Preoperative patient optimization using extracorporeal life support improves outcomes of INTERMACS Level I patients receiving a permanent ventricular assist device†

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INTRODUCTION

Ventricular assist device (VAD) implantation as bridge to transplantation, recovery or destination therapy is a standard treatment for patients with terminal heart failure [1]. Survival after VAD implantation is primarily determined by the patients’ preoperative state [2]. Worst results are achieved in patients with refractory cardiogenic shock (RCS), who are currently graded as Interagency Registry for Mechanical Assisted Circulatory Support (INTERMACS) Level I or ‘crash and burn’ patients [3]. This patient subgroup continues to have the highest in-hospital and 1-year mortality ranging from 23.8 to 28.6% despite permanent improvement in devices and medical care [3, 4].

The high mortality of INTERMACS Level I patients in RCS with the traditional approach of immediate permanent VAD implantation is the result of a summative process. RCS with hypotension and low cardiac output leads to end-organ damage caused by ischaemic injury [2]. Right heart dysfunction with high filling pressures and venous congestion further aggravates this condition [2]. Additionally, inflammatory mediators are released in shock, leading to a systemic inflammatory response syndrome that affects peripheral circulatory response, necessitating high vasopressor support and further negatively influences outcomes [5, 6]. Permanent VAD implantation can reverse this downward spiral by normalization of cardiac output. However, the surgical trauma...
and the exposure to cardiopulmonary bypass often outweigh the benefits of permanent VAD implantation in the setting of RCS. Furthermore, implantation of a BiVAD or temporary RVAD often becomes necessary to achieve an adequate cardiac output as RCS predisposes to right heart failure.

Extracorporeal life support is a highly effective technique for providing emergent circulatory support in patients with RCS. The main advantage of ECLS over permanent VAD implantation is given by the ease and pace of implantation with minimal surgical trauma. ECLS can be implanted in a bed-side fashion, additionally provides lung support and is nowadays available in many centres without VAD programmes. Therefore, the use of ECLS as part of a bridge-to-bridge concept is becoming increasingly popular in INTERMACS Level I patients. However, there are a number of disadvantages, including a limited duration of support, a high rate of thromboembolic events, risk of bleeding and infection, with sepsis and multiple organ dysfunction syndrome being the major cause of death during ECLS. The risk of experiencing one of these complications is increasing with the duration of ECLS, and therefore, patients should be evaluated for further therapy within the first week after initiation.

We report our institutional experience with a bridge-to-bridge approach consisting of initial short-term support provided by ECLS and deferral of VAD implantation to patient optimization and recovery of end-organ function in INTERMACS Level I patients with RCS.

**MATERIALS AND METHODS**

**Study population**

This single centre study included 22 consecutive INTERMACS Level I patients with RCS who received an ECLS for haemodynamic stabilization and recovery of end-organ function as part of a bridge-to-bridge concept to permanent VAD implantation (VAD used: HeartMate II left ventricular assist device, Thoratec Corp., Pleasanton, CA, USA; HeartWare HVAD ventricular assist device either as left or biventricular assist device, HeartWare International, Inc., Framingham, MA, USA; DeBakey left ventricular assist device, MicroMed, LLC, Indianapolis, IN, USA) between June 2004 and March 2013 at the Department of Cardiac Surgery, Medical University, Vienna. Data were obtained from the Vienna Mechanically Circulatory Support database.

**Bridge-to-bridge concept**

Since June 2004, a bridge-to-bridge concept with ECLS implantation for immediate haemodynamic stabilization and deferral of permanent VAD implantation to patient optimization, defined as recovery of end-organ function, normalization of volume status and right ventricular (RV) filling pressures, has been followed in all INTERMACS Level I patients with RCS referred to our department. Institutional criteria for ECLS implantation are RCS despite maximal pharmacological or intra-aortic balloon pump (IABP) support, defined as a systolic blood pressure of <90 mmHg, a cardiac index of <2.0 and signs of acute end-organ damage (typically acute anuria and shock liver).

