Timely extracorporeal membrane oxygenation assist reduces mortality after bypass surgery in patients with acute myocardial infarction

Marwan Hamiko MD¹ | Ingo Slottosch MD² | Max Scherner MD² | Christopher Gestrich MD¹ | Thorsten Wahlers MD³ | Christian Putensen MD⁴ | Fritz Mellert MD¹ | Hendrik Treede MD¹ | Oliver Dewald MD¹ | Georg Daniel Duerr MD¹

¹Department of Cardiac Surgery, University Clinical Centre, Bonn, Germany
²Department of Cardiothoracic Surgery, University Hospital, Magdeburg, Germany
³Department of Cardiothoracic Surgery, University Hospital, Cologne, Germany
⁴Department of Anaesthesiology and Intensive Care Medicine, University Clinical Centre, Bonn, Germany

Abstract

Background: Patients with acute myocardial infarction (AMI) are at high risk when undergoing emergency coronary artery bypass graft (CABG)-surgery. Their outcome remains poor despite increased use of extracorporeal membrane oxygenation (ECMO). We investigated the impact of timing for perioperative ECMO-support in these patients.

Methods: In this retrospective double-center study, we evaluated 201 patients with AMI undergoing CABG, dividing them into the following groups: No-ECMO (n = 101), preoperative ECMO (pre-ECMO, n = 6), intraoperative ECMO (ECC-ECMO, n = 67), and postoperative ECMO (post-ECMO, n = 27). We evaluated the impact of ECMO timing on postoperative mortality, organ function, and length of stay, comparing these to predicted outcome using different risk-scores.

Results: Post-ECMO patients showed lowest 30-day-survival (40.7%), while earlier ECMO-start was associated with better outcome (50.7% in extracorporeal circulation [ECC]-ECMO and 66.7% in pre-ECMO patients). On admission, only pre-ECMO and ECC-ECMO patients showed higher surgery- and intensive-care-unit (ICU)-related risk-scores. In pre- and ECC-ECMO patients, the first significant increase in lactate levels (>4 mmol/L) was observed preoperatively, while this occurred 1 hour postoperatively in post-ECMO patients. Bilirubin was increased in all patients, decreasing after 3 and 12 days in pre- and ECC-ECMO patients, respectively, but only after 18 days in post-ECMO patients. Multiple ICU risk-scores did not discriminate survival-probability correctly. Only the ECMO-related survival after veno-arterial-ECMO-score correctly predicted the significantly lower survival in post-ECMO patients.

Conclusion: Our study shows that timely ECMO-support is associated with earlier bilirubin-downtrend and higher survival in patients with AMI after CABG.
Lactate-increase greater than 4 mmol/L seems to be a helpful threshold to trigger the timely onset of ECMO-therapy, providing better survival.

**KEYWORDS**
acute myocardial infarction, cardiogenic shock, circulatory support, coronary artery bypass graft, extracorporeal membrane oxygenation

1 | INTRODUCTION
Emergent revascularization is necessary to preserve myocardial function in patients with acute myocardial infarction (AMI). Especially ST-elevation myocardial infarction (STEMI) often causes cardiogenic shock (CS) with hemodynamic instability and low cardiac output syndrome (LCOS). This leads to multiple organ dysfunction and is associated with 30-day mortality-rate of more than 40% irrespectively of the procedure used for revascularization—percutaneous intervention (PCI) or coronary artery bypass graft (CABG)-surgery. The concept of early revascularization led to improved long-term outcome in patients with CS after AMI and established primary PCI as the dominant therapy option during the past decade in Europe.

In patients with STEMI, PCI is currently recommended for treatment of culprit lesion only. The treatment of remaining lesions could either be accomplished using PCI or CABG depending on the extent of the disease and complexity of stenosis at a later time-point. Still, CABG can provide good results in patients with STEMI without CS, especially since CABG results in a more complete revascularisation than PCI. Even more, emergency CABG may be necessary in patients with AMI, which are anatomically unsuitable for PCI or with mechanical complications during PCI. Mortality of either PCI or CABG in this situation remains high (>40%), but STEMI-patients with CS, initially treated with PCI, showed a better survival when subjected to subsequent CABG instead of PCI.

Emergency-CABG is associated with a significant operative risk in patients with AMI because of the risk of developing CS. In these patients, mechanical circulatory support (MSC) is an option to support the left ventricle (LV) to preserve cardiac function and provide a better perfusion of organs particularly vulnerable to hypoxia, eg, liver, kidneys, or brain. The "IABP-SHOCK-II-Trial" showed no significant short-term or long-term survival benefit of intra-aortic balloon counter pulsation (IABP) in AMI-patients with CS, as recently shown by the long-term 6-year outcome data. Still the use of other MSC-systems, eg, Impella or extracorporeal membrane oxygenation (ECMO), emerged during the last decade. An investigation from the Impella-EUROSHOCKregistry evaluated 120 AMI-patients with CS and showed reduced lactate-concentration suggesting a better organ-perfusion, but no effect on 30-day-mortality of greater than 60%. Also, TandemHeart did not reduce 30-day-mortality when compared with IABP in small randomized controlled trials (RCTs). On the other hand, primary PCI has been performed with veno-arterial (VA)-ECMO-support in hemodynamically preserved AMI-patients with beneficial outcome and lower 30-day-mortality. A meta-analysis described a survival benefit for patients with CS during cardiac surgery if treated with VA-ECMO-assist preoperatively. The few studies examining VA-ECMO therapy in patients with AMI subjected to CABG were either based on a low patient number (<10), or excluded patients with preoperative ECMO therapy. Therefore, these studies were unable to investigate optimal timing of ECMO-start. At the same time, several studies investigated ECMO-support before or during emergency PCI, and showed that only early onset of ECMO therapy leads to significantly better clinical outcome. In support of this, experimental data from a porcine model with delayed reperfusion suggested that early "unloading" of the LV, using an intracorporeal axial flow-catheter, is associated with myocardial protection.

