Percutaneous mechanical circulatory support in cardiogenic shock
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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. 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 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. However, in 2009 a meta-analysis of cohort studies showed no improved clinical outcome in patients treated with IABP after acute myocardial infarction. 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. 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.
Intra-aortic balloon pump

Impella / HeartMate PHP

TandemHeart

Extra-corporeal life support

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 cannula 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.
INTRODUCTION

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 the 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.

REFERENCES


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