Implantation of the permanent VAD is delayed until end-organ function recovers, RV filling pressures are normalized, either the patient is extubated or sufficient tidal volumes are achieved with low respiratory support and vasopressor support can be significantly reduced. In case of an episode of cardiopulmonary resuscitation prior to ECLS implantation, patients have to be free of any clinically overt neurological deficit prohibiting permanent VAD implantation. Adequacy of neurology is checked by discontinuing sedation. Should there be any doubt on the neurological status, a neurologist is consulted.

**Conduct of extracorporeal life support**

ECLS cannulation techniques and circuit have been described in detail before. In brief, the circuit consisted of a centrifugal pump (usually BPX-80 Bio-Pump®, Medtronic, Inc., Minneapolis, MN, USA) and a hollow-fibre microporous membrane oxygenator (Affinity NT®, Medtronic, Inc.) with an integrated heat exchanger. In case of plasma leakage, our policy was to switch to a plasma-tight membrane oxygenator (Maquet Quadrox). Anticoagulation during ECLS is performed either with iv heparin (target apt 60–70 s) or with iv Agatroban in case of suspected or proven heparin-induced thrombocytopenia (target apt 60–70 s). According to our institutional standards, ECLS cannulation is preferentially performed via the subclavian artery (side graft) and femoral vein (percutaneously). If the ECLS is implanted during cardiopulmonary resuscitation, percutaneous cannulation of the femoral artery and vein is performed. Central cannulation is restricted to post-cardiotomy patients. If patients develop pulmonary oedema during ECLS due to a non-ejecting left ventricle, we either place a left ventricular vent via a small thoracotomy or a small atrial septal defect is created in the cath-lab in order to unload the left ventricle. This was never necessary in the present series.

**Ventricular assist device systems and implantation techniques**

The detailed implantation technique for the three used VADs was previously described. The Heartmate II® and the DeBakey® VAD were used as left VADs only, whereas the Heartware HVAD® was used as left or BiVAD. Cardiopulmonary bypass at the time of VAD implantation in addition to ECLS is reserved to patients in need of additional procedures adjunctive to VAD implantation (e.g. aortic valve replacement and tricuspid valve repair). Both Heartmate II® and Heartware HVAD® can safely be implanted with ECLS only.

**Outcome measures**

The study endpoints were (i) recovery of end-organ function defined as improvement in serum creatinine (Cr), modification of diet in renal disease-glomerular filtration rate (MDRD-GFR), aspartate aminotransferase (AST), alanine aminotransferase (ALT) and bilirubin or decrease in invasiveness of ventilation depicted by fraction of inspired oxygen (FiO2), positive end-expiratory pressure (PEEP) and peak inspired pressure (PIP); (ii) development of catecholamine and vasopressor support; (iii) 30-day and in-hospital mortality and (iv) 1-year survival or bridge to transplant success.
Statistical analysis

Categorical variables were presented as numbers and percentages, and mean values and standard deviations (SDs) were determined for continuous variables. Comparison of means was performed using the paired t-test or Wilcoxon test, when appropriate. A P-value of <0.05 was considered statistically significant. Survival was determined using the Kaplan–Meier method. The IBM SPSS version 21 (SPSS, Inc., Chicago, IL, USA) software was used for statistical analysis.

RESULTS

Patient characteristics

Twenty-two INTERMACS Level I patients (mean age 54 ± 14 years; age range 17–69 years) with pre-implantation to implantation of a permanent VAD (DeBakey LVAD 9.1%, Heartmate II LVAD 18.2%, Heartware HVAD 68.2% and HeartWare BiVAD 4.5%) with ECLS. Heart failure was of ischaemic origin in 50%, dilative in 40.9% and other origin in 9.1% (myocarditis in 1 patient and post-cardiomyopathy in 1 patient) of patients. The majority of patients were male (72%) and a considerable proportion were already supported with an IABP (45.5%) or underwent cardiopulmonary resuscitation (40.9%) prior to ECLS implantation. Detailed patient characteristics are given in Table 1.

Development of end-organ function during extracorporeal life support

Renal function. All patients had laboratory (Cr 1.86 ± 0.91 mg/dl and MDRD-GFR 48.73 ± 26.64 ml/min/1.78 m²) and/or clinical signs (typically anuria) of renal dysfunction before ECLS implantation, with 5 (22.7%) patients already depending on veno-venous haemofiltration. ECLS improved renal function (Cr 1.32 ± 0.52 mg/dl, P = 0.02 and MDRD-GFR 66.26 ± 28.33, P = 0.01) over a period of 8 ± 7 days. Importantly, none of the patients remained dialysis dependent after intensive care unit (ICU) discharge.

