Impact of left ventricular unloading using a transfemoral micro-axial pump in eCPR patients

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Abstract

Objectives: Extracorporeal cardiopulmonary resuscitation (eCPR) is a rapidly growing treatment strategy due to increasing survival rates in selected patients. Additional left ventricular mechanical unloading, using a transfemoral micro-axial blood pump (Impella®), might improve patients' outcomes. In this regard, we sought to investigate patients who suffered OHCA (out- of hospital cardiac arrest) or IHCA (in-hospital cardiac arrest) with subsequent eCPR (extracorporeal cardiopulmonary resuscitation) via VA-ECMO (veno-arterial extracorporeal membrane oxygenation) and concomitant Impella® implantation. Methods: From January 2016 until December 2019, 71 patients underwent eCPR at our institution. Data prior eCPR and early outcome parameters were analyzed comparing patients who were supported with an additional transfemoral micro-axial blood pump (ECMO+Impella®, n= 7) and patients without additional (ECMO, n=64) support during VA-ECMO therapy. Results: Baseline data did not significantly differ between groups. All-cause mortality was significantly lower in the ECMO+Impella® group (83% vs. 29%, p= 0.01). The time of circulatory support was shorter in the ECMO+Impella® cohort (3.16±2.09 vs. 6.5±2.79, p=0.01). Additionally, ECMO weaning was significantly more feasible in patients with ECMO+Impella® (71% vs. 29%, p =0.02). Patients treated with additional Impella® showed more acute kidney injury (AKI) with the need for dialysis (71% vs. 21%, p=0.09). Conclusion: From our data, concomitant Impella® support might increase survival and successful ECMO weaning in eCPR patients. Treatment associated complications such as AKI were more common in this highly selected patient group. Further studies with larger numbers are necessary to evaluate concomitant LV-unloading's clinical relevance in eCPR patients, using an Impella® device.

Introduction

The frequency of extracorporeal cardiopulmonary resuscitation (eCPR), either in out-of-hospital or in-hospital cardiac arrest (OHCA / IHCA) scenarios, is increasing due to advances in interdisciplinary treatment of these patients (1). Moreover, mortality rates have been shown to be improving in recent years, despite still relatively low overall-survival (2). In particular, eCPR remains a specialized rescue-therapy and is mainly performed in high volume centers (3, 4).

In eCPR patients, left ventricular function might be massively impaired due to myocardial infarction (MI), decompensated heart insufficiency (HI), pulmonary embolism (PE), or a primary arrhythmogenic event.

Furthermore, experimental data show that due to its retrograde flow, VA-ECMO causes left ventricular (LV) distension and an increase in left ventricular end-diastolic volume (LVEDV), left ventricular end-systolic volume (LVESV), as well as increased myocardial wall stress (5). The potential formation of an LV-thrombus is a fatal consequence of impaired and dilated LV without sufficient ejection (6).

Several strategies are being discussed to avoid or limit left ventricular dilation (7). Up to now, there are no particular indications for LV-unloading regimes and no specific guidelines (8). The decision for LV-unloading is depending on clinical parameters, such as echocardiographic measures, radiological findings, and the hemodynamic situation (9). The question of routine implementation of LV unloading or selection of appropriate parameters and patients is the subject of a widespread scientific work in recent literature (9-11).

In clinical practice, short-term left ventricular assist with Impella® is frequently used for LV- unloading in ECMO patients (11). Besides beneficial hemodynamic effects, differences in favorable clinical outcomes might be affected by the underlying disease.

In this regard, we sought to analyze the effect of concomitant Impella® implantation in eCPR patients in order to analyze the impact on short-term outcomes.

Patients and Methods

From January 2016 until December 2019, 71 patients underwent eCPR at our institution. They were retrospectively analyzed and divided into two groups: ECMO (n=64) and

ECMO+Impella? (n=7). The investigation was approved by the institutional review board of the University of Cologne and conformed to the principles outlined in the Declaration of Helsinki. Due to its retrospective study, the need for written informed consent was waived.