Hence, it seems plausible that preoperative or intraoperative relief of the LV with ECMO could be a potential new strategy for patients with AMI subjected to emergency-CABG. Still, one must bear in mind that ECMO does not lead to unloading of the LV, but rather supports the circulation and can even cause LV-overload.

We hypothesized, that preoperative or intraoperative LV-support with VA-ECMO is associated with better survival in patients with AMI subjected to emergency-CABG. The aim of this study was to compare outcome, complications, and predictive value of risk-scores after preoperative, intraoperative, and postoperative ECMO-assist.

2 | MATERIAL AND METHODS

2.1 | Patients
In this retrospective double-center study, we investigated 201 consecutive patients with AMI who underwent emergency isolated CABG-surgery between January 2008 and December 2017. Indications for CABG were left main or three-vessel disease, unsuitable anatomy for PCI, unsuccessful PCI, or angiographic accident. All cases were emergency-admissions from the heart catheterization laboratory of our university hospitals or were assigned from the catheter labs of surrounding smaller hospitals without cardiothoracic surgery departments. The heart-team decided whether to perform CABG immediately or at a later stage. This decision was based on the patients’ symptoms, progress in heart enzymes-levels, and signs of inotropes-and vasopressors-refractory CS. The study was in accordance with the declaration of Helsinki. The ethical review-board of our institutions waived the need for patient-consent in this retrospective study.
2.2 | Group definition

AMI-patients with therapy-refractory CS received ECMO therapy before CABG-procedure and were defined as pre-ECMO group (n = 6). Patients with AMI with good preoperative hemodynamics and development of intraoperative CS were transferred directly from the extracorporeal circulation (ECC) to ECMO therapy and were defined as ECC-ECMO group (n = 67). AMI-patients with acceptable intraoperative hemodynamic situation under moderate catecholamines and lactate-increase and postoperative deterioration into CS within the first 12 hours received ECMO therapy on the intensive-care-unit (ICU); post-ECMO group (n = 27). Patients without need for ECMO therapy were defined as No-ECMO group (n = 101).

Details on CABG-surgery and postoperative care, indication for ECMO-implantation, ECMO-management, weaning-criteria, and data-acquisition are described in the the Section S2.

2.3 | CABG-surgery and postoperative care

All patients underwent CABG-surgery using median sternotomy and cardiopulmonary bypass (CPB) after cannulating the ascending aorta and the right atrium. Myocardial arrest and cardioprotection were induced using Calafiore blood-cardioplegic or Bretschneider-solution. Mild hypothermia (34°C) was established via heat exchanger/cooler (HCU-40; Maquet, Rastatt, Germany). Graft choice was left to the surgeons’ decision and included left and/or right mammary artery, radial artery, and saphenous veins. After the surgical procedure, patients were transferred to the cardiothoracic ICU. No-ECMO patients remained sedated with propofol and sufentanyl or piritramide if an uncomplicated postoperative course was anticipated. Patients with ECMO or patients needing mechanical ventilation for greater than 48 hours were sedated with midazolam and sufentanyl until weaning from ECMO was accomplished.

2.4 | Indication for ECMO-implantation

The indication for ECMO therapy was supported by perioperative diagnostic tools: transoesophageal echocardiography (TEE), pulse contour cardiac output or pulmonary artery catheter-analysis. Regarding these, CS was defined as a state of LCOS with systolic arterial hypotension (<90 mmHg) and/or low cardiac index (<2.2 L/min/m²). Other indicators of LCOS were signs of organ arterial hypotension (<90 mmHg) and/or low cardiac index (arterial hypotension (<90 mmHg) and/or low cardiac index). Regarding these, CS was defined as a state of LCOS with systolic hypotension (<90 mmHg) and/or low cardiac index. Further indications were metabolic and organ failure (oliguria <0.5 mL/kg/h), signs of anabolic metabolism (lactate >2.5 mmol/L, bilirubin >3 mg/dL), and signs of vascular shock (systolic blood pressure/heart rate) less than 1.

2.5 | ECMO-management and weaning criteria

In all six pre-ECMO patients, cannulation was performed via femoral vessels. In ECC-ECMO patients the system was connected intraoperatively to the central cannulas in the ascending aorta and right atrium during full heparinisation, and after protamine infusion (50% of the initial heparin-dose) activating clotting time was kept between 150 and 200 seconds. In these patients, the chest remained open during ECMO-support, except for two patients, where the thorax was closed after cannulating the right subclavian artery and femoral vein. In post-ECMO patients, ECMO was installed on ICU using peripheral cannulation of the femoral vessels except in two cases with arterial cannulation via the right subclavian artery. In all patients who received peripheral arterial ECMO cannulation via the superficial femoral artery, a reperfusion cannula was inserted distally into the superficial femoral artery to provide lower limb perfusion. After bleeding cessation on the ICU, heparin was given targeting a partial thromboplastin time of 50 to 60 seconds. Cardiowcirculatory recovery was evaluated by stepwise reduction of ECMO flow (0.5–1.0 L/min every 24 hours) and assessment of myocardial function in TEE, as well as metabolic and organ-perfusion related parameters (SvO2, lactate, diuresis, creatinine, bilirubin). ECMO-weaning was started when a stable cardiopulmonary condition was reached under only a moderate inotropic support (adrenaline <0.2 µg/kg/min, dobutamine <3 µg/kg/min, and/or milrinone <0.4 µg/kg/min) and a FiO2 less than 0.7 at a maximum ECMO flow of 1 to 2 L/min. In case of inadequate recovery, full ECMO flow was reinstalled for another 24 hours before the next weaning attempt. Successful weaning from ECMO was defined as survival for greater than 48 hours after ECMO-expantion.

