21 (5)	0.28
Prior PCI, n/n (%)	1/24 (4)	0/21 (0)	0.34
Prior CABG, n/n (%)	0/24 (0)	0/21 (0)	-
Hemodynamic variables before randomization			
Heart rate (beats/min)	80 ± 17	84 ± 30	0.55
Systolic blood pressure (mm Hg)	83 ± 16	83 ± 19	0.90
Diastolic blood pressure (mm Hg)	56 ± 12	59 ± 23	0.60
Catecholamines or inotropes before device placement, % (n/n)	23/25 (92)	23/23 (100)	0.17
Blood values *			
Lactate (mmol/l)	6.9 ± 4.4	9.9 ± 5.7	0.07
Hemoglobin (mmol/L)	8.8 ± 1.2	8.4 ± 1.2	0.31
Creatinine (mg/dl)	92 ± 23	107 ± 27	0.04
Glucose (mmol/l)	14.6 ± 5.3	15.7 ± 5.0	0.52
Arterial pH	7.2 ± 0.1	7.1 ± 0.2	0.002
Resuscitation before randomization			
Cardiac arrest before admission, n/n (%)	24/25 (96)	20/23 (87)	0.26
Witnessed arrest (% of patients with cardiac arrest)	23/24 (956)	16/20 (80)	0.10
First rhythm VT/VF, n/n (%)	23/24 (96)	16/20 (80)	0.10
Time till return of spontaneous circulation (min)	15 [10-23]	44 [27-63]	<0.001
Traumatic injuries at admission, n/n (%)	2/25 (8)	5/23 (22)	0.18
Baseline left ventricular ejection fraction on echocardiography (%)			0.88
< 30%	9/20 (45)	9/20 (45)	
30-50%	9/20 (45)	8/20 (40)	
> 50%	2/20 (10)	3/20 (15)	

Supplementary Table 3 30-day survivors versus non-survivors. (continued)

	Survivor	Non-survivor	
	n = 25	n = 23	*p*
Procedural characteristics			
Moment of device placement			0.15
Device placement before revascularization, n/n (%)	6/25 (24)	2/23 (9)	
Device placement after revascularization, n/n (%)	19/25 (76)	21/23 (91)	
Infarct-related artery, n/n (%)			0.84
Left main	1/25 (4)	2/23 (9)	
Left anterior descending	17/25 (68)	14/23 (61)	
Left circumflex	5/25 (20)	4/23 (17)	
Right coronary artery	2/25 (8)	3/23 (13)	
Multi-vessel disease	19/25 (77)	17/23 (75)	0.87
Immediate PCI of non-culprit lesion, n/n (%)	3/19 (16)	4/17 (24)	0.47
TIMI flow pre-PCI			0.90
0/1, n/n (%)	21/25 (84)	19/23 (83)	
2/3, n/n (%)	24/25 (96)	23/23 (100)	
Clinical course during admission			
Mechanical circulatory support			
Duration of support (hours)	50 [42-88]	38 [19-67]	0.07
Upgrading to device with more support, n/n (%)	1/25 (4)	3/23 (13)	0.26
Other support before randomization, n/n (%)	0/25 (0)	1/23 (4)	0.29
Mechanical ventilation			
Patients treated, n/n (%)	25/25 (100)	23/23 (100)	-
Duration (days since device placement)	4 [3-13]	4 [2-8]	0.16
Catecholamines or inotropes during admission, n/n (%)	25/25 (100)	23/23 (100)	-
Renal replacement therapy, n/n (%)	7/25 (28)	8/23 (35)	0.61
Therapeutic hypothermia, n/n (%)	20/25 (80)	16/23 (70)	0.41
Any blood products during admission, n/n (%)	10/25 (40)	9/23 (39)	0.95
Length of stay on ICU (days)	9 [6-20]	4 [3-9]	0.002
Clinical outcomes			
Stroke, n/n (%)	0/25 (0)	2/23 (9)	0.13
Major vascular complication, n/n (%)	0/25 (0)	1/23 (4)	0.29
Major bleeding, n/n (%)	6/25 (24)	4/23 (17)	0.57
Hemolysis requiring extraction of the device, n/n (%)	1/25 (4)	1/23 (4)	0.95
Myocardial (re)infarction, n/n (%)	2/25 (8)	1/23 (4)	0.60

** Values are available for: lactate (23 survivors and 18 non-survivors), hemoglobin (23 survivors and 20 non-survivors), creatinine (24 survivors and 22 non-survivors, glucose (23 survivors and 20 non-survivors), pH (20 survivors and 16 non-survivors). Numbers are presented as frequencies (percentages), mean (±standard deviation) or median [25th – 75th percentile].*

Supplementary Table 4 Cardiac function parameters.

	pMCS	IABP
Combined imaging modalities[#]	n=12	n=9
Left ventricular ejection fraction (%)	46 ± 15	47 ± 12
Echocardiography †	n=12	n=9
Left ventricular dimensions and systolic function		
Ejection fraction (%)	46 ± 11	49 ± 9
End-diastolic volume (ml)	122 ± 41	115 ± 30
End-systolic volume (ml)	65 ± 31	59 ± 19
Left ventricular diastolic function		
E (m/s)	72 ± 22	75 ± 19
A (m/s)	70 ± 27	63 ± 21
E/A - ratio	1.3 ± 1.1	1.3 ± 0.6
DT (ms)	199 ± 49	173 ± 23
IVRT (ms)	98 ± 11	98 ± 17
Left atrial volume/BSA (ml/m^2)	34.8 ± 20.3	33.8 ± 14.7
e' (cm/s)	6.3 ± 1.3	7.5 ± 1.7
E/e' - ratio	12.0 ± 6.9	10.8 ± 3.5
Right ventricular function		
Severe or moderate dysfunction, n/n (%)	0/12 (0)	0/9 (0)
Tapse (mm)	25 ± 4	23 ± 5
Tricuspid annular systolic velocity (cm/s)	13 ± 2	12 ± 3
Right ventricle systolic pressure (mmHg)	26 ± 6	30 ± 9
Valve function		
Mitral valve insufficiency - moderate or severe, n/n (%)	1/12 (8.3)	2/9 (22.2)
Tricuspid valve insufficiency -moderate or severe, n/n (%)	2/10 (20.0)	1/8 (12.5)
Aortic valve stenosis - moderate or severe, n/n (%)	1/11 (9.1)	0/9 (0)
Aortic valve insufficiency -moderate or severe, n/n (%)	1/12 (8.3)	0/9 (0)
MRI ¥	n= 6	n= 2
Left ventricular function		
Ejection fraction (%)	54 ± 14	51 ± 25
End-diastolic volume (ml)	184 ± 32	235 ± 75
End-systolic volume (ml)	86 ± 31	125 ± 97
Stroke volume (ml)	98 ± 31	110 ± 21
Stroke volume index (ml/m^2)	48 ± 14	43 ± 16
LV cardiac output (l/min)	7.3 ± 2.6	6.6 ± 0.2
LV cardiac index (l/min/m^2)	3.5 ± 1.2	3.0 ± 0.7
Nuclear imaging ‡	n=3	n=2
Left ventricular ejection fraction (%)	33 ± 15	40 ± 5

First imaging after 2 months. # Imaging modalities after 2 months were combined from MRI, nuclear scan and echocardiography. Preferable, MRI data was used, if not available, alternative nuclear or echocardiography was used. Medium FU 204 days [170-370]. Modalities used: MRI (n=8), nuclear (n=5 and echocardiography (n=8). † *Median follow-up time is 191 [176-297] days.* ¥ *median follow-up time was 199 [174-245] ;* ‡ *Median follow-up time was 447 [369-455] days.Numbers are presented as frequencies (percentages), mean (±standard deviation) or median [25th – 75th percentile].*

Supplement F: Events specification

Cause of death
Other reasons:
IABP group: one patient had a asystole due to pulmonary embolism. Two patients had respiratory failure.
pMCS group: One patient had a retroperitoneal bleeding after pMCS insertion in calcified and stented trajectory. One patient developed a sepsis and one patient had respiratory insuffiency;

Major vascular complication
pMCS group: One patient had a retroperitoneal bleeding after pMCS insertion in a calcified and stented trajectory for which surgery was performed. The patient deceased.

Major bleeding
IABP group: One patient had a bleeding from puncture site of IABP after removal (device related bleeding) and one patient had a gastro-intestinal bleeding 14 days after IABP removal (non-device related).

pMCS group: Device related: One patient had a retroperitoneal bleeding after pMCS insertion in calcified and stented trajectory. One patient had a bleeding from the pMCS puncture site during pMCS and one patient had a bleeding from the pMCS puncture site after removal of the device. Non-device related: One patient had bleeding from the mouth and from all venous access sites during pMCS support. One patient had diffuse bleeding after multiple trauma from a car accident during pMCS support. One patient had a bleeding from an intercostal artery during pMCS support, and one patient had bleedings form his mouth and lungs during pMCS support. There was one patients who was bleeding from the puncture site for dialysis 11 days after removal of the pMCS.

Hemolysis requiring extraction of the device
pMCS group: In one patient the pMCS was stopped due to hemolysis in combination with an improved ejection fraction. In one patient pMCS was removed after the decision to withhold further therapy due to multi-organ failure, recurrent ventricular arrhythmia, hemolysis, and hemodynamic instability.

Surgery
pMCS group: One patient had a retroperitoneal bleeding after pMCS insertion in calcified and stented trajectory for which laparotomy was performed. One patient had an

intrapleural bleeding due to rib fracture for which coiling of the intercostal artery was performed.

Myocardial (re)infarction
IABP group: One patient had an MI related to dissection after additional PCI 3 weeks after the initial MI. One patient had a NSTEMI, 2 days after IABP removal.

pMCS group: Myocardial infarction after 3 days, secondary to ischemic imbalance.

Re-hospitalization
IABP group: Pneumonia.

pMCS group: One patient was admitted with congestive heart failure requiring mechanical ventilation. One patients was hospitalized multiple times with an atrial flutter. One patients was hospitalized due to hyperventilation. One patient was readmitted with incomplete healing of the groin resulting in leg ischemia for which thrombectomy was performed (pMCS leg, 40 days after pMCS removal. One patient was hospitalized due to bacteremia associated with a central venous catheter infection used for dialysis.

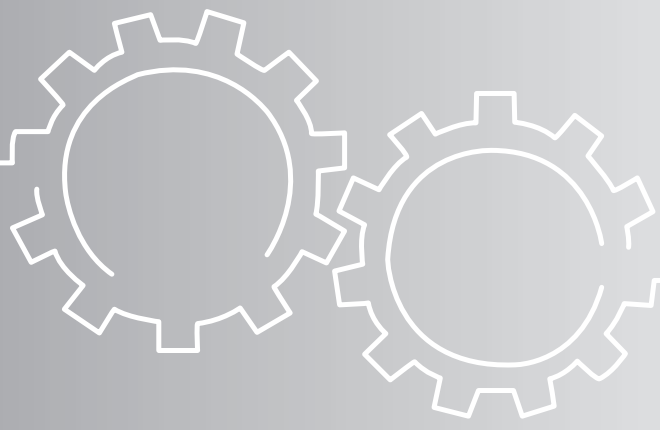
Stroke
IABP group: Ischemic stroke with hemorrhagic conversion on same day as initial MI, during IABP support.

pMCS group: Ischemic stroke 2 days after initial MI, during pMCS support.

Supplement G: Weaning

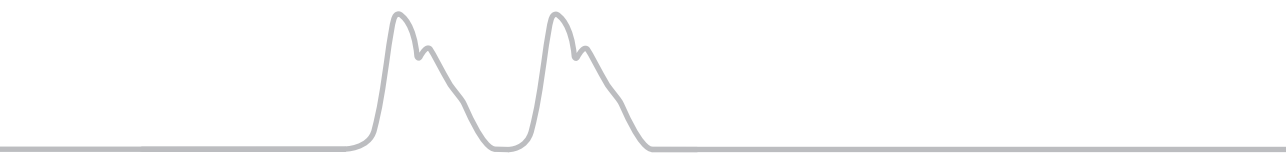
Weaning was left to the attending physicians at the intensive care unit. pMCS performance was set to a maximum level without console alarms (usually position or suction). Weaning was typically started usually 12-24 hours after PCI upon hemodynamic recovery allowing reduction of the inotropes and vasopressors in combination with echocardiography when needed. Weaning usually occurred in two steps. From maximum possible support (P7-8) to more or less half support (P4-5) and if needed patient were observed a couple of hours (typically overnight with Impella support P2-3) on low levels before device removal.

CHAPTER 9



PERCUTANEOUS MECHANICAL CIRCULATORY SUPPORT VERSUS INTRA-AORTIC BALLOON PUMP FOR TREATING CARDIOGENIC SHOCK: META-ANALYSIS

Dagmar M. Ouweneel, Erlend Eriksen, Melchior Seyfarth, José P.S. Henriques



Journal of the American College of Cardiology. 2017; 69(3):358-360.

In patients with cardiogenic shock after acute myocardial infarction (AMI), mortality remains high despite advances in treatment. Short-term percutaneous circulatory support devices provide superior hemodynamic support compared with the intraaortic balloon pump (IABP). American guidelines have downgraded the recommendation for usage of the IABP from Class I to IIa, and European guidelines to Class III. Both American and European guidelines endorse usage of other mechanical assist devices that provide more hemodynamic support. The Impella platform (Abiomed, Danvers, Massachusetts) is a frequently used percutaneous circulatory support device providing from 2.5 to 5.0 l/min depending on the model used. A few randomized controlled trials have compared the Impella device with IABP. All trials were underpowered to adequately evaluate mortality. Therefore, we pooled the data from these trials to compare Impella with IABP on 30-day and 6-month all-cause mortality and left ventricular ejection fraction (LVEF) during follow-up. If the endpoint was not available in the original paper, the data was provided by the investigators. All measurements of LVEF closest to 6 months were included, independent of the imaging modality.

There were 3 randomized controlled trials comparing Impella with IABP in cardiogenic shock after AMI.[1-3] Inclusion criteria of the 3 trials were slightly different, as the definition of cardiogenic shock was different in each trial. One trial aimed for inclusion of pre-shock patients, excluding full-blown cardiogenic shock[2]; 1 trial applied the generally used SHOCK (Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock) trial criteria[1]; the other trial aimed for inclusion of mechanically ventilated severe shock patients[3]. Two trials compared IABP with the Impella 2.5 (2.5 l/min), and 1 trial with the Impella CP (3.5 l/min).

A total of 95 patients were randomized to either Impella (n=49) or IABP (n=46). As reported in Figure 1, there was no difference in all-cause mortality between the patients treated with Impella or IABP at 30 days (relative risk [RR]: 0.99; 95% confidence interval [CI]: 0.62 to 1.58; p=0.95) and at 6 months (RR: 1.15; 95% CI: 0.74 to 1.48; p=0.53). Data on LVEF during follow-up was available in 47 patients. Seyfarth et al. measured LVEF by angiography at 6 months (not previously published)[1], Ouweneel et al. reported cardiac magnetic resonance measurements at 4 months[2] and Ouweneel et al. reported echocardiography after 2 months[3]. There was no difference in LVEF between Impella and IABP-treated patients during follow-up (mean difference -2.6%; 95% CI: -9.1 to 3.8; p=0.42).

This meta-analysis of 3 randomized controlled trials comparing Impella with IABP shows no difference in 30-day and 6-month all-cause mortality. Also, no difference was observed in LVEF between surviving IABP- and Impella-supported patients. Although the Impella has repeatedly shown to provide more hemodynamic support than the IABP, this did not translate into improved clinical outcomes in these very sick patients who have a high mortality risk.

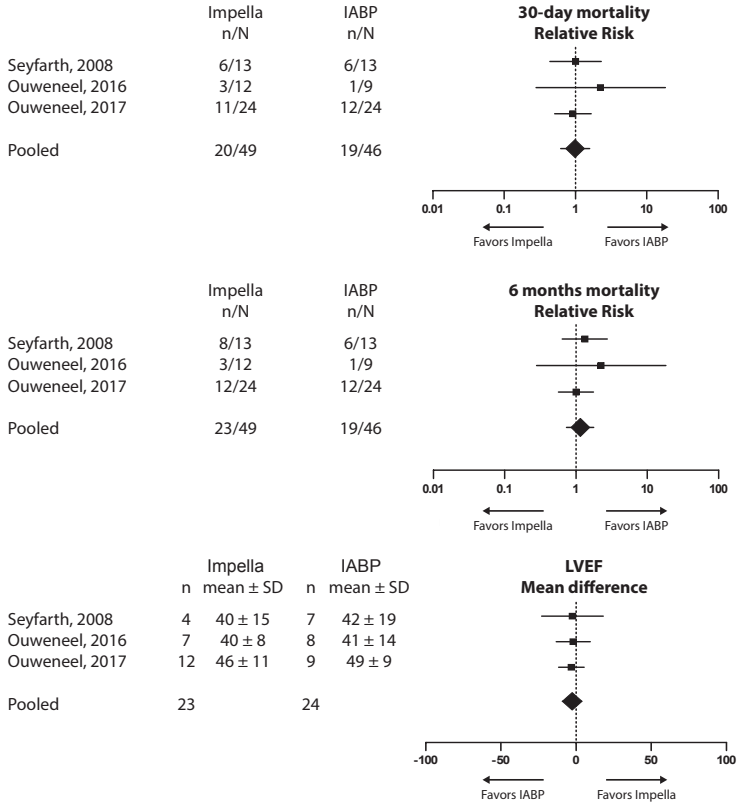


Figure 1 Meta-analysis showing the relative risk of 30-day and 6-month all-cause mortality with the use of Impella and IABP.

Relative risks and 95% confidence intervals are presented of the individual trials as well as the pooled analysis for (top) 30-day and (middle) 6-month all-cause mortality. (Bottom) Difference in left ventricular ejection fraction (LVEF) with 95% confidence intervals.

Our findings should be interpreted with caution. First, the studies included relatively unselected patients. To some extent, this may result in an almost "all-comer" shock population with the risk of underestimating the effect of increased circulatory support in patients that may benefit more than the relatively high number of resuscitated patients in all trials. It is possible that a subgroup of patients may benefit from support with the Impella device. Cohort studies have shown that earlier initiation of Impella support, even before revascularization of the occluded artery, is associated with reduced mortality[4]; this is supported by experimental studies that have shown that pre-revascularization Impella initiation is associated with reduced infarct size in improved left ventricular function.[5] It is, therefore, important to note that the vast majority of patients enrolled in the studies were treated with mechanical support therapy after revascularization. How-

ever, large randomized controlled trials or large-scale observational studies are needed to show which patients may benefit from this therapy. Another contributing factor is the fact that cardiogenic shock after AMI is complex, and patients experience not only cardiac ischemia but also diminished organ perfusion, anoxic brain damage, and systemic inflammatory responses. Therefore, providing more hemodynamic support only may not be enough to save these very ill patients, and the addition of other therapies may yield better outcomes. This meta-analysis is limited by the relatively small number of included studies and patients and by the inclusion of studies with different inclusion criteria for the severity of the cardiogenic shock (from pre-shock to severe shock). Also, the studies differed in the usage of the kind of Impella device (Impella 2.5 and Impella CP). The Impella 2.5 has gone through several improvements and recently received U.S. Food and Drug Administration approval on the basis of data from the USpella registry.[4]
In conclusion, although there is only limited data available, this meta-analysis shows no difference in mortality or LVEF in cardiogenic shock patients who are treated with Impella compared with IABP. A pooled analysis comprising undersized studies may mitigate the true effect, but in the absence of largescale, sufficiently sized trials, pooled data are the next best source of evidence.

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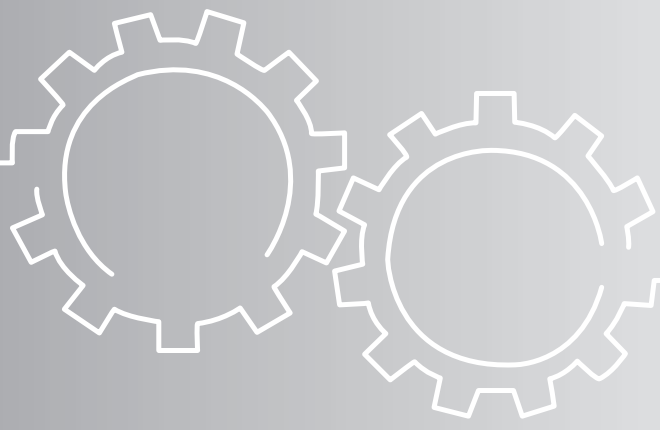
CHAPTER 10



PERCUTANEOUS SHORT-TERM ACTIVE MECHANICAL SUPPORT DEVICES IN CARDIOGENIC SHOCK: A SYSTEMATIC REVIEW AND COLLABORATIVE META-ANALYSIS OF RANDOMISED TRIALS

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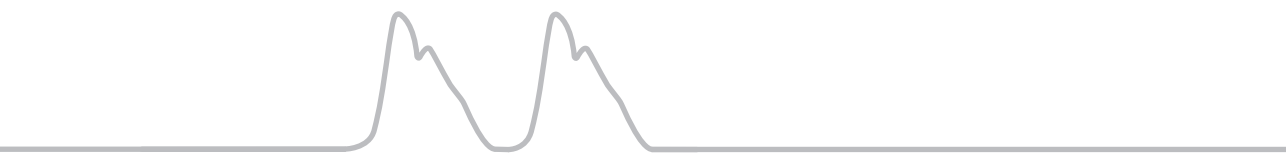


Submitted

ABSTRACT

Aims

Evidence on the impact on clinical outcome of active mechanical circulatory support (MCS) devices in cardiogenic shock (CS) is scarce. This collaborative meta-analysis of randomised trials thus aims to investigate the efficacy and safety of percutaneous active MCS versus control in CS.

Methods

Randomised trials comparing percutaneous active MCS to control in patients with CS were identified through searches of medical literature databases. Risk ratios (RR) and 95% confidence intervals (95%CI) were calculated to analyse the primary endpoint of 30-day mortality and device-related complications including bleeding and leg ischaemia. Mean differences (MD) were calculated for cardiac index (CI), mean arterial pressure (MAP), pulmonary capillary wedge pressure (PCWP), and arterial lactate.

Results

Four trials randomising 148 patients to either TandemHeart™ or Impella® MCS (n=77) versus control (n=71) were identified. There was no difference in 30-day mortality (RR 1.01, 95%CI 0.70 to 1.44, p=0.98) for active MCS compared to control. Active MCS significantly improved haemodynamic variables (CI: MD 0.32 l/min/m2, 95%CI 0.04 to 0.59, p=0.02; MAP: MD 11.85 mmHg, 95%CI 6.76 to 16.94, p<0.001; PCWP: MD -5.59 mmHg, 95%CI -10.13 to -1.06, p=0.02) as well as arterial lactate (MD -1.36 mmol/l, 95%CI -2.52 to -0.19, p=0.02). No significant difference was observed in the incidence of leg ischaemia (RR 2.64, 95%CI 0.83 to 8.39, p=0.10) but an increased rate of bleeding (RR 2.50, 95%CI 1.55 to 4.04, p<0.001) in MCS compared to control.

Conclusions

Results of this collaborative meta-analysis do not support the unselected use of active MCS patients with CS complicating AMI.

INTRODUCTION

Cardiogenic shock (CS) is defined as a state of critical endorgan hypoperfusion due to reduced cardiac output. Advances in treatment led to mortality reduction over the last decades, mainly driven by early revascularisation in patients with infarct-related CS. Nevertheless, CS mortality rates are still approaching 40-50% according to recent registries and randomised trials.[1-4]

The use of active mechanical circulatory support (MCS) appears to be a promising therapeutic concept to improve cardiac output while avoiding the possible cardiotoxicity of catecholamines. Passive intraaortic balloon pumping (IABP) has been the most widely used MCS device for the last decades.[5] Based on negative results of the IABP-SHOCK II trial,[3,6] European guidelines downgraded routine IABP use in CS to a class III A recommendation.[7-9] The lack of efficacy of IABP led to an increased use of more potent active MCS devices.[5,10] Among the currently available percutaneous devices left atrial-to-femoral artery MCS such as the TandemHeart™ (TandemHeart, Cardiac Assist, Pittsburgh, PA, USA), axial flow MCS from the Impella® family (Impella 2.5 and Impella CP, Abiomed Europe, Aachen, Germany) and extracorporeal membrane oxygenation (ECMO) are predominantly used for short-term support.[4,10]

Several controlled trials comparing the efficacy and safety of active percutaneous MCS versus control in CS complicating acute myocardial infarction (AMI) have been performed.[11-14] The individual trials were underpowered to adequately evaluate a potential mortality benefit. Consequently, clinical evidence on the impact of MCS use on outcome is scarce.[15]

We thus performed a collaborative meta-analysis to investigate the effects of MCS versus control with respect to mortality, haemodynamic variables as well as major device-related complications.