eCPR protocol University Hospital Cologne

The interdisciplinary eCPR team of the University Hospital Cologne is running by the Department of Cardiothoracic Surgery and the Department of Cardiology. In situations of ongoing CPR, physicians of both divisions are involved in further treatment. ECMO (Maquet, Rastatt, Germany) implantations are performed in the catheterization laboratory, intensive care unit (ICU), or emergency room. After a general clinical examination and initial echocardiographic evaluation, the left or right groin is sterilized and prepared for ECMO implantation. Additional concomitant blood gas analysis is performed with the view to assessing initial metabolic parameters. ECPR is performed in the interdisciplinary consensus of the participating disciplines. The decision to cannulate is based on participating physicians' judgment, following institutional criteria:

eCPR inclusion criteria

- No terminal illness
- Age [?] 75 years
- Observed cardiac arrest
- No-flow-time [?] 5 mins
- Low-flow-time [?] 90 mins
- refractory shockable rhythm or non-shockable in case of cardiac tamponade or pulmonary embolism

eCPR exclusion criteria

arterial pH < 6.6

non-shockable rhythm > 20 mins after examination for cardiac tamponade or pulmonary embolism

hemoglobin < 8g/dl

ECMO cannulas are implanted via femoral vessels in Seldinger's technique, as already published by our study group (12-15). Extracorporeal circulation is established by using a Rotaflow centrifugal pump (Maquet,

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Rastatt, Germany) with a Quadrox membrane oxygenator (Maquet, Rastatt, Germany) and the PLS2050 circuit system (Maquet, Rastatt, Germany).

After initiation of ECMO flow and stabilization of hemodynamics, the next steps of treatment were initiated.

Moreover, to avoid thromboembolic events during ECMO circulation, our anticoagulatory protocol included the intravenous infusion of unfractionated heparin, with a target activated clotting time (ACT) of 180 to 200 seconds and PTT between 60 to 80 seconds.

Laboratory data were drawn along with initial blood gas analysis or after the patient's transfer to ICU.

Definitions

Low flow time was defined as the time of advanced CPR until the commencement of ECMO circulation. Renal failure was defined as a rise in serum creatinine levels of more than 0.3mg/dL (26.5 µmol/L) over 48 hours or a rise in serum creatinine 1.5 times higher than average levels or newly developed reduction of urine at <0.5mL/kg/h over 6h.

Implementation of concomitant Impella® support

Impella® (Abiomed, Danvers, Massachusetts, USA) implantation was realized either simultaneously with VA-ECMO in the heart catheter laboratory or after ECMO implantation on the intensive care unit, due to clinical findings as mentioned above.

- End diastolic LV-size (LVEDD) [?] 6.8cm (male), 6.1cm (female)
- spontaneous contrast in TTE/TEE
- Reticular lung edema in chest x-ray

Impella(r) implantation was guided by transoesophageal echocardiography. Additional Impella(r) therapy resulted in a target ACT of 180-220.

Variables of interest

The analysis was performed using a retrospectively maintained institutional patient database. The variables evaluated included: patient demographics (age, height, weight, sex), patients' status before ECMO support CPR, duration of CPR, the cause of OHCA/IHCA, CPR characteristics, and initial blood gas analysis), early outcome data (pH and lactate after 12 and 24 hours, blood transfusions, in-hospital mortality, discharge, hospital, and ICU stay. As well as analyzation of end-organ damaging; acute kidney injury (AKI) requiring dialysis, stroke, bleeding, and ischemia.

Endpoints of the study

The primary endpoints of our analysis were early outcomes after initiation of eCPR and in-hospital mortality.

Statistical methods

Statistical analysis was performed using Statistical Package for Social Sciences, version 26.0 (SPSS IBM, Chicago, Illinois). All data were presented as continuous or categorical variables. Categorical data were expressed as total numbers and percentages. Continuous data were evaluated for normality using a one-sample Kolmogorov-Smirnov test and were expressed as the mean +- standard deviation (SD) in normally distributed or median (interquartile range) in cases of non-normally distributed continuous variables. Univariate analysis was performed using either Student t or Mann-Whitney U test for normally and non-normally distributed continuous variables, respectively. Pearson's χ^2 or Fisher exact tests were used to comparing categorical data depending on the minimum expected count in each cross-tab. P values < 0.05 were considered statistically significant. We performed a linear regression analysis with ANOVA for further analysis of the variable's effect. Subgroup analysis of male gender was performed.

Results

Patient's baseline characteristics before eCPR

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Baseline demographics are presented in Table 1. The ECMO group accounted for 64 patients, of which 53 were male (82.5%) and 11 females (17.5%). The ECMO+Impella® group included seven male (100%) patients. The median age was 59(55;65) years in the ECMO group and 56(42;64) years in the ECMO+Impella® group (p=0.32).

Scenarios of eCPR did differ between the groups (OHCA: 86% ECMO+Impella® vs. 39% ECMO, p=0.21; IHCA: 14% ECMO+Impella® vs 38% ECMO, p=0.21). Low-flow time was 60 minutes on average in both groups.

Laboratory parameters before eCPR

Laboratory parameters before eCPR are presented in Table 2. There were no statistically significant differences between both groups.