2.6 | Statistical analysis

SPSS Statistics V24 (IBM, Armonk) and GraphPad Prism V 5.0.f (La Jolla) were used. Normal distribution was confirmed using the D’Agostino and Pearson omnibus normality test. Results for categorical variables are expressed as percentages and the Pearson χ² test was performed. For continuous variables, results demonstrated in tables are expressed as mean ± SD, data from diagrams are expressed as mean ± SEM. If two groups were compared, the unpaired t test was performed. If data from more than two groups were compared over time, two-way analysis of variance (ANOVA) with Bonferroni multiple comparison-statistics was applied when appropriate, and if significant, changes between the groups at each time-point were evaluated using ANOVA with the Tukey post-hoc analysis. P < .05 was considered statistically significant.

3 | RESULTS

3.1 | Patient characteristics, preoperative risk-scores, and perioperative results

Evaluation of preoperative data showed STEMI in all pre-ECMO, but only in 74.1% of post-ECMO patients (Table 1 and Table S1). Cardiopulmonary resuscitation (CPR) was most often necessary in pre-ECMO patients, and CABG was preceded by PCI within 2 days before surgery most often in this group. Longest door-to-operating room (OR)-time and longest time from PCI-to-OR were seen in pre-ECMO patients. Fastest PCI-to-OR-time was observed in ECC-ECMO patients.
At admission, stdEuroSCORE, logEuroSCORE, APS-, and APACHE-II-scores were significantly higher in pre- and ECC-ECMO when compared with No-ECMO patients. Also, shock-index was ≥1 in these groups.

Surgery duration was significantly longer in post-ECMO compared with No-ECMO group Table 2. Post-ECMO group showed the longest aortic cross clamping time. Longest CPB-time was observed in ECC-ECMO patients. No difference was observed concerning the number of peripheral bypass anastomoses. A significantly higher amount of intraoperative blood product transfusions was needed in all ECMO groups when compared with the No-ECMO group, while no difference was observed between the ECMO groups (Table S2).

Post-ECMO patients showed lowest 30-day-survival, while earlier ECMO-start was associated with higher survival rates (Figure 1A). Causes for mortality are displayed in Figure 1B.

We observed a significantly higher lactate concentration in pre-ECMO and ECC-ECMO groups on admission and preoperatively when compared with No-ECMO group (Figure 1C). Intraoperative lactate levels increased significantly in the ECC-ECMO group, while

**TABLE 1** Baseline patient data

| Preoperative variables | No-ECMO (G1; n = 101) | Pre-ECMO (G2; n = 6) | ECC-ECMO (G3; n = 67) | Post-ECMO (G4; n = 27) | P value |
|------------------------|------------------------|----------------------|-----------------------|------------------------|---------|
| STEMI, n (%)           | 94 (93.1)              | 6 (100)              | 56 (83.6)             | 20 (74.1)              | .027    |
| CPR before admission, n (%) | 9 (8.9)              | 4 (66.7)             | 26 (38.8)             | 4 (14.8)               | <.0001  |
| Prior PCI, n (%)       | 16 (15.8)              | 5 (83.3)             | 22 (32.8)             | 8 (29.6)               | .001    |
| Time from PCI to OR, h | 22.5 ± 43.5            | 49.1 ± 64.5          | 8.4 ± 20.8            | 13.1 ± 15.8            | .129    |
| APS-score              | 5 ± 6                  | 14 ± 13*             | 10 ± 9**              | 8 ± 7                  | <.0001  |
| APACHE-II-score        | 14 ± 7                 | 23 ± 12*             | 18 ± 9**              | 17 ± 6                 | .002    |
| logEuroSCORE           | 31.1 ± 19.7            | 55.1 ± 22.3*         | 39.6 ± 17.3**         | 34.5 ± 19.9            | .002    |
| stdEuroSCORE           | 12.2 ± 3.2             | 16 ± 3.5;†           | 13.4 ± 2.4**          | 12.5 ± 3.1             | .004    |

Note: Values are expressed as mean ± SD, or as number and percentage (in brackets). For categorical variables the Pearson χ² test was performed as appropriate. When describing changes of metric values, ANOVA with the Tukey post-hoc analysis was performed, and P < .05 was considered statistically significant (displayed in italics). The significant differences between certain groups are displayed as follows: * and **, P < .05 vs. G1; †, P < .05 vs. G2; #, P < .05 vs. G3; ‡, P < .05 vs. G4. For additional data see Table S1.

Abbreviations: ANOVA, analysis of variance; APACHE-II, acute physiology and chronic health; APS, acute physiology; BMI, body mass index; CPR, cardiopulmonary resuscitation; ECMO, extracorporeal membrane-oxygenation; OR, operating room; PCI, percutaneous intervention; STEMI, ST-elevation myocardial infarction.