METHODS

Studies eligible for inclusion had to compare active percutaneous MCS versus control including IABP in patients with CS predominantly complicated by AMI reporting at least short-term all-cause mortality assessed at 30 days. Medical literature databases including Pubmed/Medline, Cochrane Central Register of Controlled Trials (CENTRAL), and EMBASE as well as abstracts and presentations from major cardiovascular meetings were searched using the following keywords "ventricular assist device" OR "intra-aortic balloon pump" OR "VAD" OR "LVAD" OR "IABP" AND "cardiogenic shock". Reference lists from review articles and eligible studies were further checked to identify additional citations. The reference lists of retrieved publications as well as clinical trials registration websites

were scrutinised to identify additional trials as well as ongoing studies. The search was last updated on January 17th, 2017. No language, publication date, or publication status restrictions were imposed. The most updated and inclusive data for each study were chosen. Two investigators (HT, AJ) independently reviewed the titles, abstracts and studies to determine whether they met the inclusion criteria. Conflict between reviewers was resolved by consensus. Internal validity of randomised controlled trials was assessed by evaluating concealment of allocation, blind adjudication of events, and inclusion of all randomised patients in the analysis. Owing to the nature of the compared interventions, blinding of patients or physicians was not feasible. The present meta-analysis was performed according to PRISMA statement.[16]

Data acquisition, endpoints, and definitions

Patient and outcome data were independently extracted by two investigators (HT, AJ) from the original publications. Furthermore, the corresponding authors were contacted to provide additional data if necessary. Except for one trial where only the individual mortality data were available and the original database was not retrievable anymore [11] all other trials could confirm data from the original database. The primary endpoint of the present meta-analysis was all-cause short-term mortality assessed at 30 days after randomisation for the intention-to-treat population. Secondary endpoints were haemodynamic parameters including mean arterial pressure (MAP), pulmonary capillary wedge pressure (PCWP), and cardiac index (CI) as well as arterial lactate pre versus post (within 2 hours) MCS implantation. In addition, typical device associated complications such as bleeding and leg ischaemia were analysed. The endpoint definitions as applied in each trial were used.

Statistical analysis

Baseline characteristics including demographics, medical history, haemodynamic parameters, and angiography parameters were tabulated by treatment group for each study. Continuous variables were summarised as mean and standard deviation (SD). Frequencies and percentages were used to summarise categorical variables. Random effects meta-analyses of clinical outcomes were performed by calculating risk ratios (RR) with 95% confidence intervals (95%CI) for MCS versus control of each individual study and consecutive pooling by means of the Mantel-Haenszel method. Mean differences (MD) with 95%CI were calculated for random effects meta-analyses of continuous outcomes (i.e. haemodynamic parameters and lactate) and pooled using the inverse variance method. Between-study variances τ^2 were calculated according DerSimonian and Laird. Cochran's Q statistic and Higgins and Thompsons I^2 were calculated to assess heterogeneity. A p-value <0.05 and <0.10 were considered statistically significant for clinical outcomes and heterogeneity, respectively. Clinical outcome measures are

Table 1 Characteristics of the individual randomised trials in cardiogenic shock.

	Thiele et al.[14]	**Burkhoff et al.**[11]	**ISAR-SHOCK**[13]	**IMPRESS-IN-SEVERE-SHOCK**[12]
Number of patients	41	33	26	48
MCS	TandemHeart™	TandemHeart™	Impella® 2.5	Impella® CP
Control	IABP	IABP	IABP	IABP
Setting	Single centre	Multicentre	Multicentre	Multicentre
Inclusion period	2000-2003	2002-2004	2004-2007	2012-2015
Sequence generation	Drawing envelopes	Drawing envelopes	Drawing envelopes	Internet-based program
Allocation concealment	Sealed opaque sequentially numbered envelopes	Sealed opaque sequentially numbered envelopes	Sealed opaque sequentially numbered envelopes	Internet-based program
Blinding	Not possible	Not possible	Not possible	Not possible
Primary endpoint	Cardiac power index	Haemodynamic profile improvement	Cardiac index	30-day mortality
Haemodynamic measurements	Pulmonary artery catheter	Pulmonary artery catheter	Pulmonary artery catheter	Arterial line
Follow-up 30 days	Complete	Complete	Complete	Complete

[a]All the following four criteria needed to be met: (1) patient did not die during support or within 24 hours of device removal, (2) cardiac index ≥2.2 l/min/m^2, (3) pulmonary capillary wedge pressure ≤24 mmHg, and (4) mean arterial pressure ≥70 mmHg. MCS=mechanical circulatory support; IABP=intra-aortic balloon pump.

presented by means of forest plots. In addition, 30-day cumulative mortality rate was estimated with the Kaplan-Meier method based on individual patient data. All analyses were performed with R version 3.1.0 (The R Project for Statistical Computing, Vienna, Austria) and its meta package version 4.7-0 (cran.r-project.org/web/packages/meta/).

RESULTS

In total four randomised trials comparing active percutaneous MCS published between 2005 and 2016 were identified and included in the collaborative meta-analysis (Figure 1).[11-14] All four trials randomly assigned patients to treatment with percutaneous active MCS versus IABP. Two trials used the TandemHeart™ device [11,14] and two trials used the Impella® device (Impella 2.5 in 1 trial and Impella CP in the other trial).[12,13] All trials reported adequate sequence generation and methods for allocation concealment (Table 1). Complete 30-day follow-up was available in all trials.

Characteristics of each study are depicted in Table 1. Three trials were multicentre studies and one trial was performed at a single centre. Altogether 148 patients were included with 77 (52%) randomised to active MCS and 71 (48%) to control. Baseline characteristics of individual studies did not show major discrepancies (Table 2).

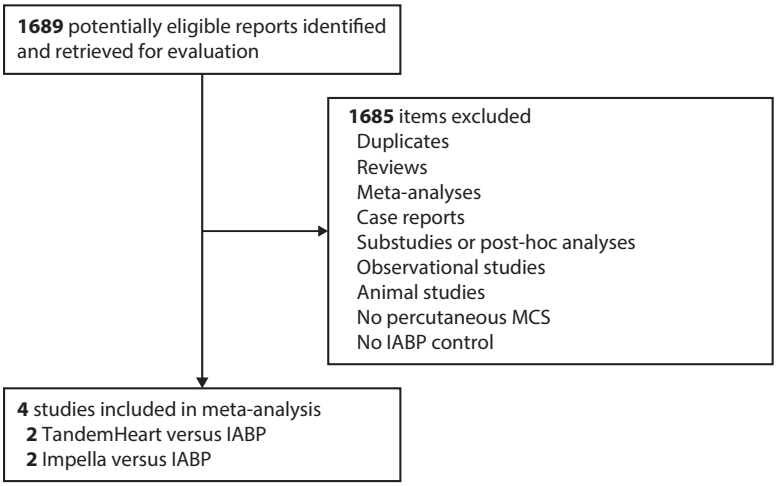


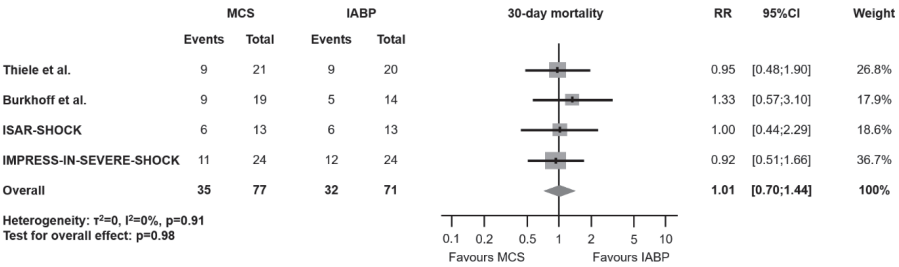
Figure 1 Flow diagram of the study selection process.
MCS=active mechanical support device; IABP=intra-aortic balloon pump

All-cause mortality

Short-term mortality was similar in patients treated with active MCS in comparison to those undergoing IABP (45.5% versus 45.1%; RR 1.01, 95%CI 0.70 to 1.44, p=0.98, Figure 2 A). Similarly, no difference in time-to-event analyses for mortality was detected (p=0.93) (Figure 2 B).

Haemodynamic and metabolic variables

Haemodynamic and metabolic variables were available for most of the trials. In IMPRESS-IN-SEVERE-SHOCK no pulmonary artery catheter monitoring was performed, thus no data on CI and PCWP were available. Arterial lactate was not assessed in the trial by Burkhoff et al. Active MCS significantly improved haemodynamic parameters including an increase



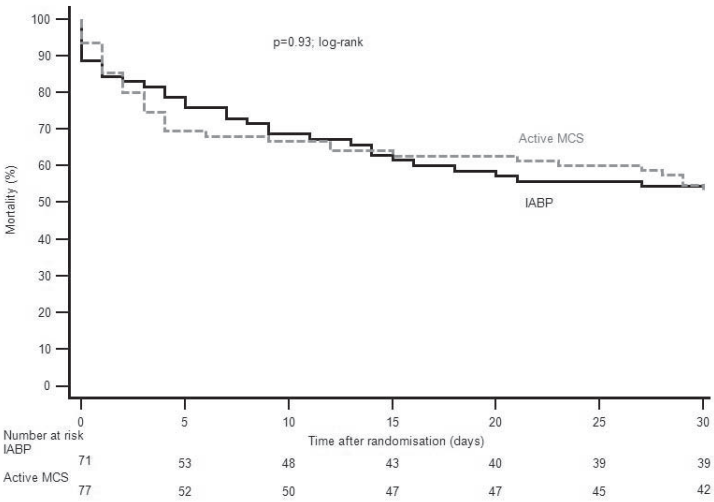


Figure 2 30-day mortality.
(A) Forest plot with results for 30-day mortality (B): Kaplan-Meier curve for 30-day mortality using individual patient data. MCS=active mechanical support device; IABP=intraaortic balloon pump; RR=relative risk; 95%CI=95% confidence interval.

in CI (MD 0.32 l/min/m^2, 95%CI 0.04 to 0.59, p=0.02; Figure 3 A), higher MAP (MD 11.85 mmHg, 95%CI 6.76 to 16.94, p<0.001; Figure 3 B), and decreased PCWP (MD -5.59 mmHg, 95%CI -10.13 to -1.06, p=0.02; Figure 3 C). Arterial lactate levels were lower in MCS patients as compared to control (MD -1.36 mmol/L, 95%CI -2.52 to -0.19, p=0.02, Figure 3 D).

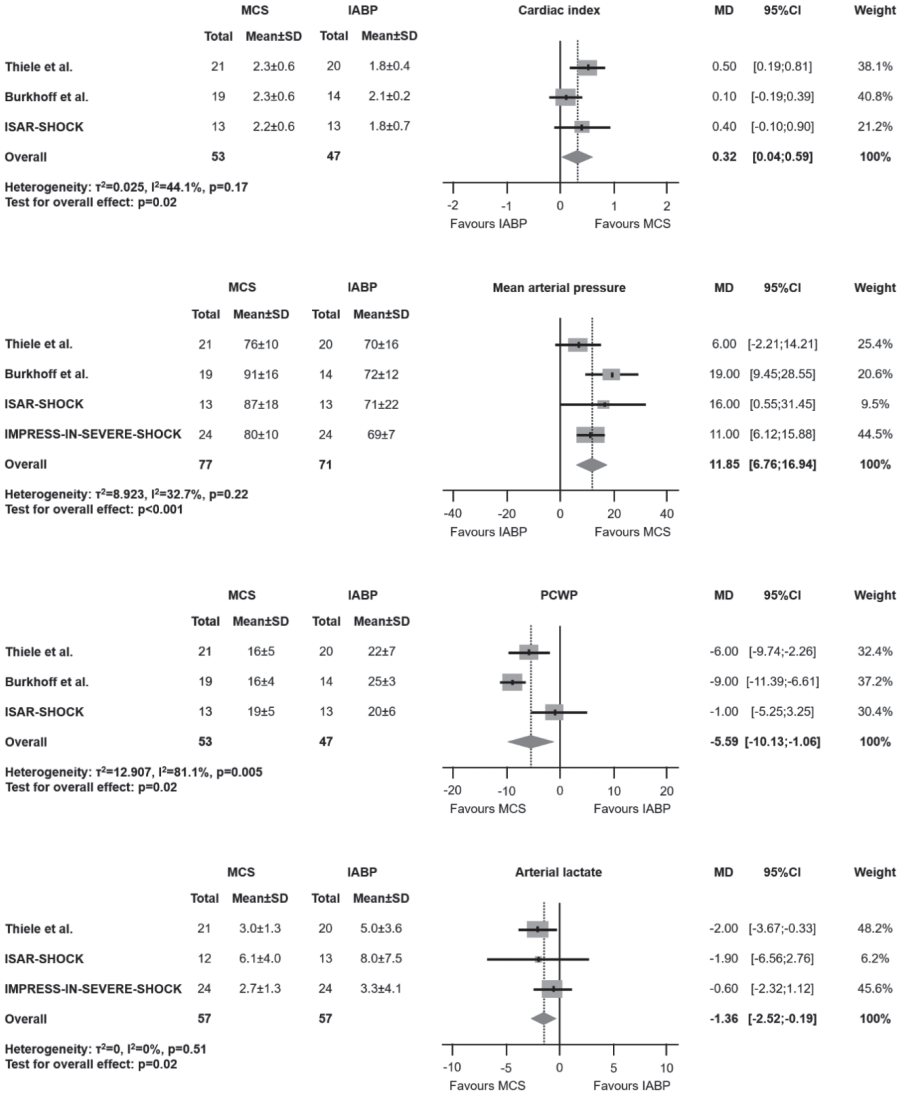


Figure 3 Mean difference with 95% confidence intervals in haemodynamic and metabolic variables (A) Cardiac index (L/min/m^2); (B) Mean arterial pressure (mmHg); (C) Pulmonary capillary wedge pressure (mmHg); (D) Arterial lactate (mmol/l). MCS=active mechanical support device; IABP=intra-aortic balloon pump; MD=mean difference; SD=standard deviation; 95% CI=95% confidence interval; PCWP=pulmonary capillary wedge pressure.

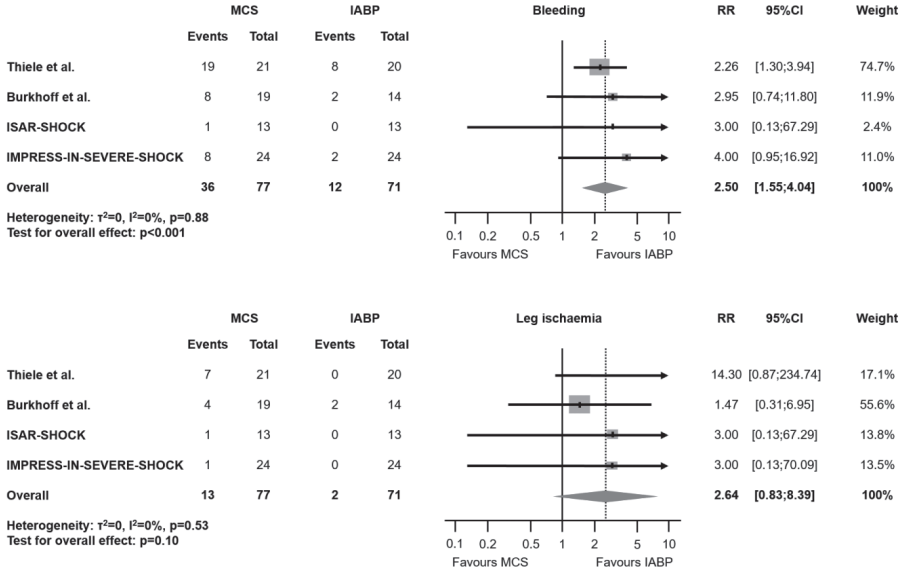


Figure 4 Potential device-related complications.
(A) Forest plot showing risk estimates of major bleeding; (B): Forest plot showing risk estimates of leg ischaemia. MCS=active mechanical support device; IABP=intra-aortic balloon pump; RR=relative risk; 95% CI=95% confidence interval.

Complications

Bleeding and leg ischaemia were reported in all trials. In the ISAR-SHOCK trial bleeding events differed from the original publication and could be confirmed by individual data. Bleeding (RR 2.50, 95%CI 1.55 to 4.04, p<0.001; Figure 4 A) occurred more frequently in MCS compared to control. The rate of leg ischaemia was numerically higher in patients undergoing MCS (RR 2.64, 95% CI 0.83–8.39, p=0.10; Figure 4 B).

DISCUSSION

This collaborative meta-analysis of four randomised trials investigating the efficacy and safety of percutaneous active MCS versus control with IABP demonstrates similar short-term mortality despite initial beneficial effects on haemodynamics and reduction of arterial lactate. There was a higher rate of bleeding and a numerically higher incidence of limb ischaemia following active percutaneous MCS.

Mortality of CS complicating AMI remains high despite modern treatment strategies including early revascularisation and optimal medical therapy. The latter mainly consists of volume management as well as administration of inotropic agents and vasopressors enhancing cardiac output and vascular tone. The haemodynamic benefits of inotropes

and vasopressors appear to be counterbalanced by adverse effects such as increased myocardial oxygen demand, arrhythmogenicity, and compromise of tissue microcirculation which may translate into an increased mortality risk. MCS are an alternative to increase systemic blood flow while avoiding the possible cardiotoxicity and long-term morbidity of medical therapy. IABP has been in place for more than five decades and remains the most widely used device. Accordingly, all trials included in the current meta-analysis used IABP as comparator as the individual studies were performed or started before the downgrading of IABP use in current European guidelines.[7-9] The recent class III recommendation for routine use of IABP in CS is based on the findings of the IABP-SHOCK II trial demonstrating similar 30-day and 12-month mortality in patients treated with or without IABP. Furthermore, IABP did not show any differences in secondary endpoints such as MAP, arterial lactate, renal function, catecholamine doses, or length of intensive care unit treatment.[3] Moreover, a previous trial also showed no beneficial haemodynamic effects in IABP versus control such as CI, cardiac power output, and systemic vascular resistance.[17] Therefore, changes in haemodynamics and arterial lactate observed in the current meta-analysis would have also been most likely observed in active MCS versus no IABP.

The current meta-analysis clearly demonstrates an initial improvement of all measured haemodynamic parameters in patients treated by active MCS. The best way to characterise a dependent system of pump (heart) and tubing (vessels) is to measure the power of the pump and the flow resistance within the tubing which is best measured by the cardiac power index. This is a comprehensive marker of circulatory function and the best risk stratification tool in CS.[18] Although not directly assessed, the initial haemodynamic effects with an increase in MAP and CI as shown in the current meta-analysis reflect an increase in cardiac power output by active MCS. However, this initial rise in cardiac power output does not necessarily result in improved outcome as shown by the results of our collaborative meta-analysis. This may be partly explained by the fact that the rise in cardiac power output reflects both the effects of extrinsic MCS as well as the intrinsic cardiac power itself. In the current meta-analysis no data were available on the persistent haemodynamic effects of an active MCS. However, there was no persistent haemodynamic improvement achieved by MCS therapy in the individual trials.[11-14] This may also be an explanation for the dissociation of beneficial haemodynamic effects without subsequent impact on mortality.

Arterial lactate as a measure of tissue hypoxemia severity in CS is a well-established prognostic marker.[6,19] Recent scores for mortality risk prediction in CS also include arterial lactate as important variable.[19,20] Lactate clearance has also been advocated as prognostic marker and is used for monitoring of treatment effects.[21] The current data indicate an early improved arterial lactate clearance by active MCS. However, in all three

randomised trials assessing lactate levels over time no persistent difference between MCS and IABP could be observed.[12-14]

The benefits of active MCS on haemodynamic parameters and arterial lactate must be weighed against the potential complications associated with the invasiveness of MCS with respect to the implantation procedure, leg ischaemia due to large arterial cannula size, bleeding and also the extracorporeal support as part of the TandemHeart™ system. Accordingly, this meta-analysis confirmed significantly higher bleeding rates in CS patients with systematic MCS use which is a well-known predictor of mortality in acute coronary syndromes. Moreover, leg ischaemia was also numerically higher in the MCS treated patients. The contact with artificial surfaces from MCS and secondary haemolysis might further promote systemic inflammatory response syndrome.[4] In a previous meta-analysis there was a trend towards more fever and sepsis in MCS treated patients, which were not assessed in the current meta-analysis due to inconsistent reporting and definitions.[22]

Based on animal studies the beneficial effects of MCS are often believed to be more pronounced when started before revascularisation. The time point of initiation of the MCS device (before PCI versus after PCI) was at the discretion of the treating physician in all four included trials. In the ISAR-SHOCK study all patients underwent MCS insertion post PCI. Conversely, MCS support was initiated before PCI in 21% of patients enrolled in the IMPRESS-IN-SEVERE-SHOCK trial and in 43% in the trial performed by Thiele et al.[11-14] Data on timing of active MCS insertion in humans in CS are limited. In the USpella registry patients directly treated with Impella® prior to PCI in CS had an overall better survival at hospital discharge compared with those treated after PCI, even when adjusting for potential confounding variables.[23] Concerning IABP, there are conflicting data with more evidence demonstrating harm rather than benefit by IABP insertion before PCI.[24,25] This might be at least partly explained by further deferral of revascularisation, which is the therapeutic cornerstone in CS complicating AMI. This is also supported by findings of a randomised trial investigating the impact of IABP insertion prior to PCI in high-risk anterior AMI patients on infarct size demonstrating neutral results.[26]

Based on the current meta-analysis active MCS does not result in reduced mortality in unselected CS patients if used on a routine basis. Therefore, patient selection may play a crucial role. It is well known, that approximately 50-60% of CS patients survive without any MCS.[3] Thus, a positive impact of MCS on outcome in this patient group appears to be unlikely. There may also be futile situations where MCS devices might not even theoretically be able to change clinical outcome such as patients with severe brain injury. MCS appears to stabilise the initial haemodynamic situation but will not be able to influence prognosis. Since CS forms a spectrum that ranges from mild hypoperfusion to profound shock active MCS may only be considered for the highest risk cohorts. In clinical practice MCS is often chosen on a subjective basis and readily available scores are currently not

well established. The newly introduced IABP-SHOCK II score may be helpful for MCS selection but this needs further evaluation in randomised trials.[20] Evidently, timing and appropriate patient selection are influenced by the balance between efficacy of the device and its device-related complications. Devices with low complication rates may be chosen more liberally in the early stage of CS whereas more aggressive devices with higher flow rates may be reserved for more severe CS. Recent animal data suggest better haemodynamic support with the TandemHeart™ in comparison to the Impella® CP,[27] however, based on the current meta-analysis no preference for any device can be made. According to current guidelines, MCS should be mainly considered in patients with refractory CS.[8,28]

The following limitations should be acknowledged. First, IMPRESS-IN-SEVERE-SHOCK contributed 32% of patients to the collaborative meta-analysis. Therefore, the statistical weight to the calculated models of mortality and the secondary as well as safety outcomes of IMPRESS-IN-SEVERE-SHOCK ranged between 11% and 46%. Second, the data on mortality need to be interpreted with caution as the overall number of included patients is still relatively low. However, the observed RR of 1.01 with a p-value of 0.98 between MCS and IABP makes a possible positive effect even in larger populations unlikely. Third, effects on haemodynamic parameters and arterial lactate also must be cautiously interpreted based on the non-blinded evaluation in the four trials.

In conclusion, despite an initial beneficial effect on haemodynamic parameters and arterial lactate active percutaneous MCS did not improve mortality in comparison to control in patients with CS complicating AMI, which may be partly explained by an excess of complications such as bleeding. The use of active percutaneous MCS may thus be restricted to selected patients.

