Percutaneous Left-Ventricular Support With the Impella-2.5–Assist Device in Acute Cardiogenic Shock

Results of the Impella–EUROSHOCK-Registry

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Background—Acute cardiogenic shock after myocardial infarction is associated with high in-hospital mortality attributable to persisting low-cardiac output. The Impella–EUROSHOCK-registry evaluates the safety and efficacy of the Impella-2.5–percutaneous left-ventricular assist device in patients with cardiogenic shock after acute myocardial infarction.

Methods and Results—This multicenter registry retrospectively included 120 patients (63.6±12.2 years; 81.7% male) with cardiogenic shock from acute myocardial infarction receiving temporary circulatory support with the Impella-2.5–percutaneous left-ventricular assist device. The primary end point evaluated mortality at 30 days. The secondary end point analyzed the change of plasma lactate after the institution of hemodynamic support, and the rate of early major adverse cardiac and cerebrovascular events as well as long-term survival. Thirty-day mortality was 64.2% in the study population. After Impella-2.5–percutaneous left-ventricular assist device implantation, lactate levels decreased from 5.8±5.0 mmol/L to 4.7±5.4 mmol/L (P=0.28) and 2.5±2.6 mmol/L (P=0.023) at 24 and 48 hours, respectively. Early major adverse cardiac and cerebrovascular events were reported in 18 (15%) patients. Major bleeding at the vascular access site, hemolysis, and pericardial tamponade occurred in 34 (28.6%), 9 (7.5%), and 2 (1.7%) patients, respectively. The parameters of age >65 and lactate level >3.8 mmol/L at admission were identified as predictors of 30-day mortality. After 317±526 days of follow-up, survival was 28.3%.

Conclusions—In patients with acute cardiogenic shock from acute myocardial infarction, Impella 2.5–treatment is feasible and results in a reduction of lactate levels, suggesting improved organ perfusion. However, 30-day mortality remains high in these patients. This likely reflects the last-resort character of Impella-2.5–application in selected patients with a poor hemodynamic profile and a greater imminent risk of death. Carefully conducted randomized controlled trials are necessary to evaluate the efficacy of Impella-2.5–support in this high-risk patient group. (Circ Heart Fail. 2013;6:23-30.)

Key Words: cardiogenic shock ▪ Impella-2.5-device ▪ mechanical circulatory support ▪ percutaneous left-ventricular assist device

Historically, cardiogenic shock (CS) attributable to acute myocardial infarction (AMI) has been associated with in-hospital mortality rates as high as 80%.1 Even in the era of prompt revascularization, mortality rates for CS remain high, and many patients with severe and profound CS succumb to multiple organ failure secondary to persistent inadequate end-organ perfusion.2–7 In addition to early revascularization and pharmacological therapy, mechanical support by means of intra-aortic balloon counterpulsation (IABP) is recommended (class I) by the current guidelines.8,9 However, as the IABP augments native cardiac function, this treatment provides only limited hemodynamic support in patients with severely depressed myocardial function or cardiac arrest. Thus, several clinical trials as well as a recent meta-analysis have failed to demonstrate the benefit of IABP therapy on left-ventricular (LV) function or survival.10–13

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New percutaneous LV assist devices (pLVAD) have been developed for mechanical circulatory support, including...
the Impella-2.5–system (Abiomed Europe GmbH, Aachen, Germany). These devices unload the left ventricle and partially replace myocardial function, thus, potentially promoting myocardial recovery. The Impella-2.5 is a catheter-mounted axial-flow pump, which can be inserted percutaneously, and provides a maximum flow of 2.5 L/min. Short-term circulatory support with the device has been demonstrated to be safe and feasible in high-risk percutaneous coronary intervention (PCI) as well as in the setting of hemodynamically stable large anterior ST-elevation myocardial infarction.14–17 In patients with CS, a small randomized clinical trial of Impella-2.5 versus IABP demonstrated an improvement in cardiac index in Impella-treated patients.18 The purpose of the multicenter Impella–EUROSHOCK-registry was to assess procedural safety and outcome of Impella-2.5–support in a large cohort of patients with acute CS.