Hepatic function. All patients had laboratory signs of shock liver (AST 1426 ± 2176 U/I, ALT 982 ± 1466 U/I and bilirubin 2.03 ± 1.30 mg/dl) prior to ECLS implantation. ECLS improved hepatic function in all patients (AST 277 ± 259 U/I, P = 0.04 and ALT 357 ± 447 U/I, P = 0.04) over a period of 8 ± 7 days. However, bilirubin levels were slightly increased after ECLS (3.08 ± 2.13 mg/dl, P = 0.05). Importantly, none of the patients in the present series developed shock-associated secondary sclerosing cholangitis. We observed no fulminant postoperative liver failures in this series.

Pulmonary function. Twenty-one (95.5%) patients were intubated before ECLS implantation. During ECLS, 6 (27.3%) patients could successfully be weaned from the ventilator. In the remainder, the initially (PEEP 7 ± 3 mbar, FiO2 52 ± 18% and PIP 21 ± 4 mbar) high respiratory effort improved (PEEP 5 ± 4 mbar, P = 0.02; FiO2 26 ± 23%, P < 0.01 and PIP 17 ± 4 mbar, P = 0.01) over a period of 8 ± 7 days on ECLS.

Development catecholamine therapy during extracorporeal life support

All patients received high-dose vasopressor and inotropic therapy (noradrenaline 0.408 ± 0.355 μg/kg/min, dobutamine 4.362 ± 5.268 μg/kg/min and levosimendan 0.056 ± 0.085 μg/kg/min) prior to ECLS implantation. After ECLS implantation, vasopressor and inotropic therapy could completely be stopped in 6 (27.3%) patients. In the remainder, vasopressor and inotropic therapy could significantly be reduced (noradrenaline 0.056 ± 0.097 μg/kg/min, P < 0.01, dobutamine 0.056 ± 0.097 μg/kg/min, P = 0.06 and levosimendan 0.010 ± 0.032 μg/kg/min, P = 0.06) after 8 ± 7 days on ECLS.

Extracorporeal life support complications

Complications related to ECLS occurred in 13.6% of patients. Complications included infection of the insertion site in the groin in 1 (4.5%) patient, vascular complications with the need for reconstruction of the femoral artery with a patch in 1 (4.5%) patient and thromboembolism to the subclavian artery requiring thrombectomy in 1 (4.5%) patient. ECLS had no impact on infection parameter [before ECLS implantation C-reactive protein (CRP) 11.3 ± 95 mg/dl, leucocytes 14.0 ± 7.9 × 10⁹ vs after 8 ± 7 days on ECLS CRP 13.2 ± 6.8 mg/dl, P = 0.80 and leucocytes 11.1 ± 3.5 × 10⁹, P = 0.21, respectively]. All assessed clinical parameters are depicted in Table 2.

Operative procedure and post-ventricular assist device outcomes

Operative procedure. VAD implantation was performed either via a full median sternotomy (68.2%) or via a bilateral thoracotomy (31.8%). Circulatory support during VAD implantation was provided by standard cardiopulmonary (mean duration 145 ± 45

Table 1: Patient characteristics

| Age (years, mean ± SD) | 54 ± 14 |
| Male, n (%) | 16 (72.2) |
| Ventricular assist device, n (%) | 40 (90.9) |
| Heartware® HVAD | 15 (68.2) |
| Thoratec® Heartmate II | 4 (18.2) |
| MicroMed® DeBakey | 2 (9.1) |
| Heartware® BiVAD | 1 (4.5) |
| Underlying disease, n (%) | 40 (90.9) |
| Ischaemic CMP | 11 (50) |
| Dilative CMP | 9 (40.9) |
| Other | 2 (9.1) |
| Arterial hypertension, n (%) | 5 (22.7) |
| Diabetes, n (%) | 15 (68.2) |
| NIDDM | 1 (4.5) |
| IDDWM | 0 (0) |
| Smoking history, n (%) | 8 (36.4) |
| Prior cardiac surgery, n (%) | 7 (31.8) |
| Prior cardiopulmonary resuscitation, n (%) | 9 (40.9) |
| Prior intra-aortic balloon pump, n (%) | 10 (45.5) |
| Ventilated >24 h prior to ECLS, n (%) | 21 (95.5) |
| Renal replacement therapy prior to ECLS, n (%) | 5 (22.7) |