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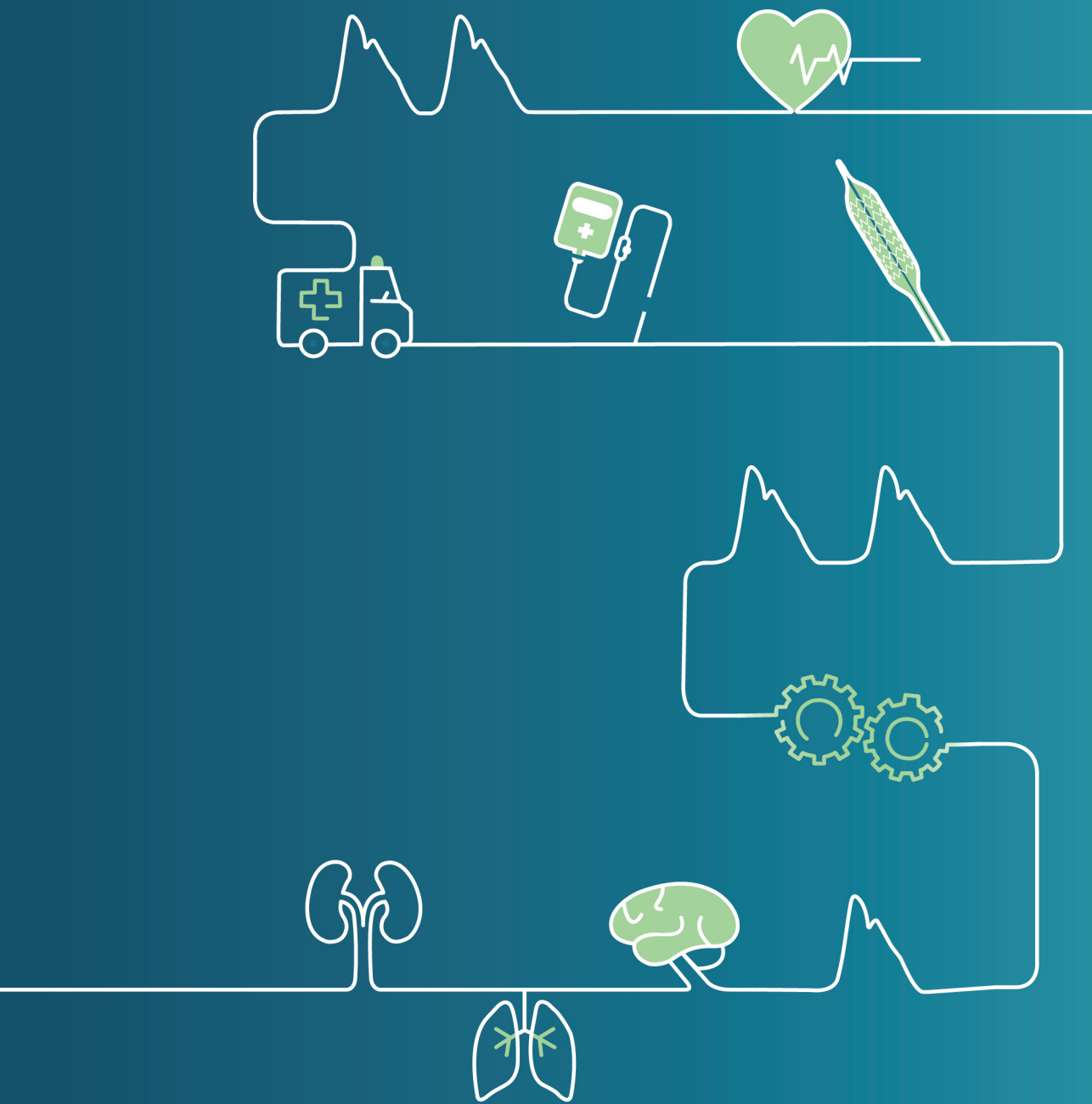
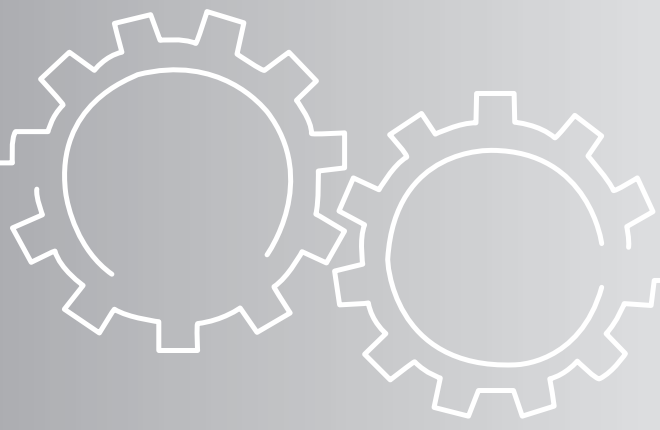


PART III

HEMODYNAMIC SUPPORT WITH EXTRACORPOREAL LIFE SUPPORT

CHAPTER 11



EXTRACORPOREAL LIFE SUPPORT DURING CARDIAC ARREST AND CARDIOGENIC SHOCK: A SYSTEMATIC REVIEW AND META-ANALYSIS

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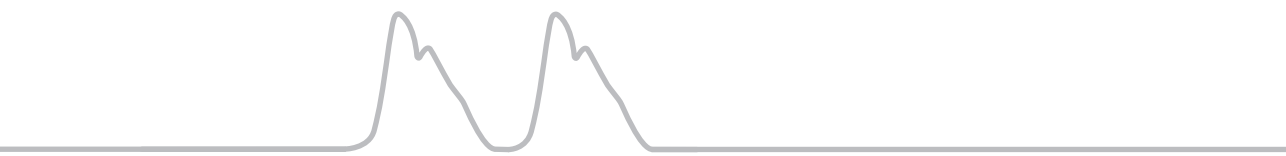

Intensive Care Medicine. 2016 Dec;42(12):1922-1934.

ABSTRACT

Purpose

Veno-arterial extracorporeal life support (ECLS) is increasingly used in patients during cardiac arrest and cardiogenic shock, to support both cardiac and pulmonary function. We performed a systematic review and meta-analysis of cohort studies comparing mortality in patients treated with and without ECLS support in the setting of refractory cardiac arrest and cardiogenic shock complicating acute myocardial infarction.

Methods

We systematically searched MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials and the publisher subset of PubMed updated to December 2015. Thirteen studies were included of which 9 included cardiac arrest patients (n=3098) and 4 included patients with cardiogenic shock after acute myocardial infarction (n=235). Data were pooled by a Mantel-Haenzel random effects model and heterogeneity was examined by the I^2 statistic.

Results

In cardiac arrest, the use of ECLS was associated with an absolute increase of 30 days survival of 13% compared with patients in which ECLS was not used (95% CI 6-20%; p<0.001; number needed to treat (NNT) 7.7) and a higher rate of favourable neurological outcome at 30 days (absolute risk difference 14%; 95% CI 7-20%; p<0.0001; NNT 7.1). Propensity matched analysis, including 5 studies and 438 patients (219 in both groups), showed similar results. In cardiogenic shock, ECLS showed a 33% higher 30-day survival compared with IABP (95% CI, 14-52%; p<0.001; NNT 13) but no difference when compared with TandemHeart/Impella (-3%; 95% CI -21 to 14%; *p*=0.70; NNH 33).

Conclusion

In cardiac arrest, the use of ECLS was associated with an increased survival rate as well as an increase in favourable neurological outcome. In the setting of cardiogenic shock there was an increased survival with ECLS compared with IABP.

INTRODUCTION

Veno-arterial extracorporeal life support (ECLS), also called extracorporeal membrane oxygenation (ECMO), is a modified form of cardiopulmonary bypass to support both cardiac and pulmonary function. Technological improvements and miniaturisation have made this technique more accessible and its use has increased over the past years, especially in patients with refractory cardiogenic shock or circulatory arrest.[1,2]

Cardiogenic shock (CS) remains the leading cause of death in patients hospitalised for ST-segment elevation myocardial infarction (STEMI), as it may lead to multiorgan failure due to insufficient organ perfusion.[3,4] In addition to pharmacological measures, treatment with mechanical circulatory support can be considered, especially in more severe forms of circulatory failure.

The aim of mechanical circulatory support in general is to support the failing heart and the overall circulation. Ideally, mechanical support is used as a bridge to either recovery or to other therapies such as a surgically implanted ventricular assist device (LVAD) or heart transplantation. It can be used in cardiogenic shock to prevent the development of multi-organ failure. In cardiac arrest patients, mechanical circulatory support enables treatment of the underlying cause while maintaining adequate perfusion.

A multitude of mechanical support devices have been developed over the past decades and this field is attracting increasing attention, especially after clinical trials did not show any clinical benefit for the intra-aortic balloon pump (IABP). Current European guidelines on cardiogenic shock no longer support routine IABP therapy, whereas short-term mechanical circulatory support holds a class IIb recommendation.[5,6]

Percutaneous cannulation techniques facilitate rapid insertion and initiation of ECLS therapy in emergency situations, such as cardiac arrest. Although ECLS usage has increased and several observational studies suggest that it has had a beneficial effect in both cardiac arrest and cardiogenic shock, no randomised controlled trials have been performed to date. Therefore, the actual evidence for its efficacy remains limited.

The main purpose of our study was to conduct a systematic review and meta-analysis of the available literature comparing ECLS with conventional therapy with regard to survival and neurological outcome in patients with cardiogenic shock after acute myocardial infarction (AMI) and patients with refractory cardiac arrest.

METHODS

Selection criteria

Studies were considered for inclusion if they described outcome data from (A) patients with ECLS support and (B) a control group without ECLS support. Also, to qualify for

inclusion, patients must have been diagnosed with either (1) refractory in-hospital or out-of-hospital cardiac arrest or (2) cardiogenic shock after AMI. Studies that did not report on survival to discharge, 30-day outcome or 6-month outcome were excluded. This meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines.[7]

Search strategy

A medical librarian (J.L.) conducted a systematic search of OVID MEDLINE, OVID EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL) and the publisher subset of PubMed from inception to 7 December 2015. The search strategy consisted of controlled vocabulary (i.e. MeSH) and free text words for two basic concepts: (1) ECLS and (2) cardiogenic shock, cardiac arrest or myocardial infarction (see Appendix 1 for the entire MEDLINE search). Non-human studies, paediatric studies, case reports and reviews were excluded by double negation (NOT animals/ NOT humans/) and/or excluding words in the title. We cross-checked the reference lists and the citing articles of the identified relevant papers for additional references. The bibliographic records retrieved were downloaded, imported and de-duplicated in ENDNOTE.

Data extraction and quality assessment

The retrieved articles were screened for relevance on title and abstract, followed by full text screening by two independent investigators (D.O. and J.S.). In the event of overlapping patient cohorts the study with the longest follow-up period was included.

The pre-specified patient and outcome data were independently extracted by two investigators (D.O. and J.S.). Differences between reviewers regarding study selection or data extraction were resolved by consensus. The quality of the studies was assessed using a modified version of the Newcastle-Ottawa Quality Assessment Scale for Cohort Studies [8].

Data analysis

The primary endpoint was 30-day survival. Secondary outcomes were long-term survival and 30-day and long-term favourable neurological outcome. Parameters describing the clinical course and complications were extracted, e.g. successful weaning from the cardiac assist device, bridging to destination therapy (long term ventricular assist device or heart transplantation), timing of device placement, the occurrence of renal failure, stroke, peripheral vessel access complications and the need for blood transfusions (erythrocyte and fresh frozen plasma). If 30-day outcome data were not reported, in-hospital outcome data were used. For long-term data, the longest available follow-up was used. Neurological status was considered favourable when reported as either Pittsburgh Cerebral Performance Category (CPC) 1 or 2, or Modified Glasgow Outcome Score

(MGOS) ≥ 4. Studies were grouped and presented by patient category: cardiac arrest or cardiogenic shock. A subcategory of propensity-matched studies is reported separately. Propensity score matching is a method used to balance observed covariates in the 2 treatment arms by matching the propensity score which represents the probability of receiving ECLS therapy.

Results are presented as absolute risk differences with a 95% confidence interval (CI) and a number needed to treat (NNT) or number needed to harm (NNH) and were combined by a Mantel-Haenzel random effects model. Heterogeneity across studies was examined by the I^2 statistic. Potential publication bias was assessed by visual assessment of constructed funnel plots. Tests were 2-tailed and a p value of <0.05 was considered statistically significant. An I^2 of > 40% was considered to be an indication of substantial heterogeneity. Review Manager (version 5.3) was used for statistical analysis.

RESULTS

Search results

The de-duplicated results yielded a total of 1403 abstracts. A total of 59 relevant articles were identified and the full-text article was independently reviewed. Figure 1 shows a flowchart for selection of studies. One article was excluded as the intervention group contained both ECLS and IABP patients.[9] Fourteen articles were identified. Ten articles consisted of patients in refractory cardiac arrest.[10-19] However, two articles described the same cohort but with additional analysis.[17,19] This resulted in a total of 9 included cardiac arrest cohorts with a total of 3098 patients (708 ECLS versus 2390 control patients) (Table 1). Five of the cardiac arrest studies reported a propensity-matched analysis, including a total of 438 patients (219 in both groups).[10,11,13,15,19] Four studies consisted of patients with cardiogenic shock with a total of 235 patients (151 ECLS versus 84 control patients) (Table 1).[20-23]

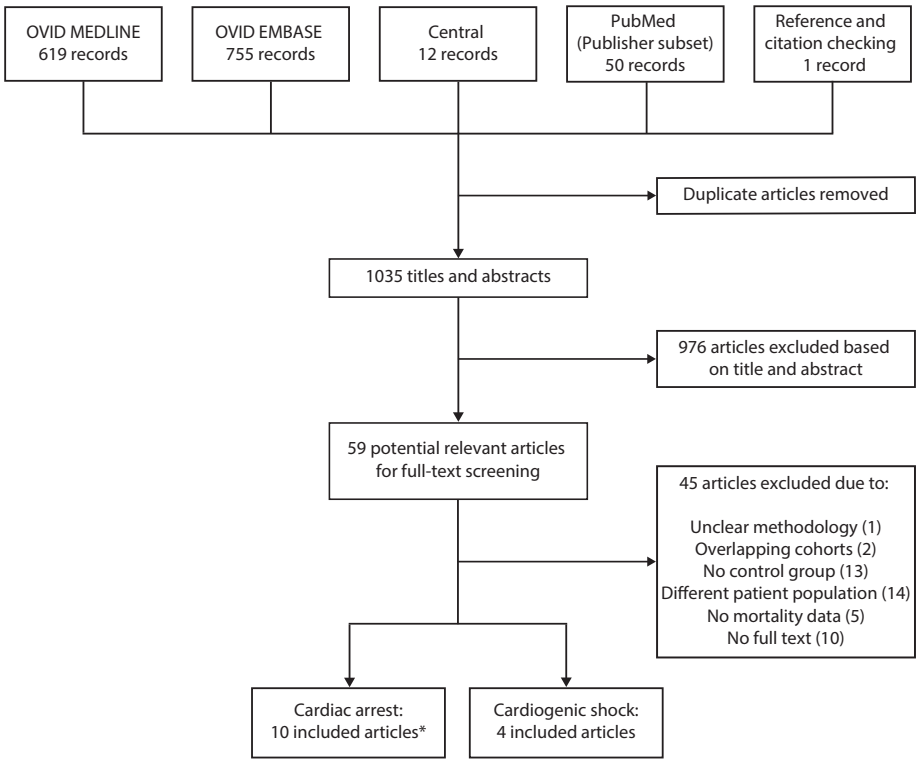

Figure 1 Flowchart of the search strategy and selection of studies.
1 article reported on the same patient cohort as another included article, but provided additional data on propensity matched analysis and was therefore included.

Quality of studies

As all studies were cohort studies and no randomised controlled trials were available, the quality of the studies was low with a high risk of bias (Appendix 2). However, funnel plots did not show skewed distributions, suggesting that no publication bias was involved (Appendix 3).

Table 1 Summary of included cohort studies on cardiogenic shock and cardiac arrest patients.

First author, year	Country	Study period	Setting	Follow-up duration	Number of patients
Cardiac arrest					
Blumenstein, 2015	Germany	2009-2013	Retrospective, single centre	long term *	353
Chen, 2008	Taiwan	2004-2006	Prospective, single centre	1 year	172
Chou, 2014	Taiwan	2006-2010	Retrospective, single centre	1 year	66
Kim, 2014	Korea	2006-2013	Prospective, single centre	3 months	499
Lee, 2015	Korea	2009-2014	Retrospective, single centre	in-hospital	955
Maekawa, 2013	Japan	2000-2004	Prospective, single centre	3 months	162
Sakamoto, 2014	Japan	2008-2011	Prospective, multi-centre	6 months	454
Shin, 2013	Korea	2003-2009	Retrospective, single centre	2 years	406
Siao, 2015	Taiwan	2011-2013	Retrospective, single centre	1 year	60
Cardiogenic shock					
Chamogeorgakis, 2013	USA	2006-2011	Retrospective, single centre	in-hospital	79
Lamarche, 2011	Canada	2000-2009	Retrospective, single centre	30 day	61
Sattler, 2014	Germany	2011-2012, 2012-2013	Retrospective, single centre	30 day	24
Sheu, 2010	Taiwan	1993-2002, 2002-2009	Prospective, single centre	30 day	71

** not defined, median long term follow-up was 1136 [823-1415] days.*

Cardiac arrest

Patient characteristics

Table 2 shows the baseline characteristics of the studies on ECLS in the setting of cardiac arrest. A total of 9 studies were included with 3098 patients in total, 708 in the ECLS group and 2390 in the control group. All studies included cardiac arrest patients, although with different inclusion criteria such as in-hospital cardiac arrest (IHCA), out-of-hospital cardiac arrest (OHCA), witnessed or non-witnessed cardiac arrest and differing durations of cardiopulmonary resuscitation (CPR). Overall, ECLS patients were more likely to be younger, male, suffer from acute myocardial infarction and to undergo primary PCI.

Table 2 Baseline characteristics of the studies on ECLS-assisted cardiac arrest.

				Number of patients (n)		Mean age (yrs)		Male (%)		Acute myocardial infarction (%)		Revascularisation (%)		CPR duration (min)		No flow time	
First author, year	**Patient population**	**Criteria for ECLS allocation/ placement**	**Control arm**	**ECLS**	**Control**	**ECLS**	**Control**	**ECLS**	**Control**	**ECLS**	**Control**	**ECLS**	**Control**	**ECLS**	**Control**	**ECLS**	**Control**
Blumenstein, 2015	witnessed IHCA	ECLS was considered by the ECLS team if CPR > 10 min and cardiac aetiology.	Conventional CPR	52	272	72	75	54	61	29	21	-	-	33 [19-47]	20 [6-40]	-[d]	-[d]
Chen, 2008	witnessed IHCA of cardiac origin, CPR > 10 min	The decision was made by the attending doctors in charge. Exclusion for ECLS: failure to wean from bypass due to post-cardiotomy shock and patients who experienced shock requiring elective ECLS.	Conventional CPR	59	113	57	60	85	65	63	71	44	6[a]	53±37	43±31	-[d]	-[d]
Chou, 2014	IHCA due to AMI, CPR > 10 min	The decision to carry out ECPR is determined by the cardiovascular surgeon.	Conventional CPR	43	23	61	70	93	74	100	100	100	43[a]	60±34	49±35	-[e]	-[e]
Kim, 2014	cardiac arrest patients with CPR (no trauma)	ECPR was indicated when presumed correctable cause of CA, witnessed arrest or presumed short no-flow time when unwittnessed arrest and informed consent of the family and in-hospital CPR > 10 min.	Conventional CPR	55	444	53	69	75	64	-	-	-	-	62 [47-89]	35 [21-50]	7 [0-13]	8 [5-12]
Lee, 2015	IHCA and OHCA CPR	Judgment of ECLS team. Only ECLS if CPR > 10 min or repetitive arrest events without ROSC > 20 min. No ECLS if unwitnessed OHCA or no bystander CPR.	Conventional CPR	81	874	59	64	69	65	67	41	-	-	43 [21-60]	30 [15-48]	-	-

Table 2 Baseline characteristics of the studies on ECLS-assisted cardiac arrest. (continued)

				Number of patients (n)		Mean age (yrs)		Male (%)		Acute myocardial infarction (%)		Revascularisation (%)		CPR duration (min)		No flow time	
First author, year	**Patient population**	**Criteria for ECLS allocation/ placement**	**Control arm**	**ECLS**	**Control**	**ECLS**	**Control**	**ECLS**	**Control**	**ECLS**	**Control**	**ECLS**	**Control**	**ECLS**	**Control**	**ECLS**	**Control**
Maekawa, 2013	Witnessed OHCA of presumed cardiac origin, CPR> 20 min	Initiation of ECPR was dependent on the attending physicians	Conventional CPR	53	109	54	71	83	73	-	-	40	6[b]	49 [41-59]	56 [47-66]	2 [0-8]	5 [0-9]
Sakamoto, 2014	OHCA based on VF/ VT, no ROSC > 15 min after hospital arrival, < 45 min between emergency call and hospital arrival; cardiac origin	Assignment of facility to ECPR or CPR group	Conventional CPR	260	194	56	58	90	89	64	59	38	11[b]	-	-	-	-
Shin, 2013	IHCA, witnessed, CPR > 10 min	According to the discretion of the CPR team leader	Conventional CPR	85	321	60	62	62	63	45	26	41	7[a]	42±26	41±37	-[d]	-[d]
Siao, 2015	Cardiac arrest with initial VF (start CPR < 5min), no ROSC after 10 min CPR	Judgment of the attending physician	Conventional CPR	20	40	55	60	90	70	60	40	60	40[c]	70±50	34±18	-[f]	-[f]

Values are presented as mean ± standard deviation or as median [IQR]. [a] reported as subsequent interventions (PCI or CABG); [b] Reported as primary PCI; [c] reported as subsequent interventions (PCI); CPR = cardiopulmonary resuscitation; PCI=Percutaneous coronary intervention; OHCA=Out-of-hospital cardiac arrest; IHCA=In-hospital cardiac arrest; ROSC=return of spontaneous circulation; AMI=acute myocardial infarction; VF=ventricular fibrillation; VT=ventricular tachycardia; CA=cardiac arrest; ECPR=ECLS-assisted cardiopulmonary resuscitation; [d] considered to be minimal as the inclusion criteria are (witnessed) IHCA. [e] IHCA so minimal no flow time. In this study CPR duration was defined as time from collapse till ROSC, death or running of ECMO machine. [f] not mentioned, but inclusion criteria state no flow less than 5 minutes.

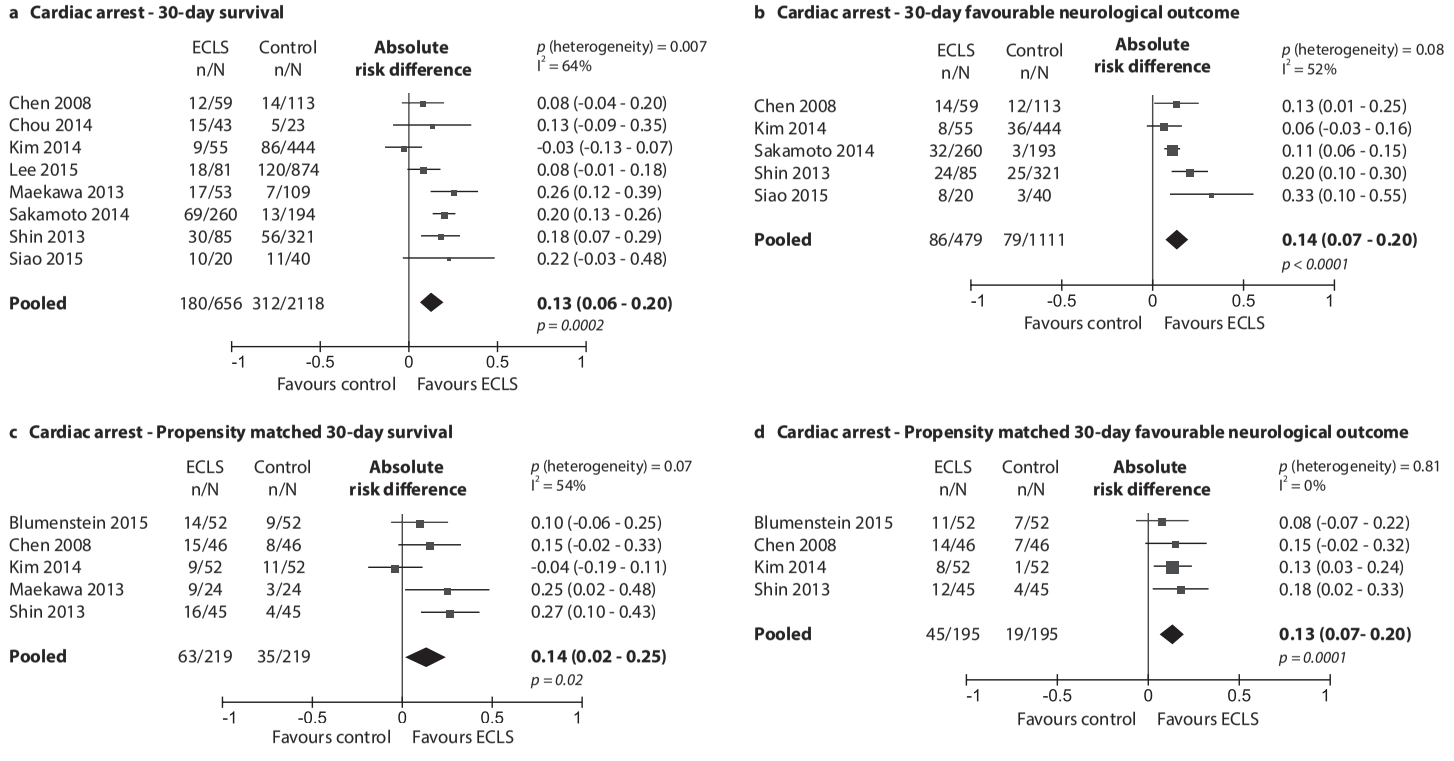

Figure 2 Risk difference of 30-day survival (A) and favourable neurologic outcome (CPC 1 or 2) (B) and propensity matched risk difference in 30-day survival (C) and favourable neurologic outcome (CPC 1 or 2) (D) in patients with cardiac arrest.

