Extracorporeal membrane oxygenation support in complex clinical scenarios of refractory cardiogenic shock in adults

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Extracorporeal Membrane Oxygenation Support in Complex Clinical Scenarios of Refractory Cardiogenic Shock in Adults

Mariusz Kowalewski, MD

Extracorporeal Membrane Oxygenation Support
in Complex Clinical Scenarios
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*To my beautiful wife, Magdalena
with love...*

CONTENTS

	Page
Chapter 1. Introduction and Outline of the Thesis	9
List of Abbreviations	10
Chapter 2. Mortality Predictors in the Elderly with Cardiogenic Shock on Veno-Arterial Extracorporeal Life Support	49
Chapter 3. Left Ventricle Unloading with Veno-Arterial Extracorporeal Membrane Oxygenation for Cardiogenic Shock. Systematic Review and Meta-Analysis	76
Chapter 4. Baseline surgical status and short-term mortality after extracorporeal membrane oxygenation for post-cardiotomy shock: A meta-analysis.	124
Chapter 5. Veno-Arterial Extracorporeal Membrane Oxygenation for Post-Cardiotomy Shock.	150
Chapter 6. The impact of centre's heart transplant status and volume on in-hospital outcomes following extracorporeal membrane oxygenation for refractory post-cardiotomy cardiogenic shock: a meta-analysis	172
Chapter 7. Cardiogenic shock and veno-arterial ECLS in heart transplantation/VAD centres as compared to non-transplant/vad units. meta-analysis.	215
Chapter 8. General Discussion	284
Valorization	290
Summary	294
Samenvatting	298
Acknowledgements	303
About the author	304
List of publications	306

CHAPTER 1

GENERAL INTRODUCTION

List of Abbreviations

ECMO = extracorporeal membrane oxygenation

V-V = veno-venous

V-A = veno-arterial

PC = post cardiectomy

VAD = ventricular assist device

ELSO = Extracorporeal Life Support Organization

AMI = acute myocardial infarction

LV = left ventricle

LA = left atrium

CABG = coronary artery bypass grafting

Htx = heart transplantation

LVAD = left ventricle assist device

RCS = refractory cardiogenic shock

RV = right ventricle

RVAD = right ventricle assist device

CPB = cardiopulmonary bypass

LVEDP = left ventricle end-diastolic pressure

IABP = intra-aortic balloon pump

ICU = intensive care unit

ECLS = extracorporeal life support

CNS = central nervous system

ECPR = extracorporeal cardiopulmonary resuscitation

TAVI = transcatheter aortic valve implantation

Preface

Refractory cardiogenic shock

Cardiogenic shock (CS) is the leading cause of mortality, and management remains challenging despite advances in therapeutic options. CS is a result