**TABLE 2** Surgery data

| Intraoperative variables | No-ECMO (G1; n = 101) | Pre-ECMO (G2; n = 6) | ECC-ECMO (G3; n = 67) | Post-ECMO (G4; n = 27) | P value |
|--------------------------|------------------------|----------------------|-----------------------|------------------------|---------|
| Duration of surgery, min | 263 ± 57               | 337 ± 108            | 283 ± 98              | 329 ± 133*             | .005    |
|                          |                        |                      |                       |                       | .014 vs G1* |
| CPB time, min            | 127 ± 34               | 152 ± 47             | 175 ± 58*             | 151 ± 48               | <.0001  |
|                          |                        |                      |                       |                       | <.0001 vs G1* |
| Cross clamp time, min    | 73 ± 21                | 61 ± 22              | 66 ± 30               | 91 ± 34**              | .012    |
|                          |                        |                      |                       |                       | .04 vs G1*  |
|                          |                        |                      |                       |                       | .01 vs G3* |
| >3 Peripheral anastomoses| 36 (35.6)              | 2 (33.3)             | 14 (20.8)             | 10 (37.5)              | .46     |
| HLM fluid-balance, mL    | 493 ± 1261             | 1598 ± 2141          | 1184 ± 1342           | 858 ± 1683             | .06     |

Note: Values are expressed as mean ± SD or as number and percentage (in brackets). For categorical variables the Pearson χ² test was performed as appropriate. When describing changes of metric values, ANOVA with Tukey post-hoc analysis was performed, and P < .05 was considered statistically significant (displayed in italics). *and**, P < .05 vs. G1; †, P < .05 vs. G2; #, P < .05 vs. G3; ‡, P < .05 vs. G4

Abbreviations: ANOVA, analysis of variance; CBP, cardiopulmonary bypass; ECMO, extracorporeal membrane-oxygenation; HLM, heart-lung machine.
there was only a tendency towards an increase in lactate levels in the post-ECMO group. But, lactate increase became significant in the post-ECMO group only 1 hour after CABG, indicating that a rapid deterioration might have started already during surgery. SvO₂ was significantly lower in ECC-ECMO when compared with No-ECMO patients on admission (Table S1).

Ejection fraction (EF) was significantly reduced on admission in pre-ECMO and ECC-ECMO patients, when compared with No-ECMO or post-ECMO patients (Figure 2A). Interestingly, the post-ECMO group developed significantly reduced EF during surgery. Mean and systolic arterial pressure was significantly reduced in ECC-ECMO patients before surgery, but only postoperatively in post-ECMO patients (Figure 2B and 2C). Accordingly, ECC-ECMO patients required significantly higher doses of norepinephrine and inotropes on admission (Figure S1). Hemodynamic status, dobutamine- and norepinephrine-doses were comparable between pre-ECMO and ECC-ECMO patients. Within the first 12 hours after CABG, diuresis was markedly reduced in the post-ECMO group compared with all other groups (Figure 2D).

3.2 | Perioperative hemodynamics, organ function, and inflammation

Perioperatively, both mean and systolic arterial pressure declined significantly in the ECC-ECMO and post-ECMO compared with
No-ECMO-group and stayed reduced until 2 days after. Both values were more stable, and systolic pressure even increased before surgery in the pre-ECMO group, most likely due to early preoperative ECMO-assist (Figure 2B and 2C). Pressure-decrease was accompanied by deteriorated EF (Figure 2A) and associated with lactate-increase in all ECMO groups perioperatively (Figure 1C). Maximum lactate of greater than 8 mmol/L was observed 1 hour after CABG in pre- and ECC-ECMO group, but also after 6 hours in post-ECMO group.

Perioperative catecholamine-therapy showed significantly higher norepinephrine-doses in the ECC-ECMO and post-ECMO group, while the pre-ECMO group showed no increase in vasopressor-need compared with No-ECMO patients (Figure 1SA). Pre-ECMO and ECC-ECMO groups showed highest preoperative dobutamine-dosage, while highest intraoperative dosage was observed in post-ECMO group (Figure 1SB). In pre-ECMO patients, epinephrine-doses were comparable to No-ECMO group, but it was significantly higher in ECC- and post-ECMO groups (Figure S1C). Its maximum was observed at the end of CPB in pre-ECMO group, which might have triggered the surgeons’ decision to switch from CPB to ECMO. Milrinone was administered in comparable doses in all ECMO groups.

Bilirubin-concentration increased in all ECMO groups (Figure 3A). The pre-ECMO group even showed a significant bilirubin-increase perioperatively. The first bilirubin-downtrend was observed after 3 days in pre-ECMO, after 12 days in ECC-ECMO, and after 18 days in post-ECMO group. A significant increase in aspartate-aminotransferase preoperatively was only found in the pre-ECMO group and postoperatively only in post-ECMO group. ALT showed a comparable trend (Figure 3B and 3C). Quick-value was significantly lower in the pre-ECMO group preoperatively, while both other ECMO groups showed significantly lower levels until 3 days after

**FIGURE 2** Perioperative hemodynamic data and diuresis. Evaluation of (A) EF, (B) mean arterial blood pressure, and (C) systolic arterial blood pressure. Panel (E) demonstrates the time course of diuresis during the first postoperative day. Two-way ANOVA was applied as appropriate, and if significant, ANOVA with Tukey post-hoc analysis was performed for each time point, and $P < .05$ was considered statistically significant. ANOVA, analysis of variance; ECMO, extracorporeal membrane-oxygenation. EF, ejection fraction; OP, operation.
FIGURE 3  Perioperative parameters of organ function. A, Prolonged elevation of bilirubin in ECC- and post-ECMO patients indicating higher possibility of liver damage if ECMO is installed too late. Panels (B), (C), and (D) show AST, ALT, and Quick. Panel (E) shows perioperative creatinine trend. Two-way ANOVA was applied as appropriate, and if significant, ANOVA with Tukey post-hoc analysis was performed for each time point, and $P < .05$ was considered statistically significant. ALT, alanine-aminotransferase; ANOVA, analysis of variance; AST, aspartate-aminotransferase; ECC, extracorporeal circulation; ECMO, extracorporeal membrane-oxygenation.
surgery (Figure 3D). Creatinine increased significantly within the first postoperative days in ECC-ECMO and post-ECMO group compared with No-ECMO group (Figure 3E).