Survival

Figure 2A shows 30-day survival of patients with refractory cardiac arrest. The usage of ECLS in this setting was associated with increased survival at 30 days (absolute risk difference 13%; 95% CI 6 to 20%; p<0.001; NNT: 7.7). The long-term difference in survival was 15% in favour of the ECLS treated patients (see supplementary file) (absolute difference 15%; 95% CI 11 to 20%; p<0.0001; NNT 6.7). Short-term outcome data displayed substantial heterogeneity (I^2=64%), but long-term survival did not (I^2=28%).

Neurological outcomes

Favourable neurological outcomes, defined as CPC score 1 or 2, are shown in Figure 2B. The use of ECLS was associated with a higher rate of favourable neurological outcome at both 30 days (risk difference 14%; 95% CI 7 to 20%; p<0.0001; NNT 7.1), and during long-term follow-up (risk difference 11%; 95% CI 6 to 16%; p<0.0001; NNT 9.1) (supplementary data). Short-term outcome data were moderately heterogeneous (I^2=52%) but the long-term survival data did not show substantial heterogeneity (I^2=28%).

Other outcomes

Peripheral vessel complications were only reported by two studies. Blumenstein reported 17.3% of patients with leg ischemia or malperfusion in the ECLS arm and 2.9% in the control arm. Maekawa et al. reported 7.7% cannulation site infection, 15.4% leg ischemia requiring reperfusion and 2.9% compartment syndrome in the ECLS patient group (Supplementary data) 15. Complication rates were very poorly reported. Only one of the cardiac arrest studies reported on renal failure (1.9% in the ECLS patients versus 7% in the control patients) 10. Stroke and blood transfusions were not reported.

Propensity score matching

Five studies performed a propensity matched analysis to balance observed covariates in the two treatment groups. The propensity score reflects the probability of receiving ECLS therapy. The baseline characteristics, after matching based on propensity score, can be seen in the supplementary data.

The included patient population differed between studies in terms of location of the arrest (IHCA versus OHCA), witnessed or unwitnessed arrest, presumed cardiac origin and duration of CPR. After propensity matching, the patients treated with ECLS and control patients were comparable in terms of age and gender. There were more patients in the ECLS arm than in the control arm receiving primary PCI, as only one of the five propensity matched studies included primary PCI as a matching variable. The use of ECLS was associated with a higher survival rate at 30 days (difference 14%; 95% CI 2 to 25%; p=0.02; NNT 7.1) and in the long term (difference 13%; 95% CI 6 to 20%; p=0.001; NNT 7.7) (Figure 2C and supplementary data). Also, the use of ECLS was associated with

a higher rate of favourable neurological outcome at both 30 days (risk difference 13%; 95% CI 7 to 20%; p=0.0001; NNT 7.7), and in the long term (risk difference 14%; 95% CI8 to 20%; p<0.0001; NNT 7.1) (Figure 2D and supplementary data). In the propensity matched analysis, short-term survival showed substantial heterogeneity (I^2=54%), but long term survival and the neurological outcomes showed no substantial heterogeneity (I^2=0%).

Cardiogenic shock

Patient characteristics

Table 3 shows the baseline characteristics of the studies on ECLS in cardiogenic shock patients. A total of 4 studies were included with 235 patients in total, 151 in the ECLS group and 84 in the control group. All studies included cardiogenic shock patients after myocardial infarction, albeit with different inclusion criteria such as refractory CS, progressive CS or decompensated cardiomyopathy. In two studies, the control arm consisted of IABP support, and in two other studies, the control arm consisted of patients supported by Impella 5.0, Impella RD or TandemHeart. Patients in the ECLS arm were generally younger and were less likely to suffer from acute myocardial infarction (Table 3). In the two studies with IABP support in the control group, all patients were diagnosed with STEMI and treated with primary PCI.

Survival outcomes

Figure 3 shows the absolute number of survivors among patients with and without ECLS treatment, with the absolute risk difference for each study, stratified by the different control arms. The studies with IABP in the control arm showed that ECLS support in the setting of cardiogenic shock was associated with improved 30-day survival (risk difference 33%; 95% CI 14 to 52%; p=0.0008; NNT 3). When ECLS was compared with Impella or TandemHeart, ECLS was not associated with a significant difference in 30-day survival (risk difference -3%; 95% CI -21 to 14%; p = 0.70; NNH 33). When combining the control groups (IABP and Impella/TandemHeart), the use of ECLS was not associated with a change in 30-day survival in patients with cardiogenic shock (risk difference 14%, 95% CI -8% to 35%; p=0.20; NNT 7.1). The analysis stratified according to control arm did not show any heterogeneity (I^2=0%), but the overall effects were substantially heterogeneous (I^2=60%). The long-term survival and neurological outcomes were not described in these studies.

Table 3 Baseline characteristics of the studies on ECLS in cardiogenic shock patients.

				Number of patients (n)		Mean age (yrs)		Male (%)		Acute myocardial infarction (%)		Primary PCI (%)	
First author, year	**Patient population**	**Criteria for ECLS allocation/placement**	**Control arm**	**ECLS**	**Control**	**ECLS**	**Control**	**ECLS**	**Control**	**ECLS**	**Control**	**ECLS**	**Control**
Chamogeorgakis, 2013	postinfarction or decompensated cardiomyopathy (ischaemic or nonischaemic) cardiogenic shock	Patients receiving heart compressions, ECLS is the only option. For more stable patients, TandemHeart or Impella. For isolated right ventricular failure, TandemHeart is favoured. In left ventricular failure, Impella 5.0 or TandemHeart can be used.	Impella 5.0 / TandemHeart*	61	18	53	58	80	72	53	78	-	-
Lamarche, 2011	Acute, refractory, cardiogenic shock with potential for recovery and systemic perfusion did not improve with IABP and inotropes.	Biventricular failure and oxygenation problems: ECLS. Unilateral failure: Impella	Impella 5.0 / Impella RD	32	29	50	54	63	83	41	38	-	-
Sattler, 2014	Progressive cardiogenic shock due to acute myocardial ischaemia, and successful PCI	Enrollment during period with ECLS availability and ECLS is technically feasible.	IABP	12	12	55	68	83	83	100	100	100	100
Sheu, 2010	STEMI with primary PCI and profound cardiogenic shock [$]	Enrollment date in period with ECLS availability	IABP	46	25	65	67	-	-	100	100	100	100

** 7 Impella, 11 TandemHeart; $ profound shock: systolic blood pressure <75 mmHg despite inotropic agents and IABP. CPR = cardiopulmonary resuscitation; PCI=Percutaneous coronary intervention; AMI=acute myocardial infarction; VF=ventricular fibrillation; VT=ventricular tachycardia; CA=cardiac arrest; ECPR=ECLS-assisted cardiopulmonary resuscitation;*

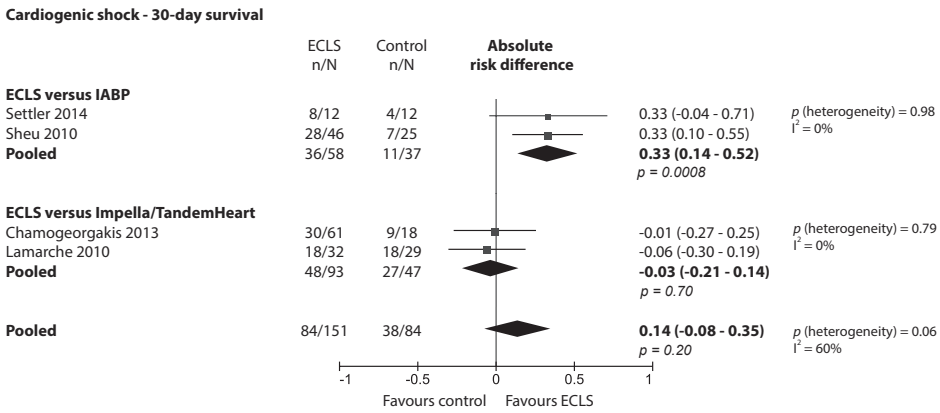

Figure 3 Difference of 30-day survival of patients with cardiogenic shock, stratified to different control therapies (IABP or Impella/TandemHeart).

Other outcomes

The percentage of patients who were successfully weaned from ECLS and the percentage of patients who were bridged to long-term ventricular assist device or heart transplant are shown in the supplementary data. Only Sattler et al. reported the time of device placement: in one patient, ECLS was placed before PCI, in 9 patients immediately after PCI and in 2 patients ECLS therapy was initiated within 24-48h after PCI with IABP support. Peripheral vessel complications and blood transfusions are shown in the supplementary data. Only one study reported the incidence of renal failure, with renal failure occurring in 58.3% of patients treated with ECLS and in 25.0% of the control patients 22. Stroke was not reported by any study.

DISCUSSION

We conducted two meta-analyses of cohort studies comparing ECLS therapy with varying control groups in the settings of cardiac arrest and cardiogenic shock. In the setting of cardiac arrest, the usage of ECLS showed an increase in survival of 13% and an increase of favourable neurological outcome of 14% at 30-day compared with no usage of ECLS. This effect was still prominent after baseline characteristics were adjusted by propensity matching. In patients with cardiogenic shock, ECLS was associated with higher 30-day survival compared with IABP, but there was no difference in survival when compared with Impella or TandemHeart.

In the absence of randomised controlled trials, we included non-randomised studies, and therefore cannot rule out the influence of confounders. As a result, there was a

difference in baseline characteristics between ECLS and control patients. ECLS-treated patients were more likely to be male, younger, suffer from acute myocardial infarction and were more likely to undergo primary PCI; all factors known to be associated with increased survival in this setting.[24-26] Another potentially important bias towards poor outcomes in the 'control/no-ECLS' group may be due to the fact that sicker patients may have been considered too ill to benefit from ECLS therapy and others may have died before they could receive ECLS therapy. As it is difficult to reliably distinguish between the effect of ECLS therapy and the effect of the bias and confounding inherent to cohort studies, the results of this analysis should be interpreted with caution. Nevertheless, the propensity-matched analysis in cardiac arrest, with matching baseline characteristics, showed results comparable with the outcome of the cohort studies.

In addition to the difference in baseline characteristics of the patients, differences in the treatment of patients might have influenced the results. Patients with cardiac arrest treated with ECLS were more likely to be revascularised. This finding suggests that the use of ECLS allows for more frequent revascularisation. Kagawa et al. investigated the effectiveness of intra-arrest PCI during ECLS, and they reported a higher survival rate in the intra-arrest PCI groups compared with delayed PCI (36% versus 12%).[27] The fact that ECLS-assisted CPR allowed for timely treatment of the underlying cause, such as intra-arrest PCI, might partly explain the increased survival in ECLS-assisted CPR.

In the cardiogenic shock patients, the difference in treatment effect may be explained by the amount of haemodynamic support that is generated by the mechanical support device. The used Impella devices (5.0 and RP) and TandemHeart actively support the circulation with around 4 L/min, which is comparable to ECLS, whereas the IABP only passively supports the overall circulation with approximately 0.5 L/min. However, a small meta-analysis of randomised trials comparing IABP (n=47) with Impella/TandemHeart (n=53) in CS complicating AMI, did not show any difference in outcome.[28] This seems to contradict the previous hypothesis that ECLS, TandemHeart and Impella 5.0 might all be superior to IABP as they provide more haemodynamic support. This apparent contradiction may be explained by the different characteristics of the patients included, the differences in definition of (profound) CS and the low number of patients included in both meta-analyses. Although the support level of the used devices may be similar (around 4 L/min), they have different specifications and therefore different clinical indications.[4,5]

The variety of inclusion criteria in the included studies is likely to have contributed to the heterogeneity. Although we aimed to include patients with acute myocardial infarction, some cardiogenic shock studies included patients with a wide variety of aetiologies (100% AMI in the IABP studies, but lower in the Impella/Tandemheart studies (no exact number reported)). In the cardiac arrest studies, there was variation in the location of the arrest, duration of no-flow and CPR. The inclusion criteria resulted in relatively low no-flow times as most studies included IHCA arrest, witnessed OHCA with bystander CPR, or

mandatory low no-flow times. It is not known whether shorter no-flow and CPR duration before deploying ECLS results in a better outcome compared with conventional CPR. However, survival and outcome deteriorate as duration of no-flow and CPR increases.[11]

Although vascular and bleeding complications are known to occur frequently during ECLS therapy, only a few of the included studies reported on these complications. Two previously published pooled-analyses of complications of ECLS both reported high complication rates.[29,30] They did not compare those rates with non-ECLS treated patients. In these pooled analyses, lower limb ischemia occured in 16.9 and 10.7%, which is comparable with our range of peripheral vessel complications, which is between 8.7 and 25%. The occurrence of events may be directly related to ECLS therapy, or indirectly to the critical conditions of patients treated with ECLS. Either way we must keep in mind that survival with good neurological outcome might outweigh the risk for complications. In addition, complications during ECLS can only occur when patients are still alive for complications to occur. Therefore, the value of complications in these extremely high risk patients is a relative one. The current meta-analysis found a survival rate of 45.2% in cardiogenic shock patients and 27.4% in the cardiac arrest patients treated with ECLS. These numbers are consistent with data from Xie et al., who performed a pooled analysis of observational cohort studies (without control arm) on patients treated with ECLS for refractory cardiogenic shock (n=659) or for cardiac arrest (n=277), and demonstrated a 30-day survival of 52.5% in CS and 36.2% in cardiac arrest.[31]

Currently, ECLS has a class IIb recommendation (may be considered) in the European and American guidelines on myocardial revascularization.[6,32] The European Resuscitation Council (ERC) guidelines recommend that ECLS assisted CPR should be considered to facilitate interventions.[33] Although the guidelines recommend consideration of ECLS, ECLS requires multidisciplinary expertise, which is often only available in a limited number of specialised centres. Experience is gained by providing ECLS support in remote locations and in the pre-hospital field to allow transfer to an experienced ECLS centre.[27,34-36] In addition, the high cost of ECLS is a limiting factor, which mandates appropriate case selection.

Although the findings of this meta-analysis were limited by the heterogeneity of included studies, in the absence of large randomised trials, this pooled analysis represents the best available method for evaluating ECLS. These data should be taken into account when updating the clinical guidelines on cardiac arrest. Ultimately, to clarify the role of ECLS in cardiogenic shock and cardiac arrest, a randomised controlled trial should be undertaken, however, many randomised trials in this patient category have been aborted as a result to low inclusion rates.[37] Therefore, while aiming for a randomised trial, large multicentre registries could be the first step towards identifying patients that may benefit from ECLS or other circulatory support devices.

In conclusion, the current meta-analysis aggregated all available evidence on the effectiveness of ECLS in the continuous field of cardiac failure, ranging from cardiogenic shock to cardiac arrest. In the setting of refractory cardiac arrest, the meta-analysis showed increased survival and favourable neurological outcomes in the ECLS treated patients. In the setting of cardiogenic shock there was an increased survival with ECLS compared with IABP.

CONFLICTS OF INTEREST

J.P.S. Henriques reports research grants outside the submitted work. The other authors do not declare any conflicts of interest.

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SUPPLEMENTARY DATA

Medline search

Database(s): Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present

Date of Search: 2015-12-07

#	Searches	Results
1	Extracorporeal Membrane Oxygenation/	6484
2	Extracorporeal Circulation/ and (heart-assist devices/ or cardiopulmonary resuscitation/ or advanced cardiac life support/)	243
3	(Extracorporeal Circulation/ or (extracorp* or extra-corp*).tw,kf.) and (((cardiopulm* or cardio-pulm*) adj2 resuscit*) or CPR).tw,kf.	500
4	((extracorp* or extra-corp*) adj6 (membran* oxygenat* or life support*)).tw,kf.	7120
5	(ECLS or E-CMO or ECLS or E-CLS).tw,kf.	4847
6	(ECPR or E-CPR or ECCO).tw,kf.	318
7	or/1-6 [ECLS/ECPR]	9983
8	(exp animals/ not humans/) or (porcine or piglet or pig or pigs or rat or rats or dogs or dog or canine).ti.	4287547
9	((child* or p?ediatr* or infant* or neonat* or prenat* or postnat* or neo-nat* or pre-nat* or post-nat* or babies or "after birth") not (adolesc* or adult* or elder*)).ti.	962506
10	8 or 9 [animals (not humans) and children (not adults)]	5206353
11	7 not 10 [human adults studies on ECLS/ECPR]	6834
12	exp Databases, Bibliographic/ or meta-analysis/ or (meta analy* or metaanaly* or meta?analy*).tw,kf. or ((systematic* adj3 (review or literature or evidence or search*)) or ((summari* or review) adj3 evidence) or (search* adj12 (literature* or ((electronic or medical or biomedical) adj3 database*) or exhaustive)) or medline or pubmed or embase or psychinfo or (CENTRAL and cochrane) or "Central Register of Controlled Trials").tw. or (cochrane or clinical evidence or EBM).jw. [SR-filter]	246553
13	11 and 12 [secondary human studies ECLS/ECPR]	127
14	(expert or current or cochrane or clinical evidence or EBM).jw. or exp guideline/ or exp Databases, Bibliographic/ or editorial/ or books/ or case reports/ or (systematic* adj3 (review or literature)).ti. or ((search* adj12 (literature* or ((electronic or medical or biomedical) adj3 database*) or exhaustiv* or systematic*)) or medline or pubmed or embase or psychinfo or (CENTRAL and cochrane) or "Central Register of Controlled Trials").tw. or (cochrane or clinical evidence or EBM).jw. or ((review/ or meta-analysis/ or (conferenc* or congress*).hw. or (meta analy* or metaanaly* or meta?analy*).ti,ot,kw. or (systematic* adj3 (review or literature)).tw,kw.) not (exp clinical trial/ or comparative study/ or feasibility studies/ or evaluation studies/ or validation studies/ or exp cohort studies/ or cross-sectional studies/ or case-control studies/ or multicenter study/)) [filter for exclusion non-primary studies]	4321268
15	11 not 14 [primary human studies on ECLS]	3893
16	shock, cardiogenic/	6795
17	heart arrest/ or out-of-hospital cardiac arrest/	25709
18	(cardiogen* adj9 shock*).tw,kf.	8266
19	((cardia* or coronar*) adj4 shock*).tw,kf.	2430
20	((card* or heart) adj3 arrest*).tw,kf.	30484
21	(IHCA or OHCA).tw,kf.	1050
22	exp myocardial infarction/co	26379
23	(post-infarct* or postinfarct*).tw,kf.	6808
24	((refractory or "secondary to" or rescue* or following or acute) adj6 (CS or AMI or MI or NSTEMI or STEMI or infarct* or coronary syndrom*)).tw,kf.	93739

#	Searches	Results
25	(refractory adj3 (ventricular arr?yt* or ventricular fibrillat* or tachycard*)).tw,kf.	1083
26	or/16-25	158791
27	13 and 26 [secondary studies ECLS + CS]	30
28	remove duplicates from 27	30
29	15 and 26 [primary studies on ECLS + CS]	640
30	remove duplicates from 29	619

Supplementary Table 1 Quality assessment.

Assessment of study quality using a modified version of the Newcastle-Ottawa Quality Assessment Scale for Cohort studies

	Selection (4)				Comparability (1)		Outcome (3)		
	Study population clearly defined	>50% AMI CS or CA with cardiac etiology	Exposed and non-exposed cohort selected from same cohort	Definition and selection of the non-exposed cohort	Study controls for age	Study controls for CPR[$]	Adequacy of follow up of cohorts	Follow-up long enough (>30 days)	Clinical course well described*
Cardiogenic shock									
Chamogeorgakis, 2013	*	*	*	-	-	-	*	-	-
Lamarche, 2011	*	-	-	*	-	-	*	-	-
Sattler, 2014	*	*	*	*	-	-	*	-	-
Sheu, 2010	*	*	-	*	-	-	*	-	*
Cardiac arrest									
Blumenstein, 2015	*	-	*	*	-	-	*	*	-
Chen, 2008	*	*	*	-	*	-	*	*	-
Chou, 2014	*	*	*	*	-	-	*	*	-
Kim, 2014	*	*	*	-	-	-	*	*	-
Lee, 2015	*	-	*	*	-	-	*	*	-
Maekawa, 2013	*	*	*	-	-	-	*	*	*
Sakamoto, 2014	*	*	-	*	-	-	*	*	-
Shin, 2013	*	-	*	*	*	*	*	*	-
Siao, 2015	*	*	*	-	-	-	*	*	-

[$] *in the cardiogenic shock cohort: before admission; in the cardiac arrest cohort: CPR duration; * revascularisation, CPR duration and complications are described.*

Supplementary Table 2 Clinical course of studies on both cardiogenic shock as cardiac arrest patients.

First author, year	Control arm	Number of patients (n)		Weaning from cardiac assist device (%)		Periferal vessel complications (%)		Bridge to long term VAD or HTX		Blood transfusions (erythrocyte)		Blood transfusions (FFP)		Duration of support (hrs)	
		ECLS	Control	ECLS	Control	ECLS	Control	ECLS	Control	ECLS	Control	ECLS	Control	ECLS	Control
Cardiac arrest															
Blumenstein, 2015	Conventional CPR	52	272	-	-	17.3	2.9	5.8	-	-	-	-	-	-	-
Chen, 2008	Conventional CPR	59	113	49.2	-	-	-	13.6	0.0	-	-	-	-	110 ± 128	-
Chou, 2014	Conventional CPR	43	23	-	-	-	-	-	-	-	-	-	-	-	-
Kim, 2014	Conventional CPR	55	444	-	-	-	-	-	-	-	-	-	-	-	-
Lee, 2015	Conventional CPR	81	874	-	-	-	-	-	-	-	-	-	-	-	-
Maekawa, 2013	Conventional CPR	53	109	-	-	25.0	-	-	-	-	-	-	-	-	-
Sakamoto, 2014	Conventional CPR	260	194	-	-	-	-	-	-	-	-	-	-	-	-
Shin, 2013	Conventional CPR	85	321	-	-	-	-	2.4	0.9	-	-	-	-	-	-
Siao, 2015	Conventional CPR	20	40	-	-	-	-	-	-	-	-	-	-	79.7 ± 35.9	-
Cardiogenic shock															
Chamogeorgakis, 2013	Impella 5.0 / TandemHeart *	61	18	19.7	33.3	13.1	22.2	42.6	27.8	-	-	-	-	-	-
Lamarche, 2011	Impella 5.0 / Impella RD	32	29	46.9	41.4	15.6	3.4	28.1	25.0	18 [9-34]	4 [2-9]	14 [8-28]	2 [0-8]	46.3 [27-99]	63.3 [41-142]
Sattler, 2014	IABP	12	12	-	-	16.7	8.3	-	-	21 ± 12	1 ± 1	8 ± 6	0	110 ± 69	-
Sheu, 2010	IABP	46	25	78.3	-	8.7	-	2.2	-	-	-	-	-	-	-

*Values are presented as mean ± standard deviation or as median [IQR]. * 7 Impella; 11 TandemHeart; CPR = cardiopulmonary resuscitation; PCI=Percutaneous coronary intervention; OHCA=Out-of-hospital cardiac arrest; IHCA=In-hospital cardiac arrest; ROSC=return of spontaneous circulation; AMI=acute myocardial infarction; VF=ventricular fibrillation; VT=ventricular tachycardia; CA=cardiac arrest; ECPR=ECLS-assisted cardiopulmonary resuscitation; VAD = ventricular assist device; HTX: heart transplantation; FFT = Fast Frozen Plasma.*

Supplementary Table 3 Baseline characteristics of the propensity matched studies on ECLS-assisted cardiac arrest.