NIDDM: non-insulin dependent diabetes mellitus; IDDWM: insulin dependent diabetes mellitus; CMP: cardiomyopathy; BiVAD: biventricular assist device; ECLS, extracorporeal life support; SD: standard deviation.
Post-VAD outcomes. In-hospital stay was \(73 \pm 46\) days after initial ECLS insertion. Bleeding requiring surgical revision occurred in 4 (18.2%) patients on postoperative day (POD) 10 or 13, including 3 pericardial and 1 retroperitoneal haematoma. The mean support time was \(221 \pm 181\) days. After a follow-up period of 1 year, 16 (72.7%) were still on device, 3 (13.6%) had been successfully transplanted and 3 patients (13.6%) were died.

Reasons for death were acute myocardial re-infarction (POD 11), multiorgan dysfunction syndrome (POD 135), and pump thrombosis with consecutive endothelial infarction (POD 135). Details of the post-VAD outcomes are given in Table 3.

Thirty-day and in-hospital mortality were \(4.5 (\%n = 1)\) and \(9.1\% (n = 2)\), respectively. The 1-year survival within this high-risk patient population was \(86.4\% (n = 19)\) and is depicted in Fig. 1.

### DISCUSSION

Despite the continuous improvement in devices and medical care, INTERMACS Level I patients in RCS have the highest early mortality after implantation of a permanent VAD. In the present study, we evaluate the success of a bridge-to-bridge strategy for INTERMACS Level I patients in RCS, consisting of ECLS implantation for haemodynamic stabilization and deferring permanent VAD implantation to patient stabilization and end-organ recovery.

RCS has a dismal prognosis with early mortality rates ranging from 40 to 80% [17,18]. The introduction of VAD and total artificial hearts has opened up a promising therapy option for patients in RCS, given the ability of these devices to normalize cardiac output. Nevertheless, even if this expensive therapy option is performed promptly, in experienced centres mortality rates remain extensive compared with stable patients undergoing VAD implantation, reaching up to 28.6% in recent years [3, 4]. It has been emphasized that the beneficial effect of VAD implantation is outweighed by the exposure of patients in cardiogenic shock with high vasopressor support and acute end-organ damage to a significant surgical trauma and cardiopulmonary bypass [19]. Furthermore, a certain proportion of patients in cardiogenic shock undergo cardiopulmonary resuscitation prior to arrival at the VAD centre, prohibiting immediate VAD implantation due to questionable neurological outcomes.
Bridge-to-bridge concept

To overcome this burden, bridge-to-bridge and bridge-to-decision concepts are increasingly followed. We have been strictly adhering to a bridge-to-bridge concept consisting of initial ECLS implantation for haemodynamic stabilization and deferral of VAD implantation to patient stabilization, end-organ recovery and neurological evaluation in all INTERMACS Level I patients with RCS since 2004. The rationale behind this approach is that ECLS implantation provides immediate biventricular and pulmonary support with minimal surgical trauma [19, 20]. Furthermore, ECLS implantation can be performed in various settings including emergency departments, ICUs as well as peripheral hospitals, and does not necessarily demand the infrastructure of a VAD centre [19, 21]. Given the increasing experience with ECLS systems and the availability of standardized management protocols for patients on ECLS, recent complication rates during ECLS are low [9, 10]. Our bridge-to-bridge concept schedules VAD implantation to reversal of cardiogenic shock, necessity of high vasopressor support, recovery of end-organ function and absence of neurological complications prohibiting VAD implantation.