Early-Outcomes

Early outcomes are summarized in Table 3. Lactate and pH values showed no significant difference in the comparison of both groups over the first 24 hours. ECMO duration was significantly shorter in the ECMO group than in the ECMO+Impella® group (3.16±2.09 days ECMO vs. 6.4±2.79 days ECMO+Impella®, p=0.01). ECMO weaning was feasible in 29% of the ECMO group and 71% of the ECMO+Impella® group (p=0.02). The rate of blood transfusions differed significantly between both groups (26(13;38) units ECMO+Impella® vs. 10(3,25;18) units ECMO, p=0.01). The rate of transfused fresh frozen plasma units did not differ between the groups (ECMO+Impella® 10(2;15) and ECMO 2 (0;7.75), p=0.09). The ECMO+Impella® group received significantly more platelet units (3(1;4) vs ECMO group 0 (0;1), p<0.01).

Overall, in-hospital mortality was significantly lower in the ECMO+Impella® group (29% ECMO+Impella® vs. 83% ECMO, p=0.01). The survival for both groups is presented in the Kaplan-Meier plot (Figure 1).

End organ failure

Data regarding end-organ failure are presented in Table 3. Significantly more renal failure requiring dialysis was observed in the ECMO+Impella® group (72% vs. 21%, p=0.09). Stroke rates did not show significant differences between the groups (ECMO 21% vs. ECMO+Impella® 29%, p=0.82). Subsequent limb ischemia occurred in 6 cases in the ECMO group and 1 in the ECMO+Impella® group (p=0.92).

Linear regression and correlation analysis

Linear regression showed a significant effect of Impella® implantation on in-hospital mortality (R^2=0.15 , ANOVA p=0.01, 95%CI = -0.853 - -0.232) , ECMO weaning (R^2=0.08 , ANOVA p=0.014, 95%CI = 0.092 – 0.805), and renal failure requiring dialysis (R^2=0.13 , ANOVA p=0.01, 95%CI =0.12 – 0.93). The need for red blood units was also significantly associated with Impella® support (R^2 =0.17, 16.132 95% CI 7.57 – 24.6, p =0.00). Data were presented in Table 4.

Subgroup analysis for male sex

After adjusting and comparing both groups concerning gender, the baseline parameter did not show significant differences (Table 5). There was a significantly higher rate of acute kidney injury (AKI) leading to dialysis in the ECMO+Impella® group, compared with the ECMO group (71% vs. 25%, p= 0.03). Also, the ECMO+Impella® group received significantly more red blood units (26 vs. 10, p=0.01) and platelets (0 vs. 3, p= 0.01). Moreover, ICU-stay was significantly longer in the ECMO+Impella® group (21 vs. 1 day, p = 0.03). Overall mortality was significantly lower in the ECMO+Impella® group (29% vs. 85%, p= 0.01).

Discussion

Our retrospective analysis, comparing simultaneous mechanical support with ECMO+Impella® versus single ECMO therapy in eCPR patients, showed improved overall-survival after concomitant Impella® support. From the data presented, Impella® assist was associated with a higher weaning rate of ECMO support.

The association of lower mortality and a higher rate of successful ECMO weaning was consistent through all investigated subgroups, including a comparison of only male patients. On the other hand, complications, including AKI with subsequent hemodialysis, were more frequently seen in the ECMO+Impella® group.

ECMO-therapy establishes an artificial cardiopulmonary bypass in severely impaired hemodynamic situations, such as ongoing CPR, and provides adequate oxygenation for vital organs (16). Besides, ECMO therapy is associated with various complications of inadequate treatment, especially the increased afterload, which might negatively impact the outcome (17).

In this retrospective analysis, we observed a significant reduction in in-hospital mortality in the ECMO+Impella® cohort, alongside a significantly higher rate of successful ECMO weaning in the ECMO+Impella® cohort. These findings are supported by a recent large multicenter cohort study by Schraege and colleagues, who analyzed data from 686 cardiogenic shock patients treated with VA-ECMO with or without left ventricular unloading by concomitant Impella® implantation (11). In their observational analysis, simultaneous Impella® implantation was associated with significantly lower mortality in cardiogenic shock and eCPR patients and more complications, such as bleeding, ischemia, and renal replacement therapy. Another broad analysis by Pappalardo et al. showed similar results, describing increased AKI rates with hemodialysis (18).

The increased survival rates observed in our cohort might be explained by the potential benefits of LV-unloading in eCPR patients. Previously, early LV-unloading has been reported to be beneficial in cardiogenic shock patients treated with ECMO via the reduction in preload (17, 19).