			Propensity matching		Number of patients (n)		Mean age (yrs)		Male (%)		Acute myocardial infarction (%)		Revascularisation (%)		CPR duration (min)	
First author, year	Patient population	Criteria for ECLS allocation/ placement	Matching	Matching variables	ECLS	Control	ECLS	Control	ECLS	Control	ECLS	Control	ECLS	Control	ECLS	Control
Blumenstein, 2015	Witnessed IHCA	ECLS was considered by the ECLS team if CPR > 10 min and cardiac aetiology.	1:1	All of the covariates such as age, gender, LVEF and all parameters revealed in the univariate analysis to be predictive of mortality were used in the propensity score. CPR duration was additionally adjusted during the matching process using the propensity score.	52	52	72	73	54	60	29	37	32	17 *	33 [19-47]	37 [30-45]
Chen, 2008	Witnessed IHCA of cardiac origin, CPR > 10 min	The decision was made by the attending doctors in charge. Exclusion for ECLS: failure to wean from bypass due to post-cardiotomy shock and patients who experienced shock requiring elective ECLS.	1:1	Age, sex, initial cardiac rhythm, time point of CPR, CPR duration, the presence of comorbidities	46	46	57	55	85	87	61	72	17	7 $	53 ± 41	47 ± 33
Kim, 2014	Cardiac arrest patients with CPR (no trauma)	ECPR was indicated when presumed correctable cause of CA, witnessed arrest or presumed short no-flow time when unwitnessed arrest and informed consent of the family and in-hospital CPR > 21 min.	1:1	Age, sex, comorbidity score, bystander CPR, witnessed cardiac arrest, first rhythm, presumed etiology, time to CPR, CPR duration and therapeutic hypothermia.	52	52	54	54	77	73	85	89	56	6 ^	63 [49 -88]	61 [40 - 84]

Supplementary Table 3 Baseline characteristics of the propensity matched studies on ECLS-assisted cardiac arrest. (continued)

			Propensity matching		Number of patients (n)		Mean age (yrs)		Male (%)		Acute myocardial infarction (%)		Revascularisation (%)		CPR duration (min)	
First author, year	Patient population	Criteria for ECLS allocation/ placement	Matching	Matching variables	ECLS	Control	ECLS	Control	ECLS	Control	ECLS	Control	ECLS	Control	ECLS	Control
Maekawa, 2013	Witnessed OHCA of presumed cardiac origin, CPR> 20 min	Initiation of ECPR was dependent on the attending physicians	1:1	Age, activities of daily living, CPR by witness, initial rhythm VF/VT, number of countershocks, time of arrest to advanced life support, CPR duration, therapeutic hypothermia, IABP usage and primary PCI	24	24	57	57	79	79	-	-	21	25 ^	49 [43-66]	52 [43-65]
Shin, 2011	IHCA, witnessed, CPR > 10 min, cardiogenic shock	At the discretion of the CPR team leader	1:1	Age, gender, study period, comorbidities, Illness category (Cardiac/Medical), SOFA-score, Deyo-Charlson score APACHE II score, any procedure before arrest (PCI, cardiotomy, non-cardiac surgery),cause of arrest, Initial rhythm, CPR duration, ROSC, location of arrest, time zone of arrest (weekend/holiday or 7AM - 11PM)	45	45	64	62	58	71	49	49	51	9 $	38 ± 19	37 ± 19

Values are presented as mean ± standard deviation or as median [IQR]. CPR = cardiopulmonary resuscitation; PCI=Percutaneous coronary intervention; OHCA=Out-of-hospital cardiac arrest; IHCA=In-hospital cardiac arrest; ROSC=return of spontaneous circulation; AMI=acute myocardial infarction; VF=ventricular fibrillation; VT=ventricular tachycardia; CA=cardiac arrest; ECPR=ECLS-assisted cardiopulmonary resuscitation;

Supplementary Table 4 Clinical course of propensity matched studies on cardiac arrest.

	Number of patients (n)		Weaning from cardiac assist device (%)		Peripheral vessel complications (%)		Bridge to long term VAD or HTX		Bleeding or haemoatoma with need for transfusion (%)		Sepsis/systemic inflammatory response syndrome (%)		Acute kidney failure (%)		Rate of ROSB/ ROSC	
First author, year	**ECLS**	**Control**	**ECLS**	**Control**	**ECLS**	**Control**	**ECLS**	**Control**	**ECLS**	**Control**	**ECLS**	**Control**	**ECLS**	**Control**	**ECLS**	**Control**
Blumenstein, 2015	52	52	-	-	17.0	2*	6	0	33	14	8	10	2	10	-	-
Chen, 2008	46	46	-	-	-	-	-	-	-	-	-	-	-	-	91	52
Kim, 2014	52	52	-	-	-	-	-	-	-	-	-	-	-	-	81	39
Maekawa, 2013	24	24	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Shin, 2011	45	45	-	-	-	-	-	-	-	-	-	-	-	-	-	-

*VAD = ventricular assist device; HTX: heart transplantation; ROSC=return of spontaneous circulation for conventional CPR; ROSB=return of spontaneous beating for ECLS assisted CPR. * Malperfusion of the le.*

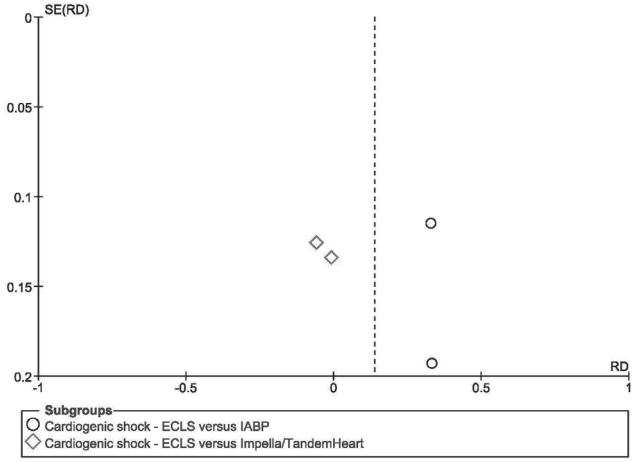
Supplementary Table 5 Configuration and set-up of the ECLS system.

First author, year	Centrifugal pump	Cannulation	Arterial catheter size	Venous catheter size	Anterograde reperfusion catheter limb	Initiation pump flow	Aim ACT value
Cardiac arrest							
Blumenstein, 2015	Rotaflow, Maquet	Percutaneous femoral artery and vein (Seldinger technique or surgical cutdown)	16-18 F	22 F	yes (8 F)	3-4 L/min	160-180 sec
Chen, 2008	Bio-Pump, Medtronic	Femoral cannulation was preferred	-	-	if necessary	50-100 ml/kg/min	160-180 sec (220 sec during weaning)
Chou, 2014	Biomedicus Pump Console - 560, Medtronic	Direct cutdown of femoral artery and vein	-	-	-	60 mL/min/kg	-
Kim, 2014	Twin-pulse life support (T-PLS), NewHeartbio	Percutaneous femoral artery and vein, Seldinger technique	15-17 F	21-23 F	-	2.5-3.0 L/min	200-220 sec
Lee, 2015	-	-	-	-	-	-	-
Maekawa, 2013	Capiox (EBC), Terumo	Percutaneous femoral artery and vein cannulation (no femoral cutdown)	15-17 F	19-21 F	if necessary	50-60 mL/min/kg	-
Sakamoto, 2014	All types allowed	Femoral artery and vein (any method is allowed)	-	-	is allowed	> 4 L/min	1.5 - 2.5 times normal value
Shin, 2013	Capiox Emergency Bypass System (EBC), Terumo	Percutaneously in the majority, surgically in challenging cases	14-21 F	21-28 F	yes	2.2 L/min/BSA	-
Siao, 2015	Bio-Pump, Medtronic	Femoral cannulation	-	-	-	> 2 L/min	180-220 sec

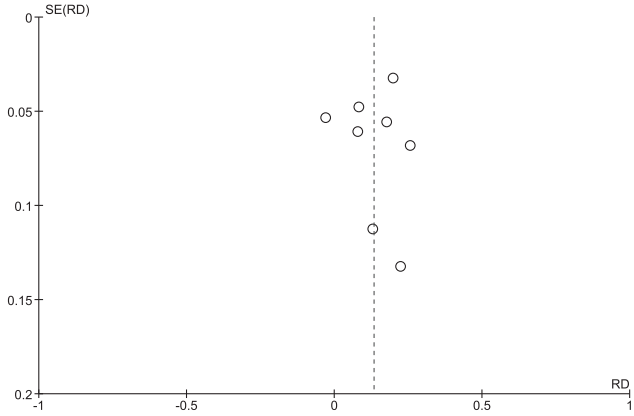
Supplementary Table 5 Configuration and set-up of the ECLS system. (continued)

First author, year	Centrifugal pump	Cannulation	Arterial catheter size	Venous catheter size	Anterograde reperfusion catheter limb	Initiation pump flow	Aim ACT value
Cardiogenic shock							
Chamogeorgakis, 2013	-	Peripheral cannulation femoral vein and axillary artery with a side graft or femoral artery with direct cannulation.	-	20-24 F	yes	-	-
Lamarche, 2011	Biomedicus, Medtronic and Rotaflow, Maquet	Percutaneous veno-arterial. In postcardiotomy patients central or peripheral veno-arterial cannulation	17-23 F	20-29 F	-	-	- [1]
Sattler, 2014	-	Femoral artery and vein	-	-	-	-	-
Sheu, 2010	Terumo	Percutaneous femoral artery and vein	-	-	yes	2-3 L/min	150-180 sec

[1] *Herparin was used during cannulation and weaning only. ACT = activated clotting time; BSA = body surface area*

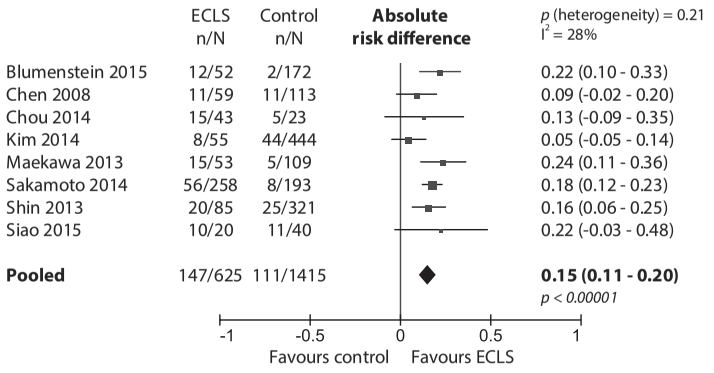


Supplementary Figure 1 Funnel plot for the 30-day survival in patients receiving ECLS for cardiogenic shock.
SE = standard error. RD=mean risk difference.

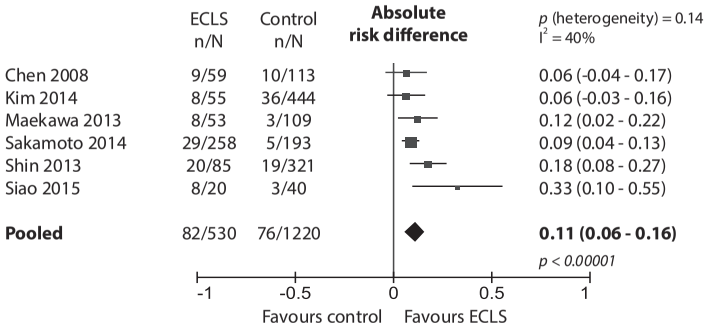


Supplementary Figure 2 Funnel plot for the 30-day survival in patients receiving ECLS for cardiac arrest.
SE = standard error. RD=mean risk difference.

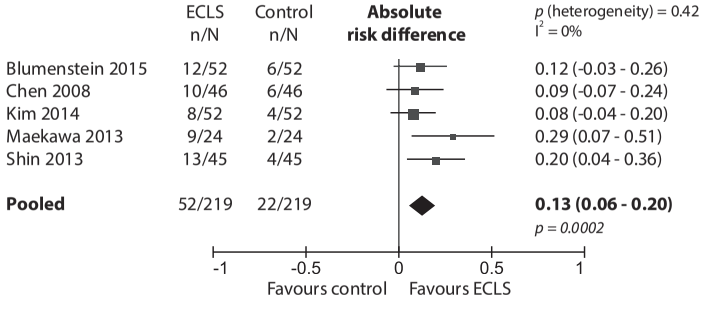
a Cardiac arrest - long term survival



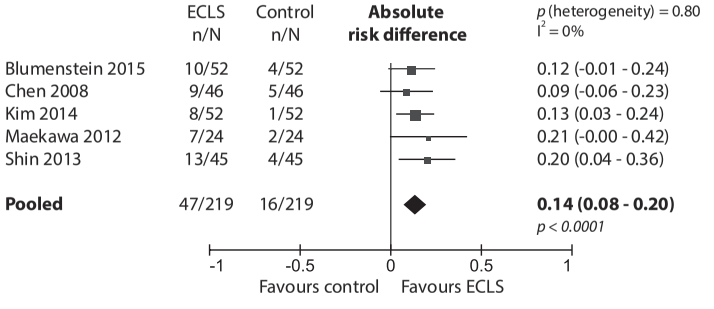
b Cardiac arrest - long term favourable neurological outcome



c Cardiac arrest - Propensity matched - long term survival



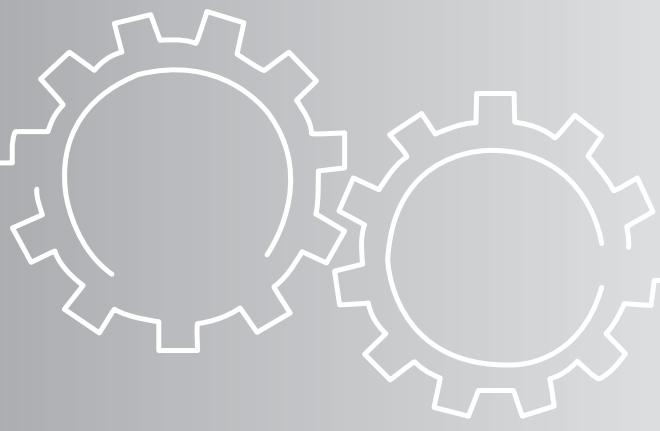
d Cardiac arrest - Propensity matched - long term favourable neurological outcome



Supplementary Figure 3 Long term outcomes cardiac arrest.

Risk difference of (A) long term survival and (B) long term favourable neurologic outcome (CPC 1 or 2) in patients with cardiac arrest. Propensity matched difference in (C) long term survival and (D) long term favourable neurologic outcome (CPC 1 or 2) in patients with cardiac arrest.

CHAPTER 12



THE ICM RESEARCH AGENDA ON EXTRACORPOREAL LIFE SUPPORT

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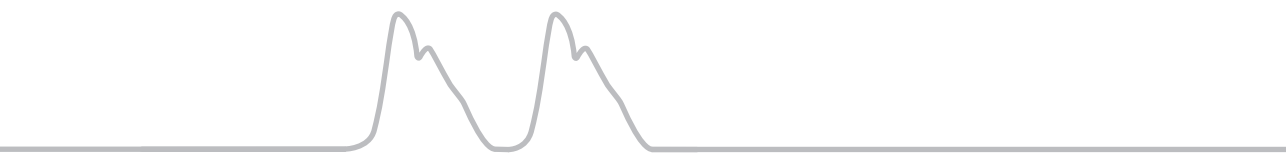

Submitted

ABSTRACT

Extracorporeal membrane oxygenation (ECMO) is an attractive technique for intensivists. The use of veno-venous ECMO (VV-ECMO) is increasing in the most severe forms of acute lung injury. In patients with cardiogenic shock, short-term veno-arterial ECMO (VA-ECMO) provides both pulmonary and circulatory support. Technological improvements and recently published studies suggest that ECMO is able to improve patients' outcomes. There are however many uncertainties regarding the real benefits of this technique both in hemodynamic and respiratory failure, the territorial organization to deliver ECMO, the indications and the use of concomitant treatments. There is no doubt that ongoing and future studies will be able to resolve these issues.

INTRODUCTION

Extracorporeal membrane oxygenation (ECMO) is an old technique that has benefiticated from recent technical improvements. Interest for venovenous ECMO (VV-ECMO) for the most severe forms of severe acute lung injury, including acute respiratory distress syndrome (ARDS) has been renewed since the publication of the CESAR study [1] and its extensive use during the H1N1 pandemic [2-5]. In patients with cardiogenic shock, mortality remains high despite advances in treatment. Short-term percutaneous mechanical circulatory support (MCS) devices can be used for cardiogenic shock patients refractory to conventional therapies. Veno-arterial ECMO (VA-ECMO) provides both pulmonary and circulatory support and can be used as a bridge to myocardial recovery or to other therapies such as transplantation or the implantation of a long-term ventricular assist device (VAD). Even with the many advances in the last decade, a lot of uncertainties remain concerning the use of ECMO during respiratory and/or cardiogenic failure. This review summarizes recent developments and identifies the main areas for future research.

CURRENT STANDARD OF CARE

VV-ECMO for acute respiratory failure

Positive results of the CESAR trial and the successful rescue of the most severe ARDS cases associated with the Influenza A(H1N1) pandemic have led to an exponential use of VV-ECMO for acute respiratory failure in the last decade.[1-7] High blood flow through ECMO circuits to provide full blood oxygenation and CO2 elimination is now considered as a reasonable option to support patients with severe acute lung injury refractory to conventional measures. Alternatively, VV-ECMO may be applied in less severe patients in whom it might allow "lung rest" by lowering airway pressures and tidal volume rather than improving oxygenation per se.[8] Cannulation strategies for VV-ECMO can either include two single-lumen cannulas or one double-lumen cannula, the latter currently can only be implanted via the right internal jugular vein.[8] Most commonly the right femoral vein for outflow and the right internal jugular vein for return flow are used, although the best cannulation configuration has not been tested in randomized trials. Less blood recirculation within the ECMO circuit occurs with double-lumen cannulas.[9] They might however be reserved for selected indications (mobilization, groin cannulation impossible), as they are more expensive, flow restricted and potentially more hazardous to implant.

Support of the cardiogenic shock patient

Although there is no strong scientific evidence to support routine MCS therapy in cardiogenic shock patients to date, its use is increasing since that it can provide emergency circulatory support while a definite solution is sought.[10,11]

Most of these highly instable patients receive a device as salvage therapy after having already developed signs of multiple organ failure. In these situations, mechanical assistance is frequently used as a bridge to decision, in which cardiogenic shock patients are rescued and optimized until cardiac recovery allowing weaning from MCS or implantation of a surgical solution such as durable VAD or heart transplantation. In the last decade, VA-ECMO has become the first-line therapy in this setting since it provides both respiratory and cardiac support, is easy to insert, even at the bedside, provides stable flow rates, and is associated with less organ failure after implantation compared to large biventricular assist-devices that require open-heart surgery. [12,13] Other short term MCS devices are the Impella© (ABIOMED Inc., Danvers, MA, USA) that is a catheter-based axial pump positioned retrogradely across the aortic valve into the left ventricle and the TandemHeart© (TandemLife, Pittsburgh, PA, USA) that is an extracorporeal centrifugal pump that drains blood from the left atrium via a cannula introduced trans-septally through the femoral vein and pumps back blood into the femoral artery.[14-16] Compared to VA-ECMO, these systems are more expensive and are not adapted to patients with severe biventricular failure. The traditional configuration for peripheral VA-ECMO involves femoral venous drainage and femoral arterial reinfusion. ECMO cannulation can also be performed by direct transthoracic access of cardiac cavities following cardiac operations. Accepted medical indications for MCS may be classified into the following categories[12,13] acute myocardial infarction complicated by cardiogenic shock[13,17,18], acute decompensated heart failure with refractory cardiogenic shock[12], fulminant myocarditis[19], cardiotoxic drug intoxication[20], stress-induced cardiomyopathy[13], post cardiac arrest resuscitation syndrome[21], decompensated pulmonary vascular disease, or massive pulmonary embolism, the highest rate of survival being reported in these case-series for acute myocardial infarction and fulminant myocarditis.[17,19,22] In a single-center, retrospective study, cardiogenic shock post MI patients treated with PCI and adjunctive ECMO had a higher 30 day survival than historical controls without ECMO (60% vs 35%).[18] MCS therapy can be initiated in case of low cardiac output syndrome after heart surgery.[23] A retrospective single-center study of 517 post-heart surgery VA-ECMO patients reported an incidence of 1.28% with hospital survival of only 25%.[24] Successful VA-ECMO therapy in primary graft failure following heart transplantation is encouraging.[25] Earlier initiation of MCS in cardiac surgery, preoperatively or postoperatively, might improve the outcomes of these patients.[26]

ECMO for cardiac arrest resuscitation (ECPR)

Extracorporeal cardiopulmonary resuscitation with ECMO (ECPR) can give a chance for better neurologic outcome than conventional CPR for in-hospital (IHCA) and out-of-hospital (OHCA) cardiac arrest patients and contribute to organ donation in those who die.[27-29] A landmark study of 46 IHCA patients demonstrated that ECPR provided significantly higher 1-year survival than conventional CPR.[30] Similar results were reported by Shin et al. in 85 IHCA ECPR patients. [31] Results of ECPR for OHCA patients are more contrasted. Single center studies from Japan in which transport time from scene to ECMO center was around 30 minutes, reported up to 30% survival with good neurological outcome. However, a French series of 51 OHCA ECPR patients for whom mean ischemic time was 120 minutes reported only two survivors.[32] Survival with favorable neurological recovery was low although better than in control patients (11% vs 2%), in the largest (260 VF/VT patients) multi-center (20 hospitals) prospective observation study of ECPR in Japan.[33] Lastly, survival was not improved in ECPR OHCA patients in a large Korean nationwide OHCA database.[34] Data from all these ECPR studies stress that shorter time from collapse to ECMO and then early coronary angioplasty are the most important determinants of outcomes.

MAJOR RECENT ADVANCES

Technical breakthrough in ECMO equipment

The renaissance of ECMO for severe cardiac and respiratory failures was accelerated by several major technical developments. First, the old silicon membrane oxygenators were replaced by miniaturized, low resistance poly-methyl-pentene oxygenators. These systems offer more effective gas exchange with lower resistance to flow, have smaller priming volumes, are more biocompatible with less platelet and plasma protein consumption and are coated with thrombo-resistant coating allowing less anticoagulation.[6,35] Second, centrifugal pumps permitted major improvement in efficacy and security over the older roller pumps, with less blood cell trauma, no requirement for venous reservoirs, and very few failure over weeks of support.[6,35] More recently, the continuing miniaturization of devices permitted the integration of pump and oxygenator within one low weight device and has facilitated transport by mobile ECMO teams.[36] Lastly, sensors without direct blood contact to continuously measure pressures as well as hemoglobin and venous saturation are useful tools for enhanced circuit and patient safety.

Extracorporeal Life Support Organization and the International ECMO Network

The Extracorporeal Life Support Organization (ELSO, https://www.elso.org) maintains a large international registry since 1989 and has collected data on over 75000 ECMO

patients. Important data regarding patients' selection, ECMO results and center organization has been derived from the registry over the last 25 years.[37-40] This organization also provides valuable resources to clinicians, ECMO center directors and coordinators, hospital directors and health care organizations [9] and organizes regular training activities and meetings. Centers providing ECMO should be encouraged to join ELSO to benchmark their results against other national and international institutions, participate to epidemiologic studies. The recently formed International ECMO Network (ECMONet http://www.internationalecmonetwork.org) is a growing consortium of ECMO centers and individuals dedicated to conducting high quality, high impact research in the field. By ensuring that expert centers adhere to current best practices for the organization and conduct of ECMO, this group aims to foster the highest quality research.