Reversal of end-organ damage and patient optimization

Acute ischaemic damage to renal, hepatic and pulmonary functions, reflected by elevated serum Cr and anuria, elevated hepatic enzymes and clinical signs of shock liver as well as high respiratory effort are strong predictors of mortality in patients undergoing VAD implantation [2, 5, 6, 9, 22]. By normalization of cardiac output, ECLS can reverse acute end-organ damage [19]. Following ECLS implantation, we observed improvement in renal, hepatic and pulmonary functions after a period of 7 days. This is in line with other studies addressing end-organ recovery during ECLS [23]. Although temporary renal replacement therapy was necessary in 45.5% of patients, none of them remained dialysis dependent. Importantly, we observed no fulminant liver failures in the present series, despite the fact that all patients had laboratory findings suggestive of acute shock liver at the time of ECLS implantation. The usefulness of ECLS implantation for renal and hepatic recovery is further underlined by an improved MELD-XI score at the time of VAD implantation, which reflects composite information on renal and hepatic function and predicts mortality after VAD implantation [2]. Interestingly, we observed an isolated increase in bilirubine during ECLS. This can relate either to ECLS-induced haemolysis or more probable to a shock-induced and reversible damage to the bile duct epithelium with disturbed excretory function of the liver. The decrease in thrombocytes is a typical finding during ECLS that relates to the use of a centrifugal pump and oxygenator and did not lead to bleeding complications in the present series. Importantly, pulmonary function also improved during ECLS. We were able to extubate 27% of patients during ECLS, and in the remainder, respiratory effort was significantly reduced after 7 days of support. As invasive ventilation with high PEEP and peak pressures increases RV load, we believe that optimization of pulmonary function prior to permanent VAD implantation reduces the risk of postoperative RV failure. In the present series, we observed no permanent postoperative RV failure necessitating secondary RVAD implantation and no mortality due to RV failure.

Operative procedure and survival

To reduce the invasiveness of VAD implantation itself, we follow two distinct concepts. Since 2011, we have been avoiding switching patients on ECLS to standard CPB (59% in the present series) for isolated VAD implantation to avoid the typical adverse effects of CPB (systemic inflammatory response, volume shifts and pulmonary damage) related to CPB and reserve CPB to patients needing additional procedures (aortic valve replacement and tricuspid valve repair). This concept has previously been shown to be safe and to reduce mortality after lung transplantation [24, 25]. Furthermore, we replaced full sternotomy by bilateral thoracotomy since 2012 and used this minimally invasive approach in 32% of patients in the present series. Besides these surgical modifications, it is our policy to remove the ECLS system immediately after VAD implantation only in completely stable patients. In the remainder, ECLS is continued as temporary RV support and source of additional cardiac output to protect end-organs and avoid high right-sided filling pressures as well as high vasopressor support.

Figure 1: Kaplan–Meier analysis of the 1-year survival.
the present series, this concept was followed in 68.2% and mean time to ECLS removal was 4 days.

**Survival**

The observed in-hospital mortality of 9.1% and 1-year survival of 86.4% seem to compare favourable to survival rates between 13 and 24% currently reported for INTERMACS Level I patients in RCS [3, 9]. Nevertheless, survival rates remain inferior to those in stable patients in higher INTERMACS levels receiving a VAD. Interestingly, only 1 patient died of multiorgan dysfunction syndrome, the most common cause of death in INTERMACS Level I patients undergoing immediate VAD implantation. The remaining patients deceased from other causes related to the pump itself and myocardial reinfarction.

**LIMITATION**

Although data were obtained from a registry, the present study has the typical limitations of a retrospective analysis. Since we have been using this approach in all INTERMACS I patients who present with RCS since 2004, we cannot make any meaningful comparisons due to a lack of an appropriate control group. The trial is not randomized. Furthermore, all patients in the present series had pulsatility during ECLS due to residual left ventricular function. If reversal of end-organ damage can be achieved in patients with no pulsatility on ECLS cannot be answered with the present paper.

**CONCLUSION**

Preoperative patient optimization using ECLS improves outcomes of INTERMACS Level I patients receiving a permanent VAD.

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APPENDIX. CONFERENCE DISCUSSION

Dr S. Park (Seoul, Korea): As you pointed out, the outcomes of permanent VADs are very disappointing in patients with preoperative cardiogenic shock, so I believe your study is very important and meaningful. I have a few questions. First, do you have any protocol or any parameters influencing the switch from ECMO to permanent VAD? If you don’t have, how do you decide the appropriate timing of VAD during ECMO?