Methods

Study Design and Collection of Data
A total of 14 tertiary cardiovascular centers located in 5 countries across Europe contributed data to the Impella–EUROSHOCK-registry. Data were collected at each site using a standardized case report form to record demographic and clinical characteristics, as well as procedural and follow-up data. Follow-up was obtained at 30 days and at the time of registry enrollment based on medical records and on physician or patient interviews. The study was approved by the Institutional Review Board of the University Heart Center Jena and supported by Abiomed Europe GmbH (Aachen, Germany) for the identification of sites of enrollment. The investigators had full access to the data and control of the data analysis.

Inclusion Criteria and Treatment
At each site, all patients receiving emergent Impella-2.5–support during a 5-year period (2005–2010) for acute CS after AMI were included. The diagnosis of AMI was based on the results of coronary angiography and on laboratory and electrocardiographic studies. CS was a clinical diagnosis based on the definition from the SHOCK (Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock) trial, including (1) the presence of a systolic blood pressure <90 mm Hg for at least 30 minutes or (2) vasopressors required to maintain blood pressure >90 mm Hg, (3) evidence of end-organ hypoperfusion (eg, urine output <30 mL or cold, diaphoretic extremities, or altered mental status), and (4) evidence of elevated filling pressures (eg, pulmonary congestion on examination or chest radiograph).19 In each patient, therapy was tailored to the rapidly changing hemodynamic status and included mechanical ventilation, fluid administration, pharmacological treatment (inotropes, vasopressors) and IABP-support if considered necessary. The amount of fluid administration as well as the choice of inotropes and vasopressors was based on current guidelines and on individual experience and institutional policy. Doses were titrated to achieve a systolic blood pressure of at least 80 mm Hg.20,21 The decision to institute circulatory support with the Impella-2.5 was made in patients with refractory CS unresponsive to high-dose inotropes and IABP-support at the time of primary PCI.

After hemodynamic improvement, weaning from circulatory support was considered in the absence of hemodynamic or clinical signs of CS. Weaning criteria included a mean arterial pressure >70 mm Hg and a cardiac index >2.2 L/min/m² without a requirement of inotropic support and evidence of end-organ hypoperfusion. Weaning was performed by decreasing the pump performance level in 2 steps in intervals of 30 to 60 minutes. After reduction to performance level P2 (range, P1–P9; P9=maximum flow) for 10 minutes without hemodynamic instability, the Impella pump was pulled back into the aorta and explanted.

Device
The Impella-2.5–device has been described previously.15 In brief, it is a catheter-mounted microaxial rotary blood pump designed for rapid percutaneous insertion under fluoroscopy to allow for temporary LV support. The device is inserted through a 13F femoral sheath and positioned retrogradely across the aortic valve in the LV. Equipped with a pigtail-tip to avoid myocardial injury and to ensure a stable position in the LV, the Impella-2.5 provides a maximum flow of 2.5 L/min by expelling blood from the LV into the ascending aorta. The degree of support can be managed by graduation of pump speed up to a maximal rotation speed of 51,000 rpm. The device has received CE-approval in Europe for 5-day use.

Study End Points
The primary end point of the study was all-cause mortality at 30 days. The secondary end points were long-term survival and parameters of device efficacy and safety. The secondary efficacy end point evaluated the change in level of plasma lactate within 24 and 48 hours after the beginning of Impella-2.5–support. Secondary end points also included procedural feasibility, the incidence of major cardiac and cerebral events (recurrent myocardial infarction or cardiovascular interventions [PCI, coronary artery bypass grafting] and stroke), device-related vascular complications (bleeding requiring transfusion or surgery), hemolysis, cardiac tamponade, and device malfunction.