Regional/National Organization of ECMO support

The soaring growth of centers performing ECMO in adult patients has occurred mostly in the absence of oversight or coordination.[41] However, recent data from the ELSO registry suggested an inverse linear relationship between case volume and mortality, with centers performing more than 30 adult ECMO cases per year having a significantly lower mortality than centers performing fewer than 6 cases per year.[40] Although the minimum acceptable case-volume for an ECMO center remains controversial, many centers conduct few cases annually and outcomes may be suboptimal in this setting.[41] By creating networks of hospitals at the local or regional level (Figure 1), and concentrating case volume in expert centers, using standardized protocols for case selection and management, outcomes would certainly improve. Recent attempts to build regional ECMO networks suggest that some of these goals can be met.[3,42,43] However, experience with directing ECMO cases to high-volume centers is limited, and has not been scientifically proven superior as a strategy. A recent study even suggested that low-volume centers have better ECMO in-hospital mortality than high-volume centers[44], questioning the existence of a positive volume-outcome relationship in this population. Another unresolved issue is the nurse-to-patient ratio for ECMO patients.[45]

ECMO retrieval teams

Since evidence has accumulated that ECMO should be performed in specialized centers to obtain better results, retrieval of patients on ECMO by mobile ECMO teams has become an indispensable precondition for ECMO centers.[9,40] The mobile team ideally should be available 24 hours a day, 7 days a week and employ experienced personnel trained in the transport of critically ill patients, insertion of ECMO cannulae, and circuit and patient management.[9] Successful transportation of patients on cardiopulmonary support by ambulance, helicopter, and fixed-wing aircraft has been reported.[42,46-48] Centers performing ECMO should develop specific guidelines and ensure adequate

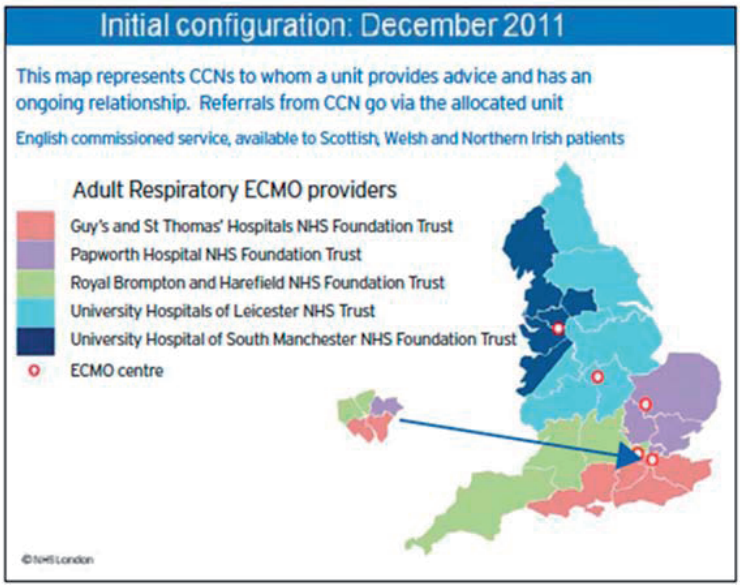

Figure 1 The regional coverage of England by the National Severe Respiratory Failure Service.

staff training to provide uninterrupted availability of transport on ECMO. Development of telemedicine is also important to improve patients selection for ECMO, but also to provide adequate advices regarding alternative strategies to ECMO to less experienced centers.

Scoring systems to predict the outcomes

In very recent years, several scoring systems to predict the outcomes of patients after ECMO for cardiac or respiratory indications have been proposed.[17,38,49-52] Respiratory scores constantly demonstrated the strong negative impact of older age, immunocompromised status, associated extra-pulmonary organ dysfunction, pre-ECMO duration of mechanical ventilation, impaired pulmonary compliance and non influenza-induced ARDS diagnosis. In addition, the RESP and the PRESERVE scores [17,52] were consistent with recent randomized controlled trials by demonstrating that pre-ECMO prone positioning and neuromuscular blockade were associated with improved survival. Interestingly, no predictive score has shown hypoxemia to be predictive of survival in this setting. The survival after veno-arterial-ECMO (SAVE)-score based on the ELSO registry data from 3846 cardiogenic shock patients showed that preexisting comorbidities, pre-ECMO organ failures and cardiac arrest, lower pulse pressure, and lower serum bicarbonate were risk factors associated with mortality.[38] The ENCOURAGE score, which was constructed on data from VA-ECMO-treated acute myocardial infarction patients, demonstrated

the major impact of age, liver and renal failure, coma and serum lactated on patients' survival.[17]

These scoring systems should only be considered appropriate for predicting survival in patients for whom ECMO has already been initiated. They might help offering population management information and might facilitate risk-adjusted comparison of outcomes between institutions, regions, and time periods. They have not been validated for prediction of survival in larger populations of patients where ECMO has not yet been instituted and should be used with great caution to select individual patients for cardiac or respiratory ECMO or to decide on futility. These scores have still to be prospectively validated and regularly recalibrated on large populations of patients.

CONTRADICTIONS IN TRIALS

What are the common beliefs that have been contradicted by recent trials (Table 1)?

Anticoagulation

Older ECMO circuits using poorly biocompatible materials required major anticoagulation and were associated with substantial bleeding. The advent of coated circuits has permitted a decrease in anticoagulation, small studies reporting that prophylactic systemic anticoagulation was possible in ECMO patients with reduced incidence of complications.[6] In the setting of severe bleeding the avoidance of anticoagulation for as long as 20 consecutive days has even been reported.[53] However, proof beyond doubt is missing, that oxygenator clotting or risk of deep vein thrombosis does not increase with less anticoagulation. Anticoagulation targets might also be higher for cardiac patients on VA-ECMO. Rigorous evaluations of anticoagulation use in ECMO patients are needed, since practices vary widely.[7,54]

Transfusion strategies

The transfusion thresholds for red blood cells and platelets in patients receiving ECMO were traditionally set to maintain values close to the normal range (120-140 g/L and >100 G/L, respectively).[1] This notion has however been challenged in recent years as transfusions of blood products are costly, induce alloimmunisation in transplant candidates and might cause specific lung injuries.[8,55] Small observational trials indicated that ECMO can be successfully conducted in patients with a hemoglobin content of less than 80 g/L with consecutive reduced need for red blood cell substitution.[56] Similarly, platelet transfusion might be discouraged except when severe thrombocytopenia is accompanied by bleeding.[8,9] More studies are however needed in order to evaluate the short and long-term consequences of lower transfusion thresholds.

Table 1 Research areas in ECMO.

	Organization	Technological improvements	Improve patients selection	Evaluate risk-benefit ratio	Better define the place of associated treatments	Identify criteria for ECMO weaning	Indications of other supportive treatments
VV-ECMO	Regionalization, nurse-to-patient ratio	Miniaturization, less blood cells injuries, less anticoagulation requirement, better membrane capacities	Non refractory hypoxaemia	including long-term outcomes	mechanical ventilation settings, prone positioning	yes	Nutrition, modulation of inflammation, blood cell requirements, anticoagulation
VA-ECMO			ECPR		IABP, Impella		Inotropes, vasodilators

Early mobilization and physical therapy on ECMO

Historically ECMO patients have been nursed with full bed rest and managed with high-levels of sedation and minimal interventions because of concerns about short-term safety.[1,7,8] However, prolonged immobility exposes to exacerbated muscle weakness and poor long-term outcomes. A recent systematic review of early rehabilitation in adults during mechanical ventilation reported that early rehabilitation may improve strength, functional recovery at hospital discharge and days alive and at home in the six-months after critical illness.[57] Patients receiving ECMO may benefit from less sedation and early rehabilitation, and recent studies found that rehabilitation, including mobilization (Figure 2), during ECMO was feasible and safe.[58,59]

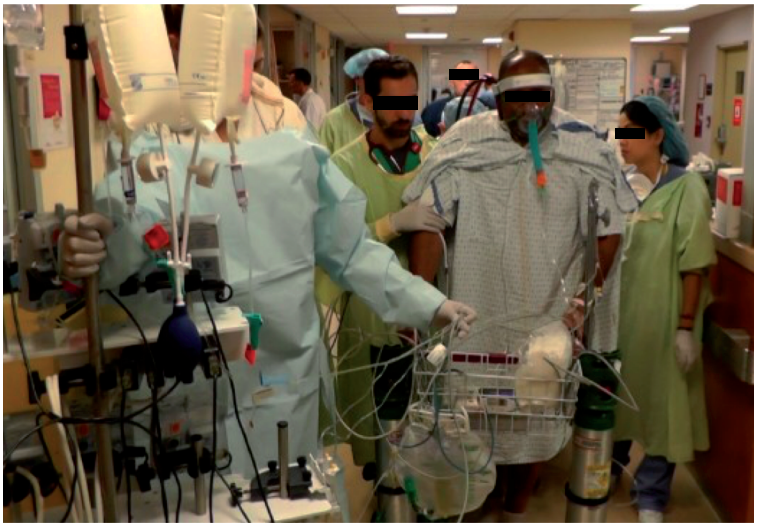

Figure 2 Ambulation in an ECMO patient at the Medical ECMO program, Columbia University Medical Center/New York-Presbyterian Hospital.
Courtesy of Dr. Daniel Brodie.

ECMO as a bridge to lung transplantation

Due to organ shortage, severe respiratory or circulatory failure develops in many patients on waiting lists for lung transplantation (LTx). Deterioration of waiting list patients commonly triggers to proceed with transplantation to avoid imminent death despite an increased risk of mortality. Therefore, VV- and VA-ECMO have been increasingly used to bridge patients with acute-on-chronic respiratory and/ or circulatory failure to LTx. In an analysis using United Network for Organ Sharing (UNOS) data from 1987 to 2008, patients supported preoperatively by mechanical ventilation or ECMO had markedly worse survival after LTx compared to those transplanted unsupported.[60] More recent analyses using UNOS data from 2010 to 2015, showed that the adverse influence of ECMO was

absent in high-volume lung transplant centers.[61] A systematic review including 14 retrospective studies pointed out that current data do not permit a definitive conclusion on the efficacy of ECMO as a bridge to transplantation.[62]. However, these patients may have an acceptable one year survival.[62-64] These data contradicted the widespread belief that outcome of ECMO patients after lung transplantation is dismal.[60,62]

Pathophysiological approach and research in cardiogenic shock

From a methodological point of view, the major advance was the proof-of-concept that large randomized trials with mechanical support devices and clinically relevant endpoints (i.e. mortality) are feasible, as shown for the use of IABP in the IABP-SHOCK II trial.[65] Common beliefs in shock research that have been contradicted in recent trials are that: a) devices that increase cardiac output do automatically improve prognosis; b) positive haemodynamic findings seen in healthy laboratory animals without cardiogenic shock can be uncritically translated to the patient with cardiogenic shock; c) what seems reasonable from a pathophysiological point of view does necessarily transforms into clinical benefit; d) cardiogenic shock is a pure hemodynamic problem. Especially the latter view must be disregarded. Cardiogenic shock is a haemodynamic problem only at the very beginning, and soon becomes a very complex disease, with bacterial translocation, overshooting inflammation and the development of multiple organ failure. Indeed, in patients with cardiogenic shock complicating myocardial infarction, APACHE II score is a better predictor of mortality than cardiac output.[66]

AREA OF UNCERTAINTIES

Risk–benefit evaluation of ECMO support

Although ECMO can improve survival of patients with advanced lung and heart disease, there is significant associated morbidity with performance of this intervention.[67] Specifically, the use of ECMO for severe ARDS remains controversial, with conflicting data regarding its impact on survival. Evidence regarding the benefits of temporary MCS in cardiogenic shock not responding to standard therapy, including inotropes, is also still limited. In a meta-analysis of three randomized clinical trials comparing a percutaneous MCS vs. IABP in cardiogenic shock patients, MCS appeared safe and demonstrated better haemodynamics, but did not improve 30-day mortality and was associated with more bleeding complications.[68] Furthermore, a recent randomized controlled trial involving 48 mechanically ventilated cardiogenic shock patients after acute myocardial infarction, the Impella CP was not associated with reduced 30-day mortality compared with IABP.[15] Based on these results, temporary MCS only received a class IIb recommendation from the European Society of Cardiology.[10]

LV unloading in VA-ECMO

Peripheral VA-ECMO increases LV afterload that may delay myocardial recovery in case of myocardial infarction or myocarditis. Excessive LV afterload and lack of LV unloading under VA-ECMO might induce serious complications such as LV stasis with thrombus formation, pulmonary edema, myocardial ischaemia caused by ventricular distension and ultimately increase mortality.[12,67,69,70] Current strategies of LV unloading in VA-ECMO patients include atrial septostomy, central percutaneous cannulation of the left atrium or ventricle, combined support with VA-ECMO and Impella, as well as concomitant utilization of an IABP.[11] Adding an IABP to VA-ECMO was shown to improve haemodynamics, to reduce LV dimensions and to decrease pulmonary artery pressures.[69] Furthermore, IABP combined with VA-ECMO was independently associated with improved mortality and successful weaning from ECMO in a Japanese national inpatient database.[70] Alternatively, association of the Impella device to VA-ECMO might provide greater reduction in LV overload while increasing the net forward flow.[14] Indeed, a recent study suggested better outcomes in patients with combined support with VA-ECMO and Impella.[71]

Mechanical ventilation under VV-ECMO

The optimal ventilator strategy in VV-ECMO patients is not clear.[72] Tidal volume can be very low, resulting in near-absent tidal stress and strain, and minimal or absent atelectrauma. While some experts endorse a higher PEEP strategy (>10 cmH2O) to keep the lung open and prevent atelectasis,[73] some endorse a strategy that includes no external PEEP (i.e., patient extubated).[74] In a recent meta-analysis of 9 VV-ECMO studies, the driving pressure was the only parameter that was independently associated with in-hospital mortality.[75] Avoiding injurious mechanical ventilation should therefore be a principle of lung protection.[5,73,75]

In general, any mode (e.g., volume/assist-control, APRV, NAVA) that can decrease harmful ventilation might be used. Once patients stabilize transitioning to spontaneous breathing on partial-assist modes (e.g., pressure support ventilation) should be considered.

Nutrition therapy in ECMO patients

Nutrition therapy is used in almost all critically ill patients, with no clear evidence about optimal administration. A study of 107 ECMO patients in Australia and New Zealand to determine current nutrition practice showed that enteral nutrition was the most commonly used nutrition- delivery mode during ECMO, but was interrupted on 53% of study days.[76] The authors reported that acceptable amounts of calories and proteins were delivered, although these were less than estimated requirements. The two most commonly reported barriers to the delivery of enteral nutrition included fasting for a therapeutic or diagnostic procedure and high gastric residual volumes.

ECPR

Rescuing cardiac arrest patients with ECMO requires disproportionate human, financial and material resources. However, to date long-term outcomes of the ECPR patients are still poor compared to other groups of ECMO patients.[32-34] Therefore, what should be patients' selection criteria for ECPR? To reduce low-flow time, should on field ECPR be preferred to rapid transport of refractory cardiac arrest patients to the closest ECMO center?[77] Would mechanical chest compression device give better results than long-term conventional CPR awaiting ECMO in this setting? Will additional therapies such as therapeutic hypothermia or other brain protection treatment to attenuate ischemic/reperfusion injuries improve neurological outcome?

TRIALS TO BE DONE IN THE NEXT 10 YEARS

What the international group of experts recommend as the top 10 studies/trials to be done in the next 10 years and what are expected outcomes/results of these trials.

1. Randomized controlled trial (RCT) of VV-ECMO for severe respiratory failure

Beyond rescuing ARDS patients dying of refractory hypoxemia, ECMO may improve the outcomes of less severe ARDS patients by facilitating less damaging ventilation. The ongoing trial international multicenter randomized Extracorporeal Membrane Oxygenation for Severe Acute Respiratory Distress Syndrome (EOLIA, NCT01470703) trial, which tests the efficacy of early VV-ECMO in patients with severe ARDS with tight control of mechanical ventilation in the control group may help to resolve the ongoing controversy in this indication.

2. RCT of VA-ECMO or other MCS devices for severe cardiogenic shock

Although widely used for over 3 decades, the IABP-SHOCK II trial demonstrated that the IABP provided no benefit over medical treatment alone in AMI-related cardiogenic shock. A large randomized trial should now be rapidly conducted to test VA-ECMO, other catheter-based MCS devices or combination MCS support in this setting.

3. RCT of restrictive or very restrictive transfusion policy in ECMO patients

A trial in ECMO patients might demonstrate non-inferiority (or even superiority regarding patients centered outcomes) of transfusion thresholds as low as 50-60 g/L or 20 G/L for red blood cells and platelets, respectively compared with more liberal strategies.

4. RCT of reduced anticoagulation in VV-ECMO patients

This study might show less bleeding complications and ultimately better short and long-terms outcomes in patients supported by VV-ECMO.

5. RCT testing early mobilization and physical therapy on ECMO

This study might prove that less sedation and early rehabilitation on ECMO is safe and feasible and is associated with improved strength, faster functional recovery and better long-term outcomes.

6. RCT comparing pre-hospital vs. in-hospital ECMO in refractory cardiac arrest

This study is already recruiting cardiac arrest patients in France (ACPAR2, NCT02527031).

7. Studies evaluating pharmacologic strategies on-top-of MCS devices

It could make sense to combine the mechanical circulatory support with some other measures dampening inflammation, autonomous dysfunction, cytopathic hypoxia and MODS. Levosimendan might also accelerate weaning from MCS.

8. Physiologic studies evaluating best ventilation strategies in VV-ECMO patients

These studies should test the effects of MV settings including PEEP, plateau and driving pressures, modes of MV and prone positioning at the different phases of VV-ECMO support.

9. Would regionalization of ECMO with ECMO retrieval teams improve outcomes?

A carefully designed trial comparing a coordinated, regionalized network of ECMO centers and satellite hospitals, with a region hosting a similar population but lacking such coordination, will need to be undertaken. This should demonstrate a cost-effective improvement in outcomes and resource utilization with regionalized care. While ECPR would clearly benefit from concentration of expertise, satellite facilities may not be served rapidly enough by specialized centers. ECPR indications might therefore require a separate study.

10. Retrospective and prospective cohorts to refine indications and to evaluate long-term outcomes after ECMO

Such studies including large cohorts of patients may refine the specific indications and scoring algorithms for patients requiring ECLS support.

CONCLUSION

Although there have been considerable advances regarding the use of ECMO in critically ill patients, the risk/benefit ratio remains under-investigated. Organization of ECMO delivery, use of adjuvant therapeutics need also to be explored. Finally, ECMO indications must be carefully identified in order to take into account the costs associated with the use of this unusual salvage therapy.

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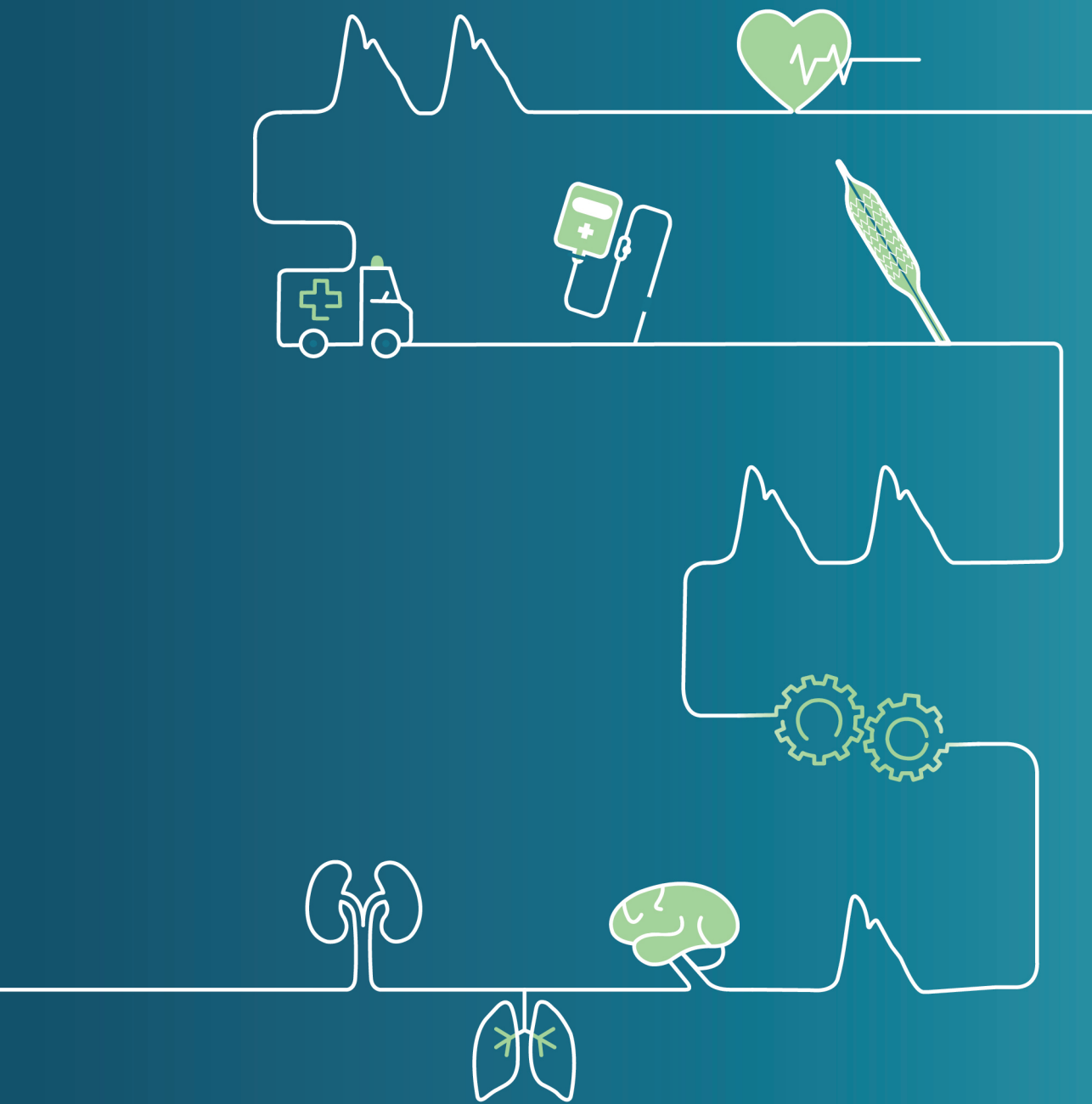
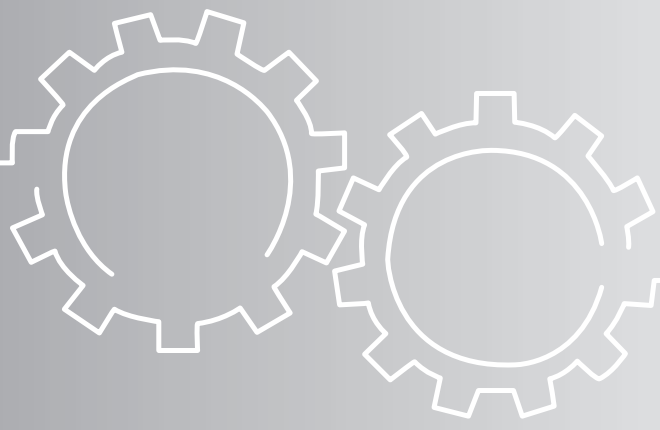
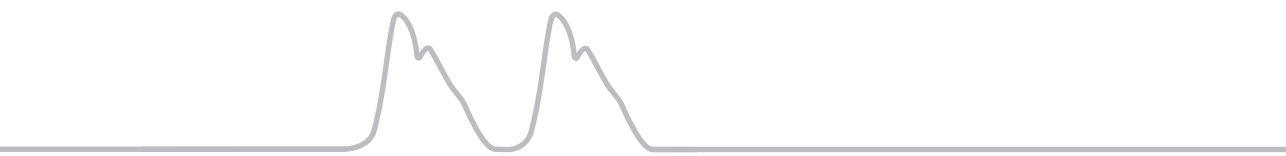


SUMMARY AND FUTURE PERSPECIVES

CHAPTER 13



SUMMARY AND FUTURE PERSPECTIVES



CARDIOGENIC SHOCK

Cardiogenic shock is the most common cause of death in patients with acute myocardial infarction. Around 10% of the patients with an ST-segment elevation myocardial infarction develop cardiogenic shock.[1-3] Mortality in cardiogenic shock has been reduced over the last few decades, but continues to be arounds 50%. Cardiogenic shock after acute myocardial infarction is caused by decreased cardiac function which results in a cascade of decreased cardiac output, hypotension, decreased coronary blood flow which will further reduce cardiac function. This vicious circle may not only lead to further myocardial ischemia, but also to diminished organ perfusion and ultimately results in multiple organ failure and death. The treatment of cardiogenic shock aims to break through this vicious circle by revascularize the occluded coronary vessel by percutaneous coronary interventions (PCI) and increasing blood pressure by pharmacological treatment with inotropes and vasopressors or additionally with mechanical circulatory support. The most commonly used mechanical support device still is the intra-aortic balloon pump (IABP). However, in the last decades several other mechanical support devices have been introduced, leading to more clinical experience and insights in the usage of these devices. Mechanical circulatory support has become a field of development and research on its own. This thesis focuses on the use of the mechanical support devices in cardiogenic shock after acute myocardial infarction. Part I describes lessons from observational clinical experience with the Impella device in various clinical settings. Part II describes the randomized comparison of Impella with IABP in cardiogenic pre-shock and severe cardiogenic shock. Part III describes the available data on the use of extracorporeal life support during refractory cardiac arrest and cardiogenic shock.