Dr Riebandt: We use the parameters I just presented. We try to look at the renal and hepatic function, with creatinine, the GFR, the hepatic enzymes, because most of the patients in cardiogenic shock have a shock liver and have very high levels of liver enzymes. We try to lower them with ECMO support. Once they’re in a normal range and kidney function also improves, we decide on switching from ECMO to a permanent assist device.

Another point that I did not mention here is infection. Some of the patients in this series did have active systemic infections and that’s another thing we tried to avoid when implanting the VAD. So during ECMO support, infection parameters should be lowered too.

Dr Park: I think, if you wanted to prove the effect of ECMO on your results, you have to compare your study patients with the control group who did not receive preoperative ECMO before VAD, because there could be various confounding factors such as percentage of CPR patients or postoperative strategy or surgical practice.

Dr Riebandt: That would be a historical group because we’ve pursued this strategy ever since 2004. From registries like the INTERMACS Registry, it’s known that patients in cardiogenic shock, or INTERMACS Level 1 patients, do have the worst outcome. We think that in patients with this condition, undergoing major cardiac surgery with cardiopulmonary bypass contributes to their bad outcome. That’s why we try to avoid it and try to optimize the patients with ECMO before undergoing major cardiac surgery because ECMO is less invasive.

Dr D. Saeed (Dusseldorf, Germany): I have a comment and a question. I think this group of 22 patients who underwent VAD implantation were patients that were already selected; they were better patients than the other ECMO patients, because I don’t think that in the last eight years you’ve done only 22 ECMOs. So my question is, what are your selection criteria? In our series, for example, we looked at the outcome predictors of ECMO patients who underwent later VAD implantation and we found that MELD score and bilirubin value were the most important factors that decide if you want to go for a permanent VAD. So what are your selection criteria?

Dr Riebandt: That’s a good question. Of course, we did not do only 22 ECMOs in the past eight years; those are only the patients that received a VAD. Selection criteria would be if during ECMO support you can see an improvement of the parameters that I just described, like the MELD score or kidney function, if you see that they are going in the right direction and if there are no contraindications like an active tumour disease or a dismal prognosis for the neurological outcome. Most of the patients in this series had emergency PCI and at the time of ECMO implantation you could not evaluate the neurological status. But if you see that all this is favourable, then you decide to put them on a permanent VAD. So those are the criteria: end-organ function, haemodynamic situation, and infection.

Dr Saeed: So renal values and a bilirubin of 10, these are criteria for implantation?

Dr Riebandt: It depends. I don’t have a real cut-off value.

Dr A. Loforte (Bologna, Italy): Concerning this comment, if you have a really high MELD score with these high parameters, high bilirubin and so on, and with the patient usually on ECMO support, which leads to more bleeders, I want to point out that if patients require more transfusions, probably sometimes, or very often, they have a high rate of right ventricular failure. So, in my opinion, sometimes these patients probably need biventricular support, even permanent biventricular support, and you implanted only one biventricular assist device. What is your opinion on that?

Dr Riebandt: Usually we try to avoid BiVADs. What we do is that in selected patients, the ECMO is not removed immediately after VAD implantation but remains for a few more days in order to give the right ventricle the chance to recover. And from our point of view, it’s a concept that does really work because, as you can see, we only needed BiVAD in one patient. So we do not see this problem.

Dr F. Beyersdorf (Freiburg, Germany): I also think that it would be interesting to know all the patients in INTERMACS Level 1, and then divide them into those receiving ECMO and that might die on ECMO (and this is probably a very high percentage too), and those who finally make it to VAD implantation. This is already a selection of patients who are improving and who can be further salvaged by VAD implantation. And very often the question comes up, ‘what to do with these patients?’ And I agree with what you said that the mortality for immediate VAD implantations in INTERMACS Level 1 patients is very high, but sometimes they don’t recover on the ECMO and then you don’t know why they don’t recover. They might have recovered with VAD, they might not have recovered with VAD. I mean that’s a dilemma. But I think your data are interesting and show that those who make it to VAD have a fairly good outcome, so that’s great.