Statistics
Continuous data are presented as mean±SD, categorical variables are presented as percentages and numbers. All variables were tested for normal distribution with the Shapiro-Wilk–test. Univariate logistic regression was performed among established predictors of 30-day mortality. Age was dichotomized to above and below the median of 65 years. Systolic blood pressure was dichotomized to above and below the median of 90 mm Hg. Lactate at baseline was dichotomized to above and below the median of 3.8 mmol/L. All covariates with a P<0.1 were included in the multivariate regression model. Backward stepwise logistic regression analysis was subsequently performed, to identify independent predictors for 30-day mortality. A covariate was removed from the model if the P value exceeded 0.10. All P<0.05 were considered statistically significant. Kaplan–Meier curves were constructed and stratified according to lactate levels above and below the median. Survival differences were tested using the log-rank statistic. All statistical analyses were performed with the Statistical Package for the Social Sciences (SPSS Inc, Chicago, IL, version 18.0).

Results

Patient Characteristics at Hospital Admission
The Impella–EUROSHOCK-registry included a total of 120 patients with AMI and CS treated with the Impella-2.5 in 14 European cardiovascular centers. Baseline characteristics are detailed in Table 1. Mean age was 63.6±12.3 years, 98 (81.7%) patients were male. In accordance with the inclusion criteria, all patients were in profound CS with a low mean arterial blood pressure (68.3±17.3 mm Hg), an elevated plasma lactate (5.8±5.0 mmol/L) and a severely reduced LV ejection fraction (0.27±0.11; determined by either echocardiography or ventriculography). At the time of device implantation, 102 (85%) patients received vasopressors and inotropics, and 35 (29.0%) were on IABP-support. In addition, 40.8% (n=49) of the patients had been resuscitated for out-of-hospital cardiac arrest. The majority of patients (n=81, 67.5%) presented with multivessel disease with a severely reduced mean thrombolytic in myocardial infarction flow at the culprit lesion of 0.4±0.8, which improved after PCI to 2.6±0.9.
Thirty-Day Mortality

Thirty-day mortality in this study cohort was 64.2% (77/120 patients). Multivariate logistic regression analysis was performed to identify independent parameters for 30-day mortality (Table 2). After stepwise backward analysis, the parameters age >65 (odds ratios, 5.46; \( P = 0.008 \)) and blood lactate >3.8 mmol/L (\( P = 0.012 \)) remained in the model as independent predictors for 30-day mortality with odds ratios of 5.245 (95% confidence interval, 1.473–18.677; \( P = 0.011 \)) and 5.245 (95% confidence interval, 1.473–18.677; \( P = 0.011 \)) respectively (Table 3).

Clinical Course

The mean duration of Impella-2.5–support was 43.5±49.6 hours in the overall study cohort. Fifty patients (42%) died during Impella-2.5–support. Within the overall study group, 53 (44.5%) patients were successfully weaned from the device after a mean support duration of 66.3±54 hours. Within the subgroup of successfully weaned patients, 18/53 (34%) patients had died after further treatment at 30 days. In 6 patients (5.0%), circulatory support with the Impella-2.5 was discontinued because of associated complications (vascular:5; hemolysis:1).

After device implantation, mean plasma lactate levels decreased from 5.8±5.0 mmol/L to 4.7±5.4 mmol/L (\( P = 0.28 \)) at 24 hours and to 2.5±2.6 mmol/L (\( P = 0.007 \)) at 48 hours. Further details on laboratory measurements are presented in Table 2.

Survival after a mean follow-up of 317±526 days was 28.3%. The Kaplan–Meier Curves for the overall-group, as well as Kaplan–Meier curves stratified by plasma lactate at admission and with or without cardiopulmonary resuscitation <72 hours, are provided in Figures 1 and 2.

