Percutaneous mechanical circulatory support in cardiogenic shock
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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.\(^1\) Mortality in cardiogenic shock has been reduced over the last few decades, but continues to be around 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 mechanical 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.\textsuperscript{9} Also, the CRISP-AMI trial did not show a beneficial effect on infarct size in patients with large anterior STEMI without shock.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{13} With little clinical evidence, the European guidelines recommended to consider ECLS in patients who continued to deteriorate after IABP implantation.\textsuperscript{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.\textsuperscript{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 the 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. 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 sympathovagal 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 para- medical 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 trial 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.

REFERENCES


