Percutaneous mechanical circulatory support in cardiogenic shock

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Citation for published version (APA):
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\(^\circledast\) 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 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 τ² were calculated according DerSimonian and Laird. Cochran’s Q statistic and Higgins and Thompsons I² 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.

<table>
<thead>
<tr>
<th></th>
<th>Thiele et al.\textsuperscript{14}</th>
<th>Burkhoff et al.\textsuperscript{11}</th>
<th>ISAR-SHOCK\textsuperscript{13}</th>
<th>IMPRESS-IN-SEVERE-SHOCK\textsuperscript{12}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>41</td>
<td>33</td>
<td>26</td>
<td>48</td>
</tr>
<tr>
<td>MCS</td>
<td>TandemHeart™</td>
<td>TandemHeart™</td>
<td>Impella® 2.5</td>
<td>Impella® CP</td>
</tr>
<tr>
<td>Control</td>
<td>IABP</td>
<td>IABP</td>
<td>IABP</td>
<td>IABP</td>
</tr>
<tr>
<td>Setting</td>
<td>Single centre</td>
<td>Multicentre</td>
<td>Multicentre</td>
<td>Multicentre</td>
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<tr>
<td>Sequence generation</td>
<td>Drawing envelopes</td>
<td>Drawing envelopes</td>
<td>Drawing envelopes</td>
<td>Internet-based program</td>
</tr>
<tr>
<td>Allocation concealment</td>
<td>Sealed opaque sequentially numbered envelopes</td>
<td>Sealed opaque sequentially numbered envelopes</td>
<td>Sealed opaque sequentially numbered envelopes</td>
<td>Internet-based program</td>
</tr>
<tr>
<td>Blinding</td>
<td>Not possible</td>
<td>Not possible</td>
<td>Not possible</td>
<td>Not possible</td>
</tr>
<tr>
<td>Primary endpoint</td>
<td>Cardiac power index</td>
<td>Haemodynamic profile improvement</td>
<td>Cardiac index</td>
<td>30-day mortality</td>
</tr>
<tr>
<td>Haemodynamic measures</td>
<td>Pulmonary artery catheter</td>
<td>Pulmonary artery catheter</td>
<td>Pulmonary artery catheter</td>
<td>Arterial line</td>
</tr>
<tr>
<td>Follow-up</td>
<td>Complete</td>
<td>Complete</td>
<td>Complete</td>
<td>Complete</td>
</tr>
</tbody>
</table>

\textsuperscript{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 \( \geq 2.2 \) l/min/m\(^2\), (3) pulmonary capillary wedge pressure \( \leq 24 \) mmHg, and (4) mean arterial pressure \( \geq 70 \) mmHg. MCS=mechanical circulatory support; IABP=intracoronary 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™ device11,14 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 in CI and PCWP.

<table>
<thead>
<tr>
<th></th>
<th>MCS</th>
<th>IABP</th>
<th>30-day mortality</th>
<th>RR</th>
<th>95%CI</th>
<th>Weight</th>
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<tr>
<td>Events</td>
<td>9</td>
<td>9</td>
<td></td>
<td>0.95</td>
<td>[0.48;1.90]</td>
<td>26.8%</td>
</tr>
<tr>
<td>Total</td>
<td>21</td>
<td>20</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Burkhoff et al.</td>
<td>9</td>
<td>19</td>
<td></td>
<td>1.33</td>
<td>[0.57;3.10]</td>
<td>17.9%</td>
</tr>
<tr>
<td>ISAR-SHOCK</td>
<td>6</td>
<td>13</td>
<td></td>
<td>1.00</td>
<td>[0.44;2.29]</td>
<td>18.6%</td>
</tr>
<tr>
<td>IMPRESS-IN-SEVERE-SHOCK</td>
<td>11</td>
<td>24</td>
<td></td>
<td>0.92</td>
<td>[0.51;1.66]</td>
<td>36.7%</td>
</tr>
<tr>
<td>Overall</td>
<td>35</td>
<td>77</td>
<td></td>
<td>1.01</td>
<td>[0.70;1.44]</td>
<td>100%</td>
</tr>
</tbody>
</table>

Heterogeneity: $I^2=0$, $p=0.91$, $p=0.99$
Test for overall effect: $p=0.98$

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/m², 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/m²); (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.
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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{11-14} Data on timing of active MCS insertion in humans in CS are limited. In the USpella registry patients directly treated with Impella\textsuperscript{®} 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.\textsuperscript{23} Concerning IABP, there are conflicting data with more evidence demonstrating harm rather than benefit by IABP insertion before PCI.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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\textsuperscript{™} in comparison to the Impella\textsuperscript{®} CP,\textsuperscript{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.\textsuperscript{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 \textit{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.

REFERENCES