In the overall study population, 10 patients (8.4%) required upgrading to other circulatory assist devices with a higher maximum pump flow (Impella-5.0: n=6; extracorporeal membrane oxygenation: n=2; surgical LVAD: n=2). Decisions for upgrade were influenced by clinical judgment and the persistence of severe hypotension or suboptimal cardiac output despite Impella-2.5 and inotropic support. The 30-day mortality in the subgroup of patients upgraded to other devices was 60% (n=6).
Patients requiring cardiopulmonary resuscitation within 72 hours before Impella-2.5–implantation had a significantly lower survival at 30 days compared with patients not requiring cardiopulmonary resuscitation (24.5% versus 43.7%; \(P=0.002\); Figure 2B). However, the requirement of cardiopulmonary resuscitation before institution of hemodynamic support was no independent predictor of early mortality in the multivariate logistic regression analysis (Table 3).

**Feasibility and Safety**

The Impella-2.5 was successfully implanted in 119 (99.2%) patients. The implantation procedure was considered easy or suitable by the implanting physician in 114 (95%) patients. In 1 patient (0.8%), transfemoral placement of the Impella-2.5 failed and intra-aortic counterpulsation was used subsequently. In patients successfully weaned or upgraded to other devices, the explantation procedure was rated easy or suitable in 66 (95.7%) patients.

Major adverse cardiac and cerebrovascular events in the overall study group were reported in 18 (15%) cases (myocardial infarction: \(n=8\); Re-PCI: \(n=13\); coronary artery bypass grafting: \(n=3\); stroke: \(n=2\)). Complications associated with Impella-2.5–support included bleeding at the vascular access site requiring transfusion in 29 (24.2%) and vascular surgery in 5 (4.2%) patients. Hemolysis resulting in blood transfusion was reported in 9 (7.5%) cases. In 2 (1.7%) patients, pericardial drainage was necessary because of hemodynamically relevant pericardial tamponade after the Impella placement. Device malfunction necessitating explantation occurred in 3 (2.5%) patients during long-term support. Details on safety end points are presented in Table 4.

**Discussion**

**Mechanical Support for CS**

In current practice, CS complicates 5% to 15% of cases with AMI and is still associated with high in-hospital mortality rates.\(^1,5,7,22\) Intra-aortic counterpulsation is considered the first line of treatment for patients requiring mechanical support and is recommended with a class I recommendation according to American Heart Association/American College of Cardiology and European Society of Cardiology guidelines.\(^8,23\) Contemporary IABP usage ranges from 11% to 86% in patients with CS.\(^1,11,19,24,25\) However, so far there is no data from randomized controlled trials demonstrating a survival benefit of IABP-therapy, and its efficacy has recently been questioned.\(^10,26,27\)

Ventricular assist devices are a promising alternative for patients with CS as they provide hemodynamic support by replacing LV function and, thus, may allow for recovery of hibernating or stunned myocardium. However, surgical LVADs frequently require time-consuming and complex implantation procedures. They are themselves associated
with a significant morbidity and mortality and their invasiveness precludes urgent implantation on presentation in patients with acute CS. Therefore, percutaneous devices have been developed, including the Impella-2.5–system.

**Current Evidence for Hemodynamic Support With the Impella-2.5 in Acute CS**

In contrast to other percutaneous devices, the Impella-2.5 is a less invasive system that allows for rapid transcatheter introduction using standard catheterization techniques and that provides a maximal pump flow of 2.5 L/min. A larger version of the Impella system is available as well, which is capable of providing a maximum flow of 5.0 L/min. However, this device requires a surgical cut-down of the femoral artery. The Impella-2.5 has been demonstrated to be safe and feasible in elective use during high-risk PCI as well as in patients with ST-elevation myocardial infarction without CS. It has been demonstrated to promote myocardial recovery by LV unloading and to result in an immediate reduction of diastolic LV wall stress and pulmonary capillary wedge pressure. Furthermore, beneficial effects of the system on cerebral perfusion during cardiac arrest have been reported in the experimental setting.

However, clinical data on efficacy of the Impella-2.5 in patients with CS is still limited. In a small series in 6 patients with CS after ST-elevation myocardial infarction, circulatory support with the Impella system resulted in hemodynamic improvement with a decrease of blood lactate levels. In the small randomized ISAR-Shock (Efficacy Study of LV Assist Device to Treat Patients With Cardiogenic Shock) trial comparing hemodynamic support with the Impella-2.5 and IABP (Impella: n=12; IABP: n=13), the device resulted in an improved cardiac index, but failed to improve survival.