Significant procalcitonin induction was observed 5 days after CABG in the post-ECMO group. All ECMO groups showed an increase in leukocyte-count between Days 5 and 18 (Figure 2SA and 2SB). Platelet-count decreased in all groups till Day 3 and normalized after 15 days in all ECMO groups (Figure 2SC).

### 3.3 | Complications

Postoperative data is displayed in Table 3 and Table S3. Ventricular tachycardia occurred most often in pre-ECMO patients. Re-infarction-rate was highest in the post-ECMO group. No significant difference was observed concerning perioperative IABP-use. Only three patients from the ECC-ECMO-group (5%) received additional Impella-assist. A significantly higher amount of perioperative and

| Table 3 Postoperative data and outcome |
|---------------------------------------|
| **Postoperative variables**           | **No-ECMO (G1; n = 101)** | **Pre-ECMO (G2; n = 6)** | **ECC-ECMO (G3; n = 67)** | **Post-ECMO (G4; n = 27)** |
|---------------------------------------|-----------------------------|---------------------------|---------------------------|---------------------------|
| CPR, n (%)                            | 19/99 (19.2)                | 4 (66.7)                  | 23 (34.4)                 | 11 (40.7)                 |
| IABP, n (%)                           | 35 (35)                     | 2 (33)                    | 32 (48)                   | 13 (48)                   |
| Impella, n (%)                        | 0 (0)                       | 0 (0)                     | 3 (5)                     | 0 (0)                     |
| Hemofiltration, n (%)                 | 22 (21.8)                   | 3 (50)                    | 36 (53.7)                 | 63 (63)                   |
| 2nd Troponin-elevation, n (%)         | 4/100 (4)                   | 3 (50)                    | 17/65 (26.2)              | 11 (40.7)                 |
| 2nd ST-elevation, n (%)               | 1/100 (1)                   | 0 (0)                     | 0 (0)                     | 3 (11.1)                  |
| Re-infarction, n (%)                  | 2/100 (2)                   | 0 (0)                     | 3/65 (4.6)                | 8 (29.6)                  |
| Ventricular tachycardia, n (%)        | 4/96 (4.2)                  | 2/5 (40)                  | 19/65 (29.2)              | 6/25 (24)                 |
| Delirium, n (%)                       | 29/99 (29.3)                | 1 (16.7)                  | 11/66 (16.7)              | 2 (7.4)                   |
| Pneumonia, n (%)                      | 24 (23.8)                   | 1 (16.7)                  | 11/24 (45.8)              | 11/15 (73.3)              |
| Re-thoracotomy, n (%)                 | 7/99 (7.1)                  | 1 (16.7)                  | 29 (43.3)                 | 9 (33.3)                  |
| Wound-healing disorder, n (%)         | 9/100 (12.4)                | 0 (0)                     | 3/24 (12.5)               | 6/15 (40)                 |
| ICU-stay after surgery (hrs)          | 197 ± 400                   | 535 ± 352                 | 555 ± 840*                | 600 ± 853**               |
| Normal ward-stay, d                  | 14 ± 14                     | 20 ± 14                   | 26 ± 36                   | 36 ± 48*                  |
| Time until rehabilitation, d         | 27 ± 17                     | 53 ± 24                   | 50 ± 24*                  | 95 ± 63,**,***<**        |
| SOFA-score after 24 h                | 9.4 ± 12.6                  | 13 ± 2.3                  | 13.7 ± 2*                 | 13.2 ± 2.1               |
| qSOFA-score after 24 h               | 0.8 ± 0.7                   | 1.8 ± 0.8*                | 1.6 ± 0.5**               | 1.6 ± 0.6**               |
| SAPSII-score after 24 h              | 35.9 ± 12.1                 | 48 ± 6.7*                 | 40.3 ± 9.5                | 45.9 ± 8.9**              |
| APS-score after 24 h                 | 9 ± 8                       | 17 ± 3                    | 17 ± 3*                   | 16 ± 4**                  |
| APACHE-II-score after 24 h           | 19 ± 8                      | 26 ± 3                    | 26 ± 4*                   | 25 ± 4**                  |

Note: Values are expressed as mean ± SD or as number and percentage (in brackets). For categorical variables the Pearson χ² test was performed as appropriate. When describing changes of metric values, ANOVA with Tukey post-hoc analysis was performed, and P < .05 was considered statistically significant (displayed in italics). *, **, P < .05 vs. G1; †, ‡, P < .05 vs. G2; ¶, P < .05 vs. G3; †, ‡, ¶, P < .05 vs. G4. For additional data see Table S3. Abbreviations: ANOVA, analysis of variance; APACHE-II, acute physiology and chronic health; APS, acute physiology; CPR, cardiopulmonary resuscitation; IABP, intra-aortic balloon counter pulsation; ICU, intensive care unit; PCI, percutaneous intervention; qSOFA, quick sepsis-related organ failure assessment; SAPS-II, simplified acute physiology-score-II; SOFA, sepsis-related organ failure assessment; STEMI, ST-elevation myocardial infarction.
postoperative blood product transfusions were needed in all ECMO patients but with no difference between the ECMO groups. Re-thoracotomy-rate was highest in the ECC-ECMO group, while wound-healing disorders were most common in post-ECMO group. Hemofiltration was most often needed in post-ECMO patients; also, the lowest diuresis, the highest 24 hours fluid-balance, and the highest incidence of pneumonia were observed in this group. The incidence of postoperative delirium was significantly higher in the No-ECMO group than in other groups.