MECHANICAL CIRCULATORY SUPPORT

In 2004 we started the Impella program at the Academic Medical Center in Amsterdam. The first experience with Impella was during elective high-risk percutaneous coronary interventions. After having gained clinical experience with the device in the elective setting and studying the unloading effects on the left ventricle and microcirculation[4-6], we expanded its usage in the acute setting in patients with acute myocardial infarction.[5,7]
In ***Chapter 2*** we describe historic evidence and guidelines of clinically available mechanic support devices. It describes the meanwhile historic evidence and guidelines available back in 2011. At that moment, the evidence for usage of IABP in the setting of acute myocardial infarction with or without cardiogenic shock was limited. A meta-analysis of the available smaller sized cohort studies showed a lack of benefit on survival.[8] The results of a randomised trial, the IABP-SHOCK II trial, were not yet available at that time,

but would later confirm the results of the meta-analysis, showing no benefit nor harm of the use of IABP in the setting of cardiogenic shock after acute myocardial infarction.[9] Also, the CRISP-AMI trial did not show a beneficial effect on infarct size in patients with large anterior STEMI without shock.[10] Due to these trials, is routine use of the IABP in patients with cardiogenic shock no longer recommended in the current European guidelines.

The overview in Chapter 2 also shows that there is only limited experience with other mechanical support devices yet. Feasibility and safety of Impella therapy in high-risk PCI and in cardiogenic shock was shown.[6,11] The first but small (n=25) randomised trial in patients with STEMI complicated by cardiogenic shock, showed that the Impella improved hemodynamic variables compared with the IABP after 12 hours of support.[12] The experience with the Impella in the AMC until 2011 suggested better results with the Impella 5.0 than the Impella 2.5 in profound cardiogenic shock, suggesting that the Impella 2.5 may not be sufficient to provide enough cardiac output in severe cardiogenic shock.[7] At that time, the Impella CP was not available yet.

The usage of ECLS in cardiogenic shock after acute myocardial infarction was described in only a few cohort studies.[13] With little clinical evidence, the European guidelines recommended to consider ECLS in patients who continued to deteriorate after IABP implantation.[14] The American guidelines recommended the use of a mechanical support device (specifically including IABP, Impella and TandemHeart) if the patient did not stabilise quickly with pharmacological therapy without evidence of its efficacy on survival.[15]

CLINICAL EXPERIENCE WITH IMPELLA

Part I of this thesis, describes the experience of the Academic Medical Center with the Impella device. ***Chapter 3*** describes the impact of the device learning curve on the outcomes of PROTECT II randomized trial that compared hemodynamic support with Impella 2.5 versus the intra-aortic balloon pump (IABP) during high-risk percutaneous coronary intervention. A total of 448 patients were randomized at 74 sites, and 58 patients were the first to receive Impella 2.5 at their site. We observed more events in the first Impella patients compared with the remaining Impella patients. This "learning curve" was not observed in the IABP treated patients. This observation suggests a learning curve associated with initial introduction of the Impella 2.5. We concluded that clinical trials should better address the training aspect of new devices, especially when compared with more established devices. This is even more important if the introduction of these devices are in the acute setting. In Japan Impella recently received approval for clinical usage

but operators may only use the device in patients with cardiogenic shock. This is a less optimal situation than introducing a new technology in a more elective setting.

Chapter 4 describes a new method to evaluate the position of the Impella device by using supine chest X-ray. When a patient in cardiogenic shock is treated with a mechanical support device, it is important to evaluate if the device is in the correct position. For the Impella it is important that the inlet area is located in the left ventricle, and the outlet is located above the aortic valve in the ascending aorta. The current method to evaluate the Impella position is by echocardiography. However, assessment of the Impella position may be challenging as these patients often have poor acoustic windows, hampering appropriate assessment of the position. Supine chest X-ray is performed on a regular basis in patients admitted to the intensive care unit and therefore it would be of additional value if these X-ray images could be used to evaluate the Impella position. We developed a ratio to determine the aortic valve location on supine chest X-ray, the Aortic Valve Location Ratio. This ratio is used to assess the position of the Impella and is compared with echocardiographic findings. We concluded that Aortic Valve Location Ratio enables accurate and reproducible localization of the aortic valve on supine chest X-ray. This ratio may be used for all temporary transvalvular devices, including the Impella but also the new HeartMate PHP.

Chapter 5 describes the experience of the AMC with the Impella technology since 2004. A total of 250 patients were treated with Impella, the majority for cardiogenic shock after acute myocardial infarction (n=112) or high-risk PCI (n=68). In patients with acute myocardial infarction, 30-day mortality was 56.2%. Independent predictors for 30-day mortality were lactate levels and placement of the Impella device after the revascularisation, even after correction for cardiac arrest duration. Complications consisted of device related major vascular complications (4.5%), major bleeding (24.1%), hemolysis (12.5%) and stroke (3.6%).

Chapter 6 describes the changes over time in treatment with Impella technology. The major advances are the availability of the Impella CP, which allow for more hemodynamic than the Impella 2.5 (3.7 L/min versus 2.5 L/min) but retains the ability to be inserted percutaneously without the need for a surgical cut-down. In the Netherlands, Impella therapy is now reimbursed and in the United States the FDA approved the use of Impella in cardiogenic shock.

RANDOMISED DATA

Part II of this thesis describes the result of randomised controlled trials comparing Impella with IABP. ***Chapter 7*** describes the IMPRESS in STEMI trial, which is a small sized multi-center trial in which patients with cardiogenic pre-shock were randomised

between Impella 2.5 and IABP. Unfortunately this trial was prematurely stopped due to insufficient inclusion, after enrolment of 21 patients. The small number of patients enrolled in the study preclude an appropriate interpretation of the results. We described which lessons were learned from this trial. This study, in addition to other studies in cardiogenic shock patients, showed that randomized controlled trials in these patients are difficult to conduct, especially when clinical assessment is part of the inclusion criteria.
In ***Chapter 8*** we describe the IMPRESS in Severe Shock trial, which is an international two-center randomised controlled trial, comparing Impella CP and IABP in mechanically ventilated patients with cardiogenic shock. It was an explorative trial with 48 patients, 24 in each arm. At 30 days, mortality in patients treated with either IABP or Impella CP was similar (50% and 46%, respectively).
In ***Chapter 9*** the results of all available randomised controlled trial comparing Impella with IABP were pooled. There are 3 randomised trials with a total of 95 randomised patients. We conclude that although there is only limited data available, the meta-analysis shows no difference in mortality or left ventricular ejection fraction in cardiogenic shock patients who are treated with Impella compared with IABP.
In ***Chapter 10*** we combine all data of randomised controlled trials with active mechanical support devices such as Impella and TandemHeart. There are 4 randomised trials with either Impella (n=2) or TandemHeart (n=2) with a total of 148 randomised patients. In this meta-analysis, there is no difference in 30-day mortality in patients treated with mechanical support/assist devices compared to IABP. However, active mechanical circulatory support significantly improved hemodynamic variables such as cardiac index, mean arterial pressure, pulmonary capillary wedge pressure as well as arterial lactate. There was no significant difference in leg ischemia, but there was an increased rate of bleeding in the mechanical circulatory support treated patients. Apparently, an immediate increase in hemodynamic and biochemical variables did not translate into a survival benefit. This is an important conclusion we need to address when designing new studies.

EXTRACORPOREAL LIFE SUPPORT

Part III of this thesis describes the role of extracorporeal life support in patients with cardiogenic shock and cardiac arrest. In ***Chapter 11*** describes a meta-analysis of cohort studies, comparing ECLS treated patient with patients who were not treated with ECLS in de setting of refractory cardiac arrest and cardiogenic shock after acute myocardial infarction. In patients with cardiogenic shock, ECLS showed a higher 30-day survival compared with IABP, but no difference when compared with TandemHeart/Impella. In patients with refractory cardiac arrest, the use of ECLS (extra-corporeal cardiopulmo-

nary resuscitation (ECPR)) resulted in an absolute increase of 30-day survival of 13% and a higher rate of favourable neurological outcome. An additional propensity matched meta-analysis in cardiac arrest showed similar results.

Chapter 12 describes the current state and future perspectives of the role of extracorporeal life support. Recently published observational studies suggest that ECLS is able to improve patients' outcomes. There are however many uncertainties regarding the real benefits of this technique both in circulatory and respiratory failure. This chapter describes the many developments over the past years, describes the areas of uncertainties and sheds light on where the focus should be on when designing new studies in the future.

CONCLUDING REMARKS AND FUTURE PERSPECTIVES

This thesis describes that despite all efforts to treat cardiogenic shock, mortality remains unacceptably high. Mechanical support devices can be used to support the heart and circulation in order to provide adequate circulation to the organs. We have shown that active mechanical circulatory support, such as Impella and TandemHeart improve hemodynamic variables such mean arterial pressure and arterial lactate levels. Unfortunately, these improved circulatory parameters do not easily translate into better survival. Although these initial results may seem discouraging, we have come a long way on understanding many aspects of the field of percutaneous circulatory support. There are still many areas of improvement which may lead to better outcomes in cardiogenic shock patients.

Overall improvements

The fact that mechanical circulatory support increases hemodynamic parameters, but do not result in better clinical outcomes, might be explained by the fact that cardiogenic shock is not only a matter of decrease overall circulation. Patients do not only suffer from cardiac ischemia but also from diminished organ perfusion, anoxic brain damage and systemic inflammatory responses. Therefore, providing more hemodynamic support only may not be enough to save these very ill patients. Other additional therapies may be needed to yield better outcomes. In these critically ill patients, treatment consists of a chain of medical treatment, from bystander CPR and the emergency response team, revascularisation, pharmacological therapy and extensive intensive care treatment. The ongoing technological improvements in all involved fields are likely to result in better overall outcome. It will take a multidisciplinary approach to yield overall better outcome.

Patient selection

Patients with cardiogenic shock after acute myocardial infarction are severely ill and are not only threatened by cardiac circulatory failure. Many patients have experienced cardiac arrest and may have severe anoxic neurological damage before treatment. Any kind of mechanical circulatory support may be of limited clinical utility in these patients. When including those patients in randomized clinical trials, a potential beneficial treatment effect is likely to be underestimated. Also, there is group of cardiogenic shock patients that would survive with pharmacological therapy only.[9] Selecting the patients who would benefit most from a mechanical support device might be the key factor for future trials but is a very difficult target. Especially as the severity of cardiogenic shock remains an area of ongoing discussion. The most commonly used definition includes the threshold of 90 mmHg for systolic blood pressure. This threshold suggests an on/off phenomenon, while cardiogenic shock is more a graduate spectrum. Therefore, the severity of the cardiogenic shock patients remains a topic of discussion. It impedes the ability to compare the results of cardiogenic shock trials.

In the future, it would be of additional value if a shock grading was available which can easily be used in clinical practice allowing better patients selection and proper comparison of shock patients. This shock grading might include hemodynamic parameters, biochemical parameters such as lactate levels and other parameters that may identify tissue hypoperfusion. Earlier identification of patients that may develop shock, would allow for preventive therapies, including the prophylactic use of mechanical support device. Parameters that could predict development of shock might include sympato-vagal balance or other novel parameters that may objectively quantify the endangered cardiac and peripheral circulation.

Mechanical support device

Mechanical support devices can provide from 2 up to 5 L/min depending on the choice of device. When patients have a diminished cardiac function in combination with an inflammatory vasodilatory response, the amount of support may be insufficient to provide adequate circulation. Ideally, the mechanically support device should be able to provide around 5 L/min or more but would still be percutaneously implantable without surgical cut-down.

The ideal device should enable both hemodynamic support and myocardial protection. Preferable, the device would maintain both cardiac output and blood pressure without concomitant vasopressor or inotrope therapy and thereby avoid the possible cardiotoxicity and long-term morbidity of these agents.

Also, a percutaneous approach is preferable to provide for a quick and easy deployment in the acute situation. In addition, the ideal device should be associated with a low complication rate, as complications may sometimes outweigh the potential beneficial

effect, especially in the light of large size devices in combination with antiplatelet and anticoagulant therapy.

One aspect that might be underexposed is the importance of a stable and correct device position. A correct position is important for all mechanical support devices, but especially in devices of which the function is completely abolished by an incorrect position, which is the case with transvalvular devices. The ideal device would have a stable position, which is effected by external factors such as movement of the patient or filling pressures.

Recent developments of percutaneous right ventricular assist devices (TandemHeart or Impella) or percutaneous biventricular assist devices (such as ECLS) make it possible to treat both left and right ventricular dysfunction in case of cardiogenic shock. Right ventricular dysfunction is known to be a predictor for mortality in cardiogenic shock patients and is frequently disregarded. Especially when left ventricular support is not sufficient, right ventricular function should be assessed and be addressed.

Early device placement

In the majority of patients treated with an mechanical support device, the mechanical support device is placed after the revascularization. There is an urge to quickly revascularize and patients undergo immediate PCI even in extremely poor clinical conditions. Several cohorts studies have demonstrated a better survival in patients who received Impella before primary PCI compared with implantation post-PCI. If these results would confirmed by future studies, the mindset of the treatment of patients in cardiogenic shock might change. There is experimental evidence but still little clinical evidence in favour of such a strategy. The treatment of these patients might shift from door-to-balloon time to door-to-circulatory support time.

Cardiac arrest, cardiogenic shock in its extreme form

Several international cohort studies have shown a beneficial effect of the usage of ECLS in patients with refractory cardiac arrest (Chapter 11). A randomized controlled trial needs to confirm this results. However, experience with the treatment of this patient category is gained in several hospitals in the world. Treatment of these patients with ECLS is a logically challenging and needs a multidisciplinary approach. Installment and optimization of a dedicated clinical pathway is necessary to achieve improved survival. This clinical pathway needs cooperation and optimal logistics between several paramedical and medical disciplines, i.e. from pre-hospital ambulance service to intensive care.

Logistics are challenging, but are needed to optimize the chance of survival of these patients. Perhaps the refractory arrest patient population may most benefit from mechanical circulatory support.

Limited data

Adequately powered randomized clinical trials are needed to ascertain the value of mechanical circulatory support in patients with cardiogenic shock after acute myocardial infarction. Although randomized trials are difficult to perform in severely ill patients, with relatively low incidence, this is the only way to appropriately overcome selection and treatment bias. These studies can only be performed when including enough patients in a reasonable time period and should only be conducted in centers that have experience with the mechanical support device. Successfully conducting this trail requires a collaborative approach with large dedicated experienced shock-centers.

Although we have gained more knowledge on mechanical circulatory support in cardiogenic shock, there are various issues that need to be resolved before embarking on large scale usage of mechanical support devices.

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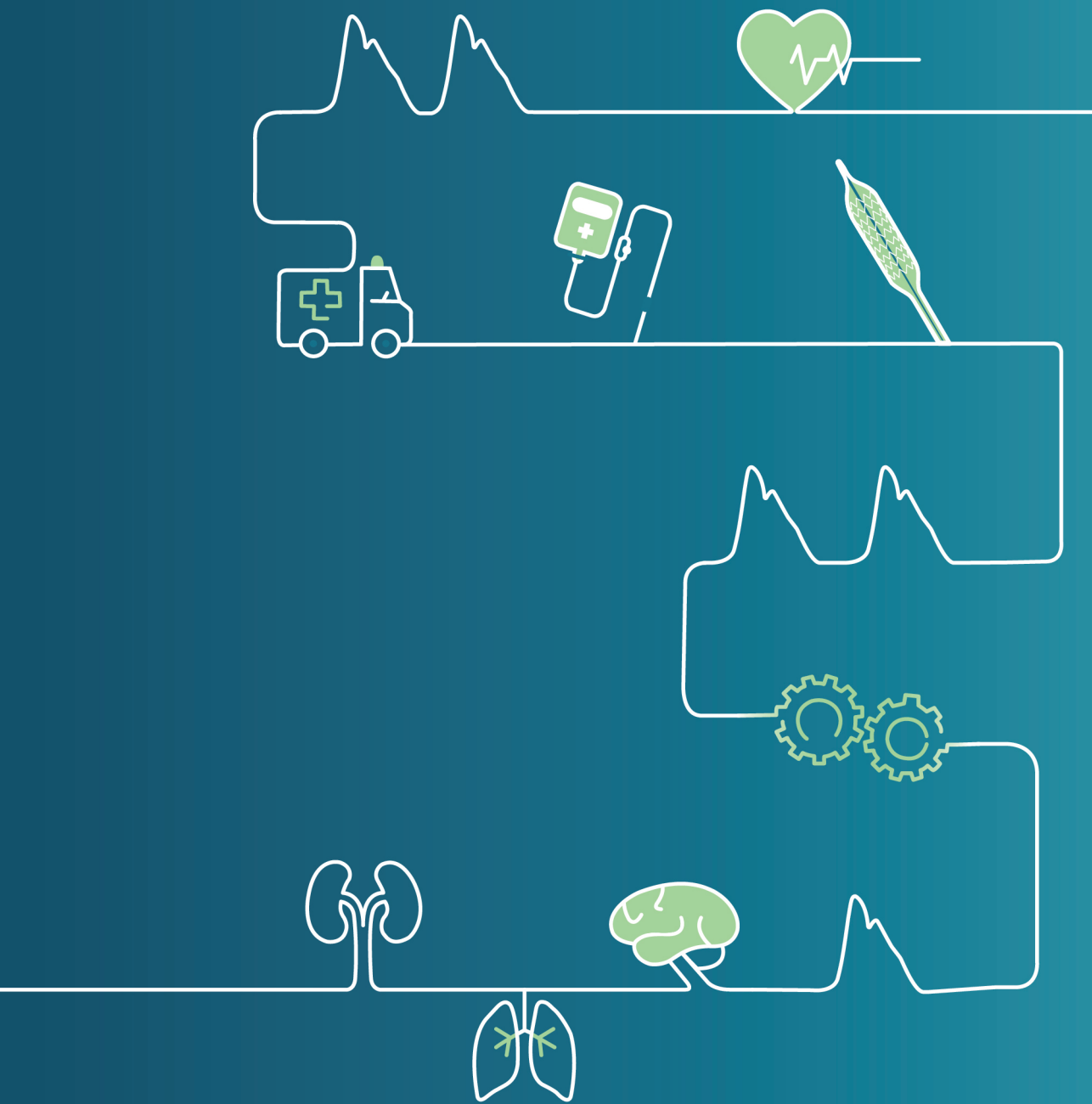

APPENDICES

NEDERLANDSE SAMENVATTING EN TOEKOMSTPERSPECTIEVEN

CARDIOGENE SHOCK

Cardiogene shock is de meest voorkomende doodsoorzaak bij patiënten met een acuut myocardinfarct. Ongeveer 10% van de patiënten met een ST-segment elevatie myocard infarct ontwikkelt cardiogene shock.[1-3] De sterfte in cardiogene shock is verminderd in de afgelopen decennia, maar het blijft steken op ongeveer 50%. Cardiogene shock na een acuut myocardinfarct wordt veroorzaakt door verminderde hartfunctie, wat zorgt voor een cascade van een verminderd hartminuutvolume, hypotensie en een verminderde coronaire perfusie, en weer zorgt voor een vermindering van de hartfunctie. Deze vicieuze cirkel zal leiden tot verdere myocardiale ischemie en tot een verminderde orgaan perfusie, wat uiteindelijk kan resulteren in multi-orgaan falen en dood.
De behandeling van cardiogene shock heeft als doel om deze vicieuze cirkel te doorbreken door het openen van het geoccludeerde kransslagvat door middel van een dotterbehandeling. Daarnaast kan de bloeddruk worden verhoogd door middel van het toedienen van medicatie (inotropica en vasopressoren) en kan een behandeling met mechanische hartondersteuning worden gestart.
De meest gebruikte hartpomp voor tijdelijke mechanische ondersteuning van het hart is de intra-aortale ballonpomp (IABP). Er zijn echter in de afgelopen decennia verschillende andere tijdelijke hartpompen beschikbaar gekomen. Deze nieuwe hartpompen worden steeds vaker gebruikt, wat zorgt voor meer ervaring en nieuwe inzichten in de toepassing van mechanische hartondersteuning. Deze ontwikkelingen hebben ervoor gezorgd dat 'mechanische hartondersteuning' een nieuw vakgebied is geworden voor klinisch onderzoek en technologische ontwikkelingen.
Dit proefschrift richt zich op het gebruik van de mechanische hartondersteuning bij patiënten in cardiogene shock na een acuut myocardinfarct. Deel I van dit proefschrift beschrijft de ervaringen met de Impella in verschillende klinische situaties aan de hand van observationele studies. Deel II beschrijft de resultaten van gerandomiseerde studies die de IABP met de Impella vergelijken in patiënten met cardiogene pre-shock en in patiënten met ernstige cardiogene shock. Deel III beschrijft de beschikbare gegevens over het gebruikt van extra-corporale hartondersteuning bij een hartstilstand en cardiogene shock.

MECHANISCHE ONDERSTEUNING VAN DE CIRCULATIE

In 2004 is het Academisch Medisch Centrum in Amsterdam begonnen met het gebruik van de Impella. De eerste ervaringen met de Impella waren tijdens electieve hoog-risico dotterprocedures. Er is sindsdien veel ervaring met deze hartpomp opgedaan tijdens geplande procedures. Tevens is er onderzoek gedaan naar effecten van de Impella op de linker ventrikel en de coronaire circulatie.[4-6] Hierna is het gebruik van de Impella verder uitgebreid naar het plaatsen van de pomp in de acute situatie, namelijk tijdens een acuut hartinfarct. [5,7]

In **Hoofdstuk 1** wordt een kort overzicht gegeven van verschillende mechanische hartpompen die in de kliniek beschikbaar zijn. **Hoofdstuk 2** geeft een gedetailleerder overzicht van verschillende soorten mechanische hartondersteuning en geeft tevens een overzicht van het beschikbare bewijs van de werking van deze hartpompen. Op het moment dat hoofdstuk 2 werd geschreven, in 2011, was er nog weinig bewijs voor de effectiviteit van de IABP, maar werd deze pomp veel gebruikt. Een meta-analyse van de beschikbare gegevens uit kleine cohort studies, toonde geen voordeel aan van het gebruik van de IABP in patiënten met een hartinfarct met en zonder cardiogene shock.[8] De resultaten van een grote gerandomiseerde studie, de IABP-SHOCK II studie, waren op dat moment nog niet bekend, maar bevestigden later de resultaten van meta-analyse: de studie liet geen voordeel, maar ook geen schadelijke effecten zien van het gebruik van de IABP bij patiënten met cardiogene shock na een hartinfarct. [9] Tevens liet de CRISP-AMI studie geen voordelen zien van de IABP op de schade aan het hart bij patiënten met een groot voorwandinfarct zonder cardiogene shock.[10] Mede door de resultaten van deze studies wordt het routinematig gebruik van de ballonpomp bij cardiogene shock na een hartinfarct niet meer aanbevolen in de Europese richtlijnen.

Het overzicht in hoofdstuk 2 laat ook zien dat er tot 2011 nog weinig ervaring was met het gebruik van de Impella. In een kleine groep patiënten was er aangetoond dat het gebruik van de Impella veilig en haalbaar was tijdens hoog risico dotterprocedures en bij patiënten met een hartinfarct.[6,11] Daarnaast was er een kleine gerandomiseerde studie in patiënten met cardiogene shock na een hartinfarct (n=25). Deze studie liet zien dat de hemodynamische variabelen, 12 uur na de start van de mechanische hartondersteuning, beter waren bij de patiënten die met een Impella ondersteund werden dan van bij patiënten die met een IABP werden ondersteund.[12]

De ervaring met de Impella in het AMC tot 2011, gaf aanwijzingen dat patiënten in ernstige cardiogene shock meer baat hebben bij behandeling met de Impella 5.0 dan met de kleinere Impella 2.5. Een mogelijke oorzaak hiervoor zou kunnen zijn dat de Impella 2.5 niet genoeg hemodynamische ondersteuning kan bieden in patiënten met ernstige cardiogene shock.[7] Op dat moment was de Impella CP nog niet beschikbaar.