The present report based on data from the Impella–EUROSHOCK-registry is the largest series to date investigating emergency support with the Impella-2.5–device for treatment-refractory CS. Although survival rates in patients with CS vary among the current literature, 30-day survival in the present study was 35.8% and seems rather low. The excess mortality is likely the result of a selection bias favoring critically ill patients with a particularly poor hemodynamic profile and a greater imminent risk of death. Although rather disappointing, this data reflect the outcome in a subgroup of patients who have failed to improve with first-line treatment and in whom the pLVAD is frequently used as last-resort therapy.
Table 4. Secondary Safety End Points

<table>
<thead>
<tr>
<th>End Point</th>
<th>Baseline (N=120)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MACCE (total)</td>
<td>18 (15.0)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>8 (6.7)</td>
</tr>
<tr>
<td>Re-PCI</td>
<td>13 (10.8)</td>
</tr>
<tr>
<td>CABG</td>
<td>3 (2.5)</td>
</tr>
<tr>
<td>Stroke</td>
<td>2 (1.7)</td>
</tr>
<tr>
<td>Bleeding requiring transfusion</td>
<td>29 (24.2)</td>
</tr>
<tr>
<td>Bleeding requiring surgery</td>
<td>5 (4.2)</td>
</tr>
<tr>
<td>Hemolysis</td>
<td>9 (7.5)</td>
</tr>
<tr>
<td>Pericardial drainage</td>
<td>2 (1.7)</td>
</tr>
<tr>
<td>Device malfunction</td>
<td>3 (2.5)</td>
</tr>
<tr>
<td>Renal failure</td>
<td>38 (31.7)</td>
</tr>
<tr>
<td>Renal failure requiring dialysis</td>
<td>28 (23.8)</td>
</tr>
<tr>
<td>Multiple organ failure</td>
<td>37 (30.8)</td>
</tr>
</tbody>
</table>

Values as n (%) or mean±SD. CABG indicates coronary artery bypass grafting; MACCE, major adverse cardiac and cerebrovascular events; and PCI, percutaneous coronary intervention.

option. This observation is also in line with the results of a recent study by Engström et al\(^16\) reporting an even lower 30-day survival rate of 24% in a series of 34 patients with CS after ST-elevation myocardial infarction.

Indeed, compared with the ISAR–Shock trial, patients enrolled in the Impella–EUROSHOCK-registry had a poorer hemodynamic profile at the time of device implantation with a lower systolic and diastolic blood pressure (106±22 and 64±15 mm Hg versus 91±21 and 57±17 mm Hg).\(^14\) Compared with other reports, a larger proportion of the study population had been resuscitated for cardiac arrest, and plasma lactate levels were higher (4.7±2.6 versus 5.97±5.0) at admission, thus, reflecting refractory CS with severe organ hypoperfusion at this time.\(^37\)

The observations made in the Impella–EUROSHOCK-registry confirm that use of the Impella-2.5 is feasible in the emergency setting and represents a rapid method of instituting hemodynamic support, also in less-experienced centers. The device was easy to implant with a high procedural success rate and performed well. Despite the prolonged duration of support (43.5 range 0–210 hours), the rate of device-associated complications was acceptable in this study population, although higher than reported from nonemergent pLVAD-application.\(^14\) Bleeding complications requiring transfusion occurred in 24.2% (n=29) patients, whereas surgical treatment of bleeding complications was required in 5 (4.2%) patients (Table 4). Although Seyfarth et al\(^18\) did not observe any vascular or bleeding complications in the ISAR–Shock-trial, this was a relatively small trial performed in a highly experienced center. Importantly, complication rate of Impella-2.5–treatment is low when compared with the TandemHeart pLVAD.\(^35,37\)