### 3.4 Evaluation of risk-scores

Patients in the post-ECMO and ECC-ECMO group revealed significantly longer ventilation-time, ICU-, and hospital-stay and higher nursing-workload-index TISS-10 when compared with the No-ECMO group (Table 3 and Figure S3). Comparison of all three ECMO groups showed no significant difference in APS- and APACHE-II-score, while they had a higher score when compared with No-ECMO group after surgery. The difference in APS- and APACHE-II-score between No-ECMO and pre-ECMO group was not significant, probably due to the small number of patients. Simplified acute physiology-score-I- and quick sepsis-related organ failure assessment-score were significantly higher in the pre-ECMO when compared with the No-ECMO group (Table 3 and Table S3). Therefore, these scores did not provide discrimination in regard to mortality-risk of the ECMO groups.

Post-ECMO group showed the longest time from admission to ECMO-implantation, while the pre-ECMO group had the longest duration of ECMO therapy. Before ECMO-implantation, survival after VA-ECMO (SAVE)-score was significantly lower in post-ECMO patients when compared with both other ECMO groups. ENCOURAGE-score was significantly lowered in the post-ECMO group when compared with the pre-ECMO group (Table 4 and Table S4). No difference was seen regarding successful ECMO-weaning, ECMO-replacement by another LVAD and ECMO withdrawal due to poor prognosis.

### TABLE 4 ECMO-related data and survival-predicting scores

| ECMO-related variables                                      | Pre-ECMO (G2; n = 6) | ECC-ECMO (G3; n = 67) | Post-ECMO (G4; n = 27) | P value (ANOVA) |
|-------------------------------------------------------------|-----------------------|-----------------------|------------------------|----------------|
| Door-to-ECMO time, h                                        | 20.6 ± 17             | 28.7 ± 104.5          | 100 ± 82.9*            | .049          |
| SAVE-score before ECMO-implantiation                        | −7.7 ± 3.5            | −8.2 ± 5.8            | −13.3 ± 4.3*#          | .008          |
| ENCOURAGE-score before ECMO-implantation                   | 29 ± 5                | 21 ± 6                | 22 ± 10*              | .021          |
| Successful weaning (>48 h survival), n (%)                 | 4 (66.7)              | 55 (82.1)             | 19/26 (73.1)           | .641          |
| Switch from ECMO to assist device, n (%)                   | 0 (0)                 | 5/66 (7.6)            | 2 (7.4)               | .784          |

Note: Values are expressed as mean ± SD or as number and percentage (in brackets). For categorical variables the Pearson $\chi^2$ test was performed as appropriate. When describing changes of metric values, ANOVA with Tukey post-hoc analysis was performed, and $P < .05$ was considered statistically significant (displayed in italics). * and **, $P < .05$ vs. G1; †, $P < .05$ vs. G2; ‡, $P < .05$ vs. G3; #, $P < .05$ vs. G4. For additional data see Table S4.

Abbreviations: ANOVA, analysis of variance; ECMO, extracorporeal membrane-oxygenation; SAVE, survival after VA-ECMO.
which are mostly limited, it is of utmost importance to identify patients which may benefit from early ECMO-support. In this sense and based on suggestions that EuroSCORE can be a useful predictor for prophylactic perioperative ECMO in patients with postcardiotomy, we also evaluated different risk-scoring-systems.

Our data show that AMI-patients with ECMO-start after CABG had the lowest 30-day-survival of 40.7%, which is comparable to other studies. Our analysis of different timing for ECMO therapy revealed that preoperative and intraoperative ECMO-start was associated with significantly better survival reaching up to 66.7%. Interestingly, experimental work in swine showed that prior “LV-unloading” with an extracorporeal axial flow-catheter while delaying coronary reperfusion provided myocardial protection. But, the Impella-support alone was not able to improve 30-day-survival in AMI-patients with CS. Still, timely LV-support using ECMO seems to be beneficial in our patients. This is also supported by the time-course of bilirubin-concentration, which influences survival in patients with ECMO-support. A recent study described the impact of dynamic bilirubin-changes on survival in patients with VA-ECMO for acute circulatory failure. Bilirubin-concentration had a downtrend on the day of ECMO explantation in survivors, while it continued to increase in weaned patients who did not survive and in patients who died on ECMO. Consistently, in our pre-ECMO group bilirubin-downtrend started after 3 days, preceded ECMO-weaning at Day 7 and was associated with highest survival-rate. In ECC-ECMO and post-ECMO patients, bilirubin-downtrend was observed after 12 and 18 days, respectively, thereby after ECMO-weaning and was associated with higher 30-day-mortality. At the same time, surgery duration and aortic cross-clamping time were the highest in post-ECMO patients, which is likely associated with prolonged CPB-weaning time, but probably not related to a higher number of peripheral bypass-anastomoses in this group (>3). Still, longer CPB-duration remains an independent risk-factor for morbidity and mortality.