De ervaringen met percutane extra-corporale hartondersteuning (ECLS) is slechts in enkele cohorten beschreven.[13] Ondanks het feit dat er weinig ervaring was met het gebruik van percutane extra-corporale hartondersteuning, beschrijven Europese richtlijnen in 2011 dat ECLS moet worden overwogen bij patiënten waarbij de hemodynamiek verslechterd ondanks gebruik van de IABP.[14] De Amerikaanse richtlijnen bevelen aan mechanische hartondersteuning (specifiek de IABP, Impella en TandemHeart) te gebruiken in patiënten die niet stabiliseren met farmacologische behandeling, met de aantekening dat er nog geen bewijs is voor de effectiviteit van deze therapie.[15]

KLINISCHE ERVARING MET IMPELLA

Deel I van dit proefschrift beschrijft de ervaring van het Academisch Medisch Centrum met de Impella. **Hoofdstuk 3** beschrijft wat het effect is van de leercurve op de uitkomsten van een gerandomiseerde studie naar het gebruik van de Impella tijdens hoog-risico dotter procedures. In totaal werden er 448 patiënten, in 74 deelnemende ziekenhuizen, gerandomiseerd tussen ondersteuning van de IABP of de Impella. Er waren 58 patiënten die de eerste waren in het betreffende ziekenhuis die met de Impella werden behandeld tijdens de studie. Bij deze eerste patiënten, waren er meer ongewenste gebeurtenissen dan bij de overige patiënten. Dit 'leerproces' werd niet waargenomen bij patiënten die met een IABP werden behandeld. Deze uitkomsten geven aanwijzingen voor het effect van een leercurve bij het gebruik van deze nieuwe hartpomp. We concluderen dat er bij het uitvoeren van wetenschappelijk onderzoek met nieuwe apparatuur meer aandacht moet zijn voor de training rondom het gebruik van deze apparatuur, vooral als deze apparatuur wordt vergeleken met apparatuur waarmee al veel ervaring is. Dit is van nog groter belang wanneer nieuwe de apparatuur in een acute situatie wordt gebruikt. In Japan is er onlangs toestemming verkregen van de overheid om de Impella te gebruiken, echter alleen bij patiënten in cardiogene shock. Het gebruik van nieuwe technologieën in deze setting is minder optimaal dan wanneer de nieuwe technologie eerst in een electieve setting kan worden toegepast.

Hoofdstuk 4 beschrijft een nieuwe methode voor beoordeling van de positie van de Impella pomp op een thoraxfoto van een liggende patiënt. Wanneer een patiënt in cardiogene shock wordt behandeld met Impella ondersteuning, is het belangrijk om te evalueren of de Impella nog in de juiste positie ligt. Voor een goede werking is het belangrijk dat de instroomopening van de Impella in het rechter ventrikel ligt, en de uitstroomopening in de aorta ascendens. De huidige manier om de positie van de Impella te evalueren is met behulp van echocardiografie. Echter is de Impella positie vaak lastig vast te stellen door verminderde beeldkwaliteit bij deze patiënten.

Bij deze patiënten worden regelmatig thoraxfoto's gemaakt, waardoor het van toegevoegde waarde zou kunnen zijn indien deze röntgenbeelden ook kunnen worden gebruikt om de Impella positie te evalueren. Wij hebben een maat ontwikkeld die de locatie van de aortaklep kan schatten, door gebruik te maken van verhoudingen die je op de thoraxfoto kan meten. Wanneer de locatie van de aortaklep kan worden geschat, kan worden gekeken of de Impella goed is gepositioneerd. We concluderen dat de locatie van de aortaklep nauwkeurig kan worden geschat op een thoraxfoto en dat deze methode gebruikt kan worden om de positie van trans-valvulaire hartpompen, zoals de Impella en de HeartMate PHP, te evalueren.

Hoofdstuk 5 beschrijft de ervaring van het AMC met de Impella sinds de technologie in 2004 voor het eerst werd gebruikt. In totaal werden 250 patiënten met een Impella behandeld, waarvan het merendeel in verband met cardiogene shock na een acuut hartinfarct (n=112) of voor een hoog-risico dotterprocedure (n=68). In patiënten met een acuut hartinfarct, was de mortaliteit op 30 dagen was 56.2%. Onafhankelijke voorspellers voor 30 dagen mortaliteit, gecorrigeerd voor hartinfarct en de duur van de reanimatie, zijn lactaat en het plaatsen van de Impella na de revascularisatie in plaats van voor de revascularisatie. De meest voorkomende complicaties bestaan uit hartpomp gerelateerde vasculaire complicaties (4,5%), grote bloedingen (24,1%), hemolyse (12,5%) en een (bloedig)herseninfarct (3,6%).

Hoofdstuk 6 beschrijft de veranderingen die hebben plaatsgevonden met betrekking tot de Impella. De grootste verandering is het beschikbaar komen van de Impella CP pomp, welke meer hemodynamische ondersteuning kan geven dan de Impella 2.5 (3.7 L/min versus 2.5 L/min), maar welke ook nog steeds percutaan kan worden geplaatst zonder dat de chirurg de aanprikplaats van de arteria femoralis hoeft vrij te prepareren. In Nederland wordt het gebruik van de Impella sinds 2012 door de zorgverzekeraar vergoed. Afgelopen jaar heeft de Amerikaanse FDA toestemming gegeven voor het gebruik van Impella in cardiogene shock.

GERANDOMISEERDE DATA

Deel II van dit proefschrift beschrijft de resultaten van gerandomiseerde studies die de Impella met de IABP vergelijken.

Hoofdstuk 7 beschrijft de IMPRESS in STEMI studie, een multi-center studie waarin patiënten met cardiogene pre-shock werden gerandomiseerd tussen behandeling met IABP of Impella 2.5. Deze studie werd helaas vroegtijdig gestopt, nadat er 21 patiënten waren geïncludeerd, omdat het includeren van de patiënten te langzaam verliep. Het kleine aantal geïncludeerde patiënten zorgt ervoor dat het niet mogelijk is de resultaten goed te interpreteren. We beschrijven in dit hoofdstuk welke lering we hebben getrok-

ken uit deze studie. Deze studie liet net als eerder studies zien dat het heel erg lastig is om gerandomiseerd onderzoek uit te voeren in deze patiënten populatie, met name wanneer een klinische beoordeling van de patiënt een inclusie criterium is.
In **Hoofdstuk 8** geven we de resultaten van de IMPRESS in Severe Shock studie. Dit is een internationale gerandomiseerde studie, met 2 deelnemende ziekenhuizen, waarin de Impella CP wordt vergeleken met de IABP bij mechanisch beademde cardiogene shock patiënten. Dit was een exploratieve studie met 48 patiënten, 24 patiënten in beide armen. Op 30 dagen was de mortaliteit gelijk tussen de patiënten die werden behandeld met een IABP of de Impella CP (50% versus 46%).
In **Hoofdstuk 9** hebben we de resultaten van alle beschikbare gerandomiseerde studies die de Impella met de IABP vergelijken bij elkaar gevoegd. In totaal waren dit 3 gerandomiseerde studies met een totaal van 95 gerandomiseerde patiënten. We concluderen dat ondanks het feit dat er slechts weinig gegevens beschikbaar zijn, de beschikbare data geen verschil laat zien in mortaliteit en linker ventrikel ejectie fractie tussen patiënten die met een IABP en Impella zijn behandeld.
In **Hoofdstuk 10** combineren we alle gegevens van gerandomiseerde studies met actieve mechanische hartondersteuning zoals Impella en Tandemheart in patiënten met cardiogene shock. Er zijn 4 studies met Impella (n=2) of TandemHeart (n=2) met een totaal van 148 gerandomiseerde patiënten. Deze meta-analyse laat geen verschil zien in 30-dagen mortaliteit tussen patiënten die zijn behandeld met actieve mechanische ondersteuning en met IABP. Echter, actieve mechanische ondersteuning laat een verbetering zien van hemodynamische variabelen zoals geïndexeerd hartminuutvolume (cardiac index), gemiddelde arteriële bloeddruk (mean arterial pressure), pulmonale capillaire wiggedruk (PCWP) alsook arteriële lactaat. Er was geen verschil in het voorkomen van beenischemie tussen beide groepen, maar er waren wel meer bloedingen bij de patiënten die met actieve mechanische hartcirculatie werden behandeld. Deze analyse laat zien dat een verbetering van de hemodynamische en biochemische variabelen zich niet laten vertalen in een verbetering van de mortaliteit. Dit is een belangrijke conclusie die we moeten meenemen in het opzetten van nieuw onderzoek.

EXTRACORPORALE HARTONDERSTEUNING

Deel III van dit proefschrift beschrijft de rol van extra-corporale hartondersteuning (ECLS) bij patiënten met cardiogene shock en een hartstilstand. In **Hoofdstuk 11** beschrijven we de resultaten van een meta-analyse van cohort-studies, waarin we patiënten die behandeld zijn met ECLS vergelijken met patiënten die geen ECLS hebben gekregen. In patiënten met cardiogene shock zorgt het gebruik van ECLS voor een verbeterde mortaliteit ten opzichte van patiënten die met een IABP worden behandeld. Er is geen

verschil in mortaliteit te zien wanneer patiënten die met ECLS zijn behandeld worden vergeleken patiënten die met TandemHeart of Impella zijn behandeld. Bij patiënten met een refractaire hartstilstand, vergelijken we een reanimatie met behulp van extracorporale hartondersteuning (extra-corporeal cardiopulmonary resuscitation (ECPR)) met conventionele reanimatie. Het gebruik van ECPR geeft een absolute verlaging van de mortaliteit van 13%, en een hoger aantal patiënten met een goede neurologische uitkomst. Een meta-analyse waarbij patiënten met dezelfde kans op een behandeling worden vergeleken (propensity-matched analyse), geeft vergelijkbare uitkomsten.
Hoofdstuk 12 beschrijft de huidige situatie en vooruitzichten van de rol van de extracorporale hartondersteuning. Recente resultaten van observationele studies geven aanleiding om te denken dat ECLS klinische uitkomsten zou kunnen verbeteren. Er zijn echter nog veel onzekerheden over de werkelijke effecten van deze techniek op klinische uitkomsten van patiënten met respiratoir of circulatoir falen. Dit hoofdstuk beschrijft de technologische ontwikkelingen van de afgelopen jaren, de onzekerheden en onderzoeksgebieden voor toekomstige klinische studies.

CONCLUSIES EN TOEKOMSTPERSPECTIEVEN

Dit proefschrift beschrijft dat ondanks alle inspanningen voor het behandelen van cardiogene shock, de sterfte nog onaanvaardbaar hoog blijft. Mechanische hartondersteuning kan worden gebruikt om het hart en de bloedsomloop te ondersteunen en hiermee de perfusie van de organen te verbeteren.
Dit proefschrift laat zien dat actieve mechanische hartondersteuning, zoals Impella en TandemHeart, hemodynamische variabelen zoals arteriële bloeddruk en lactaat verbeteren. Helaas is deze verbetering niet terug te zien in een betere overleving. Hoewel deze resultaten ontmoedigend zijn, hebben we een lange weg afgelegd om de aspecten rondom percutane hartondersteuning beter te begrijpen. Er zijn nog vele verbeteringen die zouden kunnen leiden tot betere uitkomsten voor patiënten met cardiogene shock na een hartinfarct.

Algemene verbeteringen

Het feit dat de mechanische hartondersteuning zorgt voor verbeterde hemodynamische parameters, maar niet resulteert in betere klinische resultaten, zou kunnen worden verklaard door het feit dat cardiogene shock is niet alleen een kwestie van een verslechterde circulatie. Patiënten hebben niet alleen cardiale ischemie maar ook een verminderde orgaan perfusie, anoxische hersenbeschadiging en systemische inflammatoire reacties. Daarom is alleen het verbeteren van de hemodynamische situatie mogelijk niet genoeg om de klinische uitkomsten te verbeteren. Additionele therapieën zouden kunnen zor-

gen voor een beter resultaat. Bij deze ernstig zieke patiënten, bestaat de behandeling uit een keten van behandelingen, van reanimatie door omstanders, ambulancezorg, revascularsatie, farmacologische therapie tot uitgebreide behandeling op de intensive care. Met voortdurende technologische ontwikkelingen binnen alle betrokken gebieden, is het waarschijnlijk dat dit in de toekomst zal resulteren in een beter resultaat. Het verbeteren van de uitkomsten zal een multidisciplinaire aanpak vragen.

Patiënten selectie

Patiënten met cardiogene shock na acuut myocardinfarct zijn ernstig ziek. Naast hemodynamische problematiek, hebben zij vaak een hartstilstand gehad waardoor ze voor de behandeling begint al ernstige neurologische schade kunnen hebben. Alle vormen van mechanische hartondersteuning zal in deze patiënten een gelimiteerde waarde hebben. Een deel van de patiënten die wordt behandeld, zal ook met alleen farmacologische behandeling overleven.[9] Wanneer deze patiënten in een wetenschappelijk onderzoek worden geïncludeerd, zal het effect van de mechanische hartondersteuning worden onderschat.

Het is belangrijk om de patiënten te selecteren die mogelijk baat hebben bij deze therapie. Het selecteren van deze patiënten zou de sleutel kunnen zijn voor toekomstig wetenschappelijk onderzoek, maar dit is lastig te bewerkstelligen. Vooral aangezien het beoordelen van de ernst van cardiogene shock een onderwerp van voortdurende discussie blijft. De meeste gebruikte definitie van cardiogene shock maakt gebruik van de grens van 90 mm Hg voor de systolische bloeddruk. Deze grens suggereert dat cardiogene shock een aan/uit fenomeen is, terwijl het in werkelijk een gradueel beloop heeft van hypotensie tot ernstige shock met multi-orgaan falen. Hierdoor is het moeilijk om behandelingen te differentiëren tussen patiënten en wetenschappelijk onderzoek met elkaar te vergelijken.

Een shock gradering die eenvoudig kan worden toegepast in de klinische praktijk, zou van additionele waarde zijn. Deze shock gradering zou kunnen worden gemaakt op basis van hemodynamische en biochemische parameters zoals lactaat, of bijvoorbeeld parameters die als maat dienen voor weefsel hypoperfusie. Vroegtijdige identificatie van patiënten die shock gaan ontwikkelen maakt het mogelijk om preventieve therapieën te starten, misschien zelfs het profylactisch gebruik van mechanische hartondersteuning. Een mogelijke parameter die zou kunnen voorspellen of iemand in shock raakt is bijvoorbeeld de mate van sympatho-vagale balans of andere parameters die een objectieve maat zijn voor bedreigde cardiale en perifere circulatie.

Mechanische hartondersteuning

Mechanische hartondersteuning kan ongeveer 2 tot 5 L/min ondersteuning geven, afhankelijk van de keuze van de pomp. Wanneer patiënten een verminderde hartfunctie

hebben en daarbij misschien een inflammatoire vasodilatoire reactie, is deze ondersteuning niet genoeg voor een adequate orgaanperfusie. Idealiter zou een mechanische hartpomp meer dan 5 L/min kunnen pompen, maar wel percutaan kunnen worden ingebracht. De ideale hartpomp voorkomt myocardiale schade en geeft voldoende hemodynamische ondersteuning. Het liefst zorgt het voor een goed hartminuutvolume en een goede bloeddruk zonder het gebruik van vasopressoren en inotropica, om de schadelijke effecten van deze medicatie te voorkomen. Snelle en eenvoudige percutane plaatsing is belangrijk in een acute situatie. Daarnaast zou de hartpomp een laag complicatie risico moeten hebben, omdat het nadeel van de complicaties de mogelijke voordelen niet mag overschaduwen. Dit is mede belangrijk omdat patiënten naast de mechanische hartondersteuning tevens worden behandeld met uitgebreide antistolling en plaatjesaggregatieremmers. Een ander aspect dat vaak onderbelicht blijft, is het belang van een goede en stabiele positie van het hartpomp. Een correcte positie is belangrijk voor alle mechanische hartpompen, maar vooral bij de pompen waarbij een verkeerde positie de pompfunctie teniet doet. Dit is het geval bij transvalvulaire pompen, zoals de Impella en de HeartMate PHP. De ideale hartpomp heeft een stabiele positie, die niet wordt beïnvloed door externe factoren zoals vullingsdrukken van het linkerventrikel en beweging van de patiënt.
Recente ontwikkelingen van percutane rechter ventrikel hartpompen (TandemHeart en Impella) en percutane biventriculaire hartpompen (zoals ECLS) maken het mogelijk om zowel het linker als het rechter ventrikel te ondersteunen. Rechter ventrikel dysfunctie is een bekende voorspeller van sterfte in patiënten met cardiogene shock na een hartinfarct, maar is vaak onderbelicht. Vooral in patiënten waarbij linker ventrikel ondersteuning niet voldoende is, kan rechter ventrikel ondersteuning worden overwogen.

Vroege plaatsing van de hartpomp

Bij meerderheid van de patiënten die worden behandeld met tijdelijke mechanische hartondersteuning, wordt de hartpomp na de revascularisatie geplaatst. Er is haast om zo snel mogelijk het afgesloten vat te openen en patiënten ondergaan de dotterbehandeling dan met een zeer slechte hemodynamische situatie. Meerdere cohort studies hebben laten zien dat patiënten een betere overleving hebben wanneer de hemodynamiek wordt ondersteund door een mechanische hartpomp voor de revascularisatie vergeleken met de situatie waarbij hartpomp pas na de revascularisatie wordt geplaatst. Experimenteel onderzoek bevestigd deze resultaten, maar er is nog weinig klinisch bewijs. Indien deze resultaten zouden worden bevestigd met toekomstige gerandomiseerde studies, zou dit de gedachtegang en behandeling van deze patiënten kunnen veranderen. De behandeling van patiënten met cardiogene shock na een hartinfarct, zou kunnen veranderen van het optimaliseren van deur-tot-ballon tijden naar deur–tot-mechanische hartondersteuning tijden.

Hartstilstand: cardiogene shock in het extreme

Meerdere internationale cohort studies hebben laten zien dat er een gunstig effect is van ECLS in patiënten met een refractaire harstilstand (Hoofdstuk 11). Een gerandomiseerde studie zal dit effect nog moeten bevestigen. Echter is er een meerdere landen al ervaring opgedaan met extra-corporale ondersteuning tijdens reanimatie. Het behandelen van patiënten met hartondersteuning tijdens reanimatie zorgt voor logistieke uitdagingen en kan alleen worden uitgevoerd met een multidisciplinaire aanpak. Het initiëren en optimaliseren van een klinisch pad voor deze patiënten is nodig om een betere overleving mogelijk te maken. Dit klinisch pad vraagt om samenwerking en optimale logistiek tussen verschillende (para)medische isciplines, van pre-hospitale triage tot op de intensive care. De logistiek zal uitdagend zijn, maar dit is nodig om deze patiënten een grotere kans op overleving te geven. Misschien is dit wel de patiënten categorie die het meeste baat zal hebben bij mechanische hartondersteuning.

Gelimiteerde data

Grote gerandomiseerde klinische studies, met voldoende power, zijn nodig om te bepalen wat de waarde is van mechanische ondersteuning bij patiënten met cardiogene shock na een acuut hartinfarct. Hoewel gerandomiseerde studies moeilijk uit te voeren zijn in deze ernstige zieke patiëntencategorie, is dit de enige manier om selectie uit te sluiten. Deze studies kunnen alleen worden uitgevoerd wanneer er genoeg patiënten worden gerandomiseerd binnen een afzienbare tijd en moet alleen worden gedaan met ziekenhuizen met voldoende ervaring met mechanische hartondersteuning. Om een dergelijke studie uit te kunnen voeren, is een goede samenwerking tussen ervaren shock-ziekenhuizen nodig.

Hoewel we meer kennis hebben verworven over de mechanische ondersteuning van het hart en de circulatie bij patiënten met cardiogene shock, zijn er nog meerden punten die verbeterd en aangetoond moeten worden voordat we mechanische hartondersteuning op grote schaal kunnen gaan gebruiken.

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	Year	Workload (ECTS)
General courses		
- PubMed	2012	0.1
- Basic Course Legislation and Organization – BROK (ICH good clinical practise certified)	2012	1.0
- Reference Manager	2012	0.1
- Systematic Review	2012	0.3
- Practical Biostatistics	2012	0.1
- Clinical Epidemiology	2012	1.1
- Clinical Data management	2013	0.2
- Endnote	2014	0.1
- Citation Index and Impact Factors	2014	0.1
- Computing in R	2016	0.4
- Advanced Topics in Biostatistics	2016	2.1
- Project management	2016	0.6
- Her-registratie cursus BROK	2016	0.1
- CE 2: Observational Clinical Epidemiology: Effects and Effectiveness	2016	0.6
Specific courses, workshops and masterclasses		
- Cardiovascular MRI - Hands-on course	2012	0.4
- Advanced Hemodynamics, Paris, France	2012	0.4
- Workshop dr. Drummond Rennie – "Who wrote my paper"	2013	0.1
- Master Class ICIN/CVOI: How to get your paper published? Tips & Tricks	2014	0.2
- Workshop JongAMC: 'House of Cards' – onderhandelen	2016	0.1
- Workshop JongAMC: 'Duurzame inzetbaarheid door persoonlijk leiderschap'	2016	0.1

Conferences

- Complex Cardiovascular Catheter Therapeutics: Advanced Endovascular and Coronary Intervention Global Summit (C3)	2011	1.0
- European Society of Cardiology	2012-2016	6.0
- Transcatheter Cardiovascular Therapeutics (TCT)	2011-2016	7.5
- Congres van de Nederlandse Vereniging voor Technische Geneeskunde	2011-2014	1.0

Oral Presentation

- Wetenschapsavond Nederlandse Vereniging voor Technische Geneeskunde - Heart & Lungs: Cardiac assist devices	2014	0.2
- TCT 2014 - Case presentation: Referral for Impella after myocardial infarction	2014	0.2
- TCT 2015 - Case presentation: Impella placement before primary PCI of the left main coronary artery	2015	0.2
- ESC 2016 - A systematic review and meta-analysis on extracorporeal membrane oxygenation in patients with acute myocardial infarction complicated by cardiogenic shock or with cardiac arrest	2016	0.5

Poster Presentation

- TCT 2014: Evaluating The Learning Curve In A Clinical Trial Using A New Percutaneous Left Ventricular Support System. Observations From The PROTECT II Trial.	2014	0.5
- TCT 2015 - Assessment Of Aortic Valve Location On Supine Chest X-ray. Applicability Of The Aortic Valve Location Ratio For Assessment Of Intra-cardiac Assist Device Position.	2015	0.5
- NVvTG congres 2015 - Evaluating The Learning Curve In A Clinical Trial Using A New Percutaneous Left Ventricular Support System. Observations From The PROTECT II Trial.	2015	0.5
- A-CURE Symposium 2016 - Assessment Of Aortic Valve Location On Supine Chest X-ray. Applicability Of The Aortic Valve Location Ratio For Assessment Of Intra-cardiac Assist Device Position. 26-8-2016	2016	0.5
- TCT 2016 - A systematic review and meta-analysis on extracorporeal membrane oxygenation in patients with acute myocardial infarction complicated by cardiogenic shock or with cardiac arrest	2016	0.5

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	Year	Workload (ECTS)
Lecturing		
- Lecturer general medicine for pharmaceutical representatives	2012-2013	1.0
Tutoring, Mentoring, Supervising		
- Bachelor's Thesis Medicine (3 students)	2014-2017	3.0
- Master's Thesis Technical Medicine (2 students)	2015-2017	4.0

PARAMETERS OF ESTEEM

	Year
Awards and Prizes	
- TCT Scholarship 2014 – Best Impella case	2014
- TCT Scholarship 2015 – Best Impella case	2015

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11. *Percutaneous short-term active mechanical support devices in cardiogenic shock: a collaborative meta-analysis of randomized trials.*
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CURRICULUM VITAE

Dagmar was born on May 21th 1986 in Gouda, the Netherlands. She grew up in Breda with her parents and two younger sisters. In 2004 she graduated high school with a focus on biology and technical sciences. The combination of medicine and technology had her interest and therefore she moved to Enschede to start the newly developed study Technical Medicine at the University of Twente. She obtained her Bachelor's degree in 2007. During her Master's, she specialised in medical signalling.
During her internships she developed a great interest in cardiology and hemodynamic parameters. She wrote her Master's thesis at the AMC Heart Failure Research Center under supervision of prof. J.J. van Lieshout. Her Master's thesis evaluated the value of arterial pressure variation to predict fluid responsiveness.

After her graduation in 2011, she started her PhD project at the Heartcenter of the Academic Medical Center in Amsterdam, under supervision of prof. dr. J.P.S. Henriques, prof. dr. J.J. Piek and prof. dr. B.A.J.M. de Mol. This scientific research and subsequent publications resulted in this thesis, entitled "Percutaneous mechanical circulatory support in cardiogenic shock".

During this research project, she was involved in the organisation and initiation of an investigator-initiated multicenter trial. She supervised several medical and technical medicine students during their research projects.
During her Master's she spend a year organizing the 37th Batavierenrace, the world's largest relay running contest, with 8000 participants running from Nijmegen to Enschede.

Dagmar is a passionate (beach)volleybal player, enjoys to go scuba diving and loves to make multiple-day hiking trips. She lives in Hilversum together with Koen and their cats Jimmy and Bailey.