Other mechanical support devices might also improve mortality and outcome. An intraaortic balloon pump might also be beneficial concomitant to VA-ECMO therapy in eCPR patients due to its counter pulsatile fashion (20).

On the other hand, other authors and centers advocate a conservative strategy regarding additional Impella® implantation in VA-ECMO therapy (9, 10). Today, there is no universally used unloading strategy; thus, LV-venting in VA-ECMO patients remains to be the target of ongoing scientific research. Randomized trials are necessary to confirm the reduction in mortality going along with LV unloading and determining a certainty, strategy-wise, for eCPR patients.

Safety of concomitant Impella ®-placement

In our retrospective analysis, complications such as AKI and the need for blood-transfusions occurred more frequently in the ECMO+Impella® group. This was consistent in evaluated subgroup analysis and was associated with Impella®-therapy in linear regression analysis.

A higher rate of active bleeding or limb ischemia could not be observed.

This confers to larger evaluations, such as Schraege et al., who observed a higher rate of complications such as bleeding, ischemia, and AKI in patients treated with additional Impella® implantation (11).

In regard to an increase of shear stress, hemolysis is a known complication associated with Impella® and is associated with an increased need for blood-transfusions (21). As well as limb ischemia due to large vascular access requirements of Impella® support.

In this analysis, we found a significantly higher proportion of AKI with the need for hemodialysis in the ECMO+Impella® group, which was significantly associated with the use of additional Impella® implantation. ECMO therapy is a known risk factor for renal failure (22-24). Moreover, it is thought to lead to a reduction in renal oxygen delivery and inflammatory damage. In particular, during pathological conditions requiring ECMO, biological defense mechanisms maintaining central perfusion by reducing perfusion of peripheral organs (such as the kidney) have been identified. However, the role of additional Impella® implantation on acute kidney failure remains unclear and clinical data is scarce (25-27).

In summary, complications like the higher need for renal replacement therapy, bleeding, and limb ischemia

might be explained by more increased survival. Thus, patients are more exposed to the risk of suffering complications.

Study limitations

This study was limited by its small sample size (Impella® group n = 7). Patients with Impella® might have been clinically and hemodynamically more stable, also underlined by significantly longer survival and lower mortality. Hence, clinical parameters like the need for blood transfusions and ECMO weaning are challenging to interpret in the ECMO+Impella® group. Also, hemodynamic parameters from bedside echocardiography are not captured in this analysis, and thus we cannot analyze differences in LV-distension parameters objectively between groups.

Conclusion

In this retrospective analysis, concomitant Impella® to ECMO support in eCPR patients was associated with significantly lower in-hospital mortality. Also, weaning of VA-ECMO was more often successful in the ECMO+Impella® group. ECMO+Impella® group showed significantly higher rates of blood transfusions and acute kidney failure requiring dialysis.

The realization of a simultaneous mechanical circulatory assist device might be a beneficial therapy option in eCPR patients. Further studies are needed to evaluate the clinical relevance and impact of Impella® devices in eCPR patients.

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Figure 1. Kaplan-Meier survival.

Table 1. Baseline demographic data.

Parameter	ECMO (n =64)	ECMO+Impella® (n =7)	p-value
Male	53 (82.5%)	7 (100%)	0.10
Age	59 (55;65)	56 (42;64)	0.32
OHCA	39 (62%)	6 (86%)	0.21
IHCA	24 (38%)	1 (14%)	0.21
Low-flow time (min)	60 (45;75)	60 (55;75)	0.95
Lactate prior implantation (mmol/l)	12.65 (9.65;16)	18.84 (12.68;18.5)	0.33
pH prior implantation	6.98	6.88	0.24

Table 2. Laboratory parameters.

Parameter	ECMO (n=64)	ECMO+Impella® (n=7)	p-value
Urea admission (mg(dL)	42 (32;63)	30 (25.75;48)	0.26
Creatinine admission (mg/dL)	1.32 (1.0;1.86)	1.44 (1.0;3.75)	0.79
Bilirubin admission	0.4 (0.25;0.5)	0.6(0.55;0.82)	0.02
AST admission	399 (117;668)	456 (259;857)	0.46
ALT admission	167 (72;384)	159 (86.25;304)	0.79
CK admission	705 (220;2865)	3406(1716;5132)	0.08
CK ater 24h	3290(1195;5769)	6012(1974;8778)	0.35
CK-MB % admission	16.5(13,25;30,25)	14(10;180)	0.49
CK-MB admission	195 (87;415)	376 (27;659)	0.52
Platelets admission	163 (110;244)	176 (106;200)	0.91
pH 12h after implantation	7.38 (7.33;7.43)	7.33 (7.29;7.47)	0.50
pH 24h after implantation	7.42 (7.36;7.46)	7.44 (7.38;7.50)	0.42
Lactate 12h after (mmol/l)	6.67(3.79;13)	8.95 (6.86;11.7)	0.45
Lactate 24h after (mmol/l)	3.74 (2.32;7.19)	4.0 (2.68;6.46)	0.84

Table 3. Outcomes and end-organ damage.

Parameter	ECMO (n =64)	ECMO+Impella® (n =7)	p-value
ECMO duration (days)	3.1±2.09	6.4±2.79	0.01
Cases of ECMO weaning	19 (29%)	5 (71%)	0.02
AKI requiring dialysis	13 (21%)	5 (71%)	0.09
Limb ischemia	6 (9.5%)	1 (14%)	0.92
stroke	13 (21%)	2 (29%)	0.82
Red blood (units)	10 (3.25;18)	26(13;38)	0.01
FFP(units)	2 (0.7;7.5)	10 (2;15)	0.09
Platelets (units)	0(0;1)	3(1;4)	0.00
In-hospital mortality	53 (83%)	2 (29%)	0.01

Table 4. Linear regression.

Parameter	Regression	95% CI	R^2	p-value
In-hospital mortality	-0.542	-0.853 to -0.232	0.15	0.01
ECMO weaning	0.449	0.092 to 0.805	0.84	0.01
Red blood units	16.132	7.57 to 24.69	0.17	0.00

Parameter	Regression	95% CI	R^2	p-value
Platelets	1.94	0.862 to 3.03	0.15	0.01
AKI requiring dialysis	0.531	0.12 to 0.93	0.13	0.01

Table 5. Subgroup analysis of the male gender.

Parameter	ECMO, male (n=53)	ECMO+Impella®, male (n =7)	p-value
Age	60 (46;66)	56(42;64)	0.30
OHCA	35 (66%)	6 (86%)	0.29
IHCA	18 (34%)	1 (14%)	0.29
Low-flow time (min)	60(46.25;77.5)	60(55;75)	0.90
Lactate prior implantation (mmol/l)	12.64(10;16)	18.84(12.68;18.5)	0.34
pH prior implantation	6.91	6.88	0.39
ECMO duration (days)	3.64±1.64	6.4±2.79	0.02
cases of ECMO weaning	13 (25%)	5 (71%)	0.12
AKI requiring dialysis	13 (25%)	5 (71%)	0.03
Limb ischemia	4 (8%)	1 (14%)	0.77
Stroke	12 (23%)	2 (29%)	0.93
Red blood units	10 (2.5;18)	26 (13;38)	0.01
FFP	2(0;8.5)	10 (2;15)	0.10
Platelets	0 (0;1)	3 (1;4)	0.01
In-hospital mortality	45 (85%)	2 (29%)	0.01

Figure 1. Kaplan-Meier survival (log-rank p= 0.01).

survival
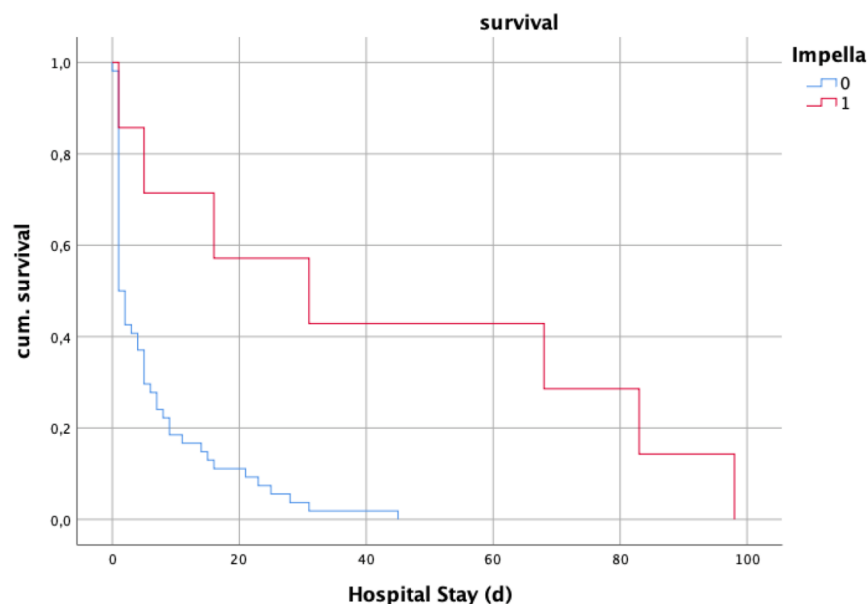
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