Regarding ECMO therapy timing and better outcome, one needs to emphasize that 83.3% of the patients in the pre-ECMO group underwent PCI within 48 hours before CABG, while this was the case in only ≥30% in the two other ECMO groups. Therefore, the low number of pre-ECMO patients appears plausible, because most of these patients were recruited after mechanical complications during PCI. However, the longest time from PCI-to-surgery was also observed in the pre-ECMO group, which might reflect cardiocirculatory improvement due to ECMO-assist and therefore postponed surgery. In contrast, patients from the ECC- and post-ECMO group did not present with metabolic or hemodynamic impairment preoperatively and therefore received no-ECMO before surgery. In this regard, some studies propagate lactate or lactate-increase as trigger for ECMO-start in patients with nonpostcardiotomy, and suggest association between higher lactate at admission and mortality. In our study, only the pre- and ECC-ECMO groups presented with significantly elevated and increasing lactate before surgery. In the post-ECMO group lactate was not enhanced preoperatively, but its concentration doubled during CABG-procedure. This was accompanied by hemodynamic impairment and a higher need in catecholamines during surgery in the pre- and ECC-ECMO groups, and reached limits of pharmacological therapy. Our data suggested that lactate-increase in aggravated hemodynamic situations may be a valuable parameter to trigger timely ECMO-implantation. This is not because we showed an association between higher lactate on admission and mortality, but between mortality and a lactate-increase greater than 4 mmol/L in patients without timely ECMO-implantation. At the same time, No-ECMO group showed perioperative lactate-increase to only minor extent with moderate hemodynamic impairment and thereby no need for ECMO.

The above-mentioned findings reflect the limitations of clinical real world and confirm the difficulty in decision-making in this complex scenario. Our analysis confirmed the high nursing-workload in patients with ECMO based on TISS-10-score and ICU-time. Several risk-scores are available to predict clinical outcome. A significantly higher shock-index was found on admission in patients from the pre- and ECC-ECMO group, which also reflected frequent CPR before admission in these groups. This finding was supported by significantly higher logEuroSCORE and stdEuroSCORE, APS-, and APACHE-II-score when compared with the No-ECMO group preoperatively. But, the differential analysis of these scores between the three ECMO groups showed no significant difference, except for the stdEuroSCORE, when comparing the pre- and post-ECMO group. These findings reflect the lack of impact ECMO therapy has on the above-mentioned scores. We therefore also analysed the value of the ECMO related SAVE- and ENCORE-score. The SAVE-score has been shown to predict survival for patients receiving ECMO for refractory CS. We found lowest SAVE-scores in the post-ECMO group, correctly reflecting the lowest survival-rate. The ENCOURAGE-score has been developed to predict in-ICU mortality of VA-ECMO, with a highest value of ≥28 being associated with a survival-probability of only 7%. Our analysis showed the highest ENCOURAGE-score in the pre-ECMO group, while ECC- and post-ECMO groups had comparable values, corresponding to an estimated survival probability of ≥25%. Therefore, our results are in contrast to the published survival-possibilities, and this may indicate the potential limitation of this score in the setting of AMI-patients with CS. Taken together, only the SAVE-score was able to correctly predict the 30-day-mortality rate in our patients. Unfortunately, the assessment of SAVE-score at admission would not have been able to correctly discriminate the patients needing ECMO, since no increase in shock-index or other parameters was observed in the post-ECMO-group. Therefore, we still do not have an appropriate scoring-system respecting pre-emptive ECMO-timing.

5 LIMITATIONS

The presented study is a retrospective study and only two major centers for cardiac surgery were included. Furthermore, the number of six patients treated with preoperative ECMO-assist does not permit normal distribution. Also, a selection bias for ECMO-treatment in regard to the time point cannot be excluded. In this retrospective study, the answer to the question how the decision was
made to use additional methods of left ventricular unloading (eg, IABP or Impella) remains speculative.

6 | CONCLUSION

Our study provides evidence for a novel concept of timely ECMO support for the failing ischemic myocardium based on association between early ECMO-start and a better survival in patients with AMI undergoing emergency CABG. While decision-making still remains complex in regard to correct timing for the ECMO-start, our findings support the use of lactate-increase above 4 mmol/L in an impaired hemodynamic situation as a valuable trigger for ECMO-implantation, as proposed in the organization chart (Figure 4). In these patients the analysed risk-scores assessment tools only gave limited support in estimating survival-probability correctly (we found only a limited support of different risk-score assessment tools for correct estimation of survival-probability). Timely ECMO-support may improve
CONFLICT OF INTERESTS
The authors declare that there are no conflict of interests.

REFERENCES

1. Neumann FJ, Sousa-Uva M. 'Ten Commandments' for the 2018 ESC/EACTS guidelines on myocardial revascularization. Eur Heart J. 2018;39:3759.

2. Babaev A, Frederick PD, Pasta DJ, et al. Trends in management and outcomes of patients with acute myocardial infarction complicated by cardiogenic shock. JAMA. 2005;294(4):448-454.

3. Chiu FC, Chang SN, Lin JW, Hwang JJ, Chen YS. Coronary artery bypass graft surgery provides better survival in patients with acute coronary syndrome or ST-segment elevation myocardial infarction experiencing cardiogenic shock after percutaneous coronary intervention: a propensity score analysis. J Thorac Cardiovasc Surg. 2009;138(6):1326-1330.

4. Hochman JS, Sleeper LA, Webb JG, et al. SHOCK Investigators. Early revascularization and long-term survival in cardiogenic shock complicating acute myocardial infarction. JAMA. 2006;295(21):2511-2515.

5. Thiele H, Desch S. CULPRIT-SHOCK (culprit lesion only PCI versus multivessel percutaneous coronary intervention in cardiogenic shock): implications on guideline recommendations. Circulation. 2018;137(13):1314-1316.

6. Hagl C, Khaladj N, Peterse S, et al. Acute treatment of ST-segment-elevation myocardial infarction: is there a role for the cardiac surgeon? Ann Thorac Surg. 2009;88(6):1768-1772.

7. White HD, Assmann SF, Sanborn TA, et al. Comparison of percutaneous coronary intervention and coronary artery bypass grafting after acute myocardial infarction complicated by cardiogenic shock: results from the should we emergently revascularize occluded coronaries for cardiogenic shock (SHOCK) trial. Circulation. 2005;112(13):1992-2001.