Clinical Implications

The Impella–EUROSHOCK-registry reflects the real-world use of the Impella-2.5 in contemporary practice outside of randomized trials. Based on these data, this potentially effective therapy is currently rather restricted to patients with refractory CS who have failed to improve with first-line treatment. This is attributable to the current lack of data demonstrating a clinical benefit with these devices as well as the current guidelines recommending intra-aortic counterpulsation as first-line for patients requiring mechanical support.\(^35,37\) Another issue is the higher cost of pLVADs when compared with IABP-therapy.\(^25\)

The present study demonstrates the feasibility and ease of Impella-2.5–implantation in patients requiring urgent hemodynamic support even in less-experienced centers. Also not based on randomized trials, this type of hemodynamic support should be considered early in patients failing to improve with first-line therapy. Furthermore, plasma lactate at the time of implantation has a prognostic impact and may also be used as metabolic marker of hypoperfusion, aiding in guiding therapy. A significant decrease in plasma lactate after the beginning of Impella treatment suggests at least partial reversal of hypoperfusion and supports the hemodynamic efficacy of the device. These findings are in line with data reported in the literature.\(^39\) Possibly, patients with lactate levels on admission above 3.8 mmol/L, as well as patients who continue to have high plasma lactate levels on Impella-2.5–support, should be considered for upgrading to more powerful assist devices (eg, the Impella 5.0), although this recommended strategy is rather based on experience than actual data.\(^36\) The present analysis failed to demonstrate a survival benefit for patients upgraded to other devices. This may be attributable to the small number of patients as well as confounding factors, such as the time delay associated with the decision to upgrade.

Study Limitations

This study represents by far the largest real-world cohort of patients treated with the Impella-2.5 in CS to date. However, several limitations should be acknowledged with regard to the current report. First, the lack of a control group as typical for a registry hampers definite conclusions on efficacy of Impella-2.5–support. Second, because of the retrospective nature of data collection, detailed hemodynamic data after Impella implantation, in particular cardiac output, are not available. In emergency situations, in patients requiring circulatory support, an extensive hemodynamic evaluation is often not possible and not performed outside of randomized trials. The availability of data was limited to standard parameters recorded during clinical routine in all participating centers. However, this might be of minor significance as the hemodynamic benefit of LVAD-support is well documented and similar effects may be assumed in the Impella–EUROSHOCK population.\(^39\) Third, selection bias may have influenced the outcome, as treatment with the Impella-2.5 has preferentially been given to the most severely ill patients. Finally, patients were included retrospectively during a period of 5 years also covering the learning curve of the participating center in use of the Impella-2.5. This may impact selection of patients as well as the time point of device implantation in the individual centers.

In conclusion, the use of the Impella-2.5 for hemodynamic support in refractory CS is feasible although associated with a high complication rate. The high 30-day mortality rate may reflect the selection of patients with major hemodynamic compromise and high risk of imminent death. In a severely ill patient population with lactic acidosis, this device may not...
provide adequate ventricular unloading or systemic perfusion. Particularly in patients with profound CS, the Impella-2.5 may need to be upgraded early to more powerful devices. Further studies and adequately powered clinical trials are necessary to improve selection and timing for device support for this indication.

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CLINICAL PERSPECTIVE

The Impella–EUROSHOCK-registry is the largest real-world cohort of patients treated with the Impella-2.5 in cardiogenic shock to date—thus, reflecting the real-world use of the device in contemporary practice. The observations demonstrate the feasibility of Impella-2.5—implantation in patients requiring urgent hemodynamic support, even in less-experienced centers. However, overall 30-day mortality remained high in this patient population with major hemodynamic compromise and a high risk of imminent death. In this severely ill patient population, the Impella-2.5 device may not provide adequate ventricular unloading or systemic perfusion. Further clarification in adequately powered clinical trials is needed to determine optimal timing and patient selection for the Impella-2.5 and subsequent definitive therapy to improve survival in this challenging patient population.
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