8. Hochman JS. Cardiogenic shock complicating acute myocardial infarction: expanding the paradigm. Circulation. 2003;107(24):2998-3002.

9. Biancari F, Onorati F, Rubino AS, et al. Outcome of emergency coronary artery bypass grafting. J Cardiovasc Surg Anesth. 2015;29(2):275-282.

10. Thiele H, Zeymer U, Neumann FJ, et al. Intra-aortic balloon counterpulsation in acute myocardial infarction complicated by cardiogenic shock (IABP-SHOCK II): final 12 month results of a randomised, open-label trial. The Lancet. 2013;382(9905):1638-1645.

11. Thiele H, Zeymer U, Thelemann N, et al. Intraaortic balloon pump in cardiogenic shock complicating acute myocardial infarction: long-term 6-year outcome of the randomized IABP-SHOCK II trial. Circulation. 2019;139:395-403.

12. Lauten A, Engström AE, Jung C, et al. Percutaneous left-ventricular support with the Impella-2.5-assist device in acute cardiogenic shock: results of the Impella-EUROSHOCK-registry. Circ Heart Fail. 2013;6(1):23-30.

13. Werdan K, Gielen S, Ebelt H, Hochman JS. Mechanical circulatory support in cardiogenic shock. Eur Heart J. 2014;35(3):156-167.

14. Sheu JJ, Tsai TH, Lee FY, et al. Early extracorporeal membrane oxygenator-assisted primary percutaneous coronary intervention improved 30-day clinical outcomes in patients with ST-segment elevation myocardial infarction complicated with profound cardiogenic shock. Crit Care Med. 2010;38(9):1810-1817.

15. Tsao NW, Shih CM, Yeh JS, et al. Extracorporeal membrane oxygenation-assisted primary percutaneous coronary intervention may improve survival of patients with acute myocardial infarction complicated by profound cardiogenic shock. J Crit Care. 2012;27(5):530.e1-11.

16. Khorsandi M, Dougerty S, Bouamra O, et al. Extra-corpooreal membrane oxygenation for refractory cardiogenic shock after adult cardiac surgery: a systematic review and meta-analysis. J Cardiothorac Surg. 2017;12(1):55.

17. Esper SA, Bermudez C, Dueweke EJ, et al. Extracorporeal membrane oxygenation support in acute coronary syndromes complicated by cardiogenic shock. Catheter Cardiovasc Interv. 2015;86(suppl 1):S45-S50.

18. Biancari F, Dalén M, Perrotti A, et al. Venoarterial extracorporeal membrane oxygenation after coronary artery bypass grafting: results of a multicenter study. Int J Cardiol. 2017;241:109-114.

19. Kapur NK, Qiao X, Paruchuri V, et al. Mechanical pre-conditioning with acute circulatory support before reperfusion limits infarct size in acute myocardial infarction. JACC: Heart Failure. 2015;3(11):873-882.

20. Donker DW, Brodie D, Henriques JPS, Broomé M, et al. Left ventricular unloading during veno-arterial ECMO: a review of percutaneous and surgical unloading interventions. Perfusion. 2018;34(2):98-105.

21. Thiele H, Zeymer U, Neumann FJ, et al. Intraaortic balloon support for myocardial infarction with cardiogenic shock. N Engl J Med. 2012;367(14):1287-1296.

22. Pappalardo F, Schulte C, Pieri M, et al. Concomitant implantation of Impella® on top of veno-arterial extracorporeal membrane oxygenation may improve survival of patients with cardiogenic shock. Eur J Heart Fail. 2017;19(3):404-412.

23. Guihaire J, Dang Van S, Rouze S, et al. Clinical outcomes in patients experiencing cardiogenic shock complicating acute myocardial infarction: is there a role for the cardiac surgeon? JACC: Heart Failure. 2017;5(9):926-932.

24. Schopka S, Philipp A, Lunz D, et al. Single-center experience with extracorporeal life support in 103 nonpostcardiotomy patients. Artif Organs. 2013;37(2):150-156.

25. Freundt M, Lunz D, Philipp A, et al. Impact of dynamic changes of elevated bilirubin on survival in patients on veno-arterial extracorporeal life support for acute circulatory failure. PLOS One. 2017;12(10):e0184995.

26. Salis S, Mazzanti VV, Merli G, et al. Cardiopulmonary bypass duration is an independent predictor of morbidity and mortality after cardiac surgery. J Cardiothorac Vasc Anesth. 2008;22(6):814-822.

27. Rigamonti F, Montecucco F, Boroli F, et al. The peak of blood lactate during the first 24h predicts mortality in acute coronary syndrome patients under extracorporeal membrane oxygenation. Int J Cardiol. 2016;221:741-745.

28. Slottosch I, Liakopoulos O, Kuhn E, et al. Lactate and lactate clearance as valuable tool to evaluate ECMO therapy in cardiogenic shock. J Crit Care. 2017;42:35-41.

29. Lazzeri C, Valente S, Chiostrli M, Gensini GF. Clinical significance of lactate in acute cardiac patients. World J Cardiol. 2015;7(8):483-489.

30. Schmidt M, Burrell A, Roberts L, et al. Predicting survival after ECMO for refractory cardiogenic shock: the survival after veno-arterial-ECMO (SAVE)-score. Eur Heart J. 2015;36(33):2246-2256.
31. Muller G, Flecher E, Lebreton G, et al. The ENCOURAGE mortality risk score and analysis of long-term outcomes after VA-ECMO for acute myocardial infarction with cardiogenic shock. Intensive Care Med. 2016;42(3):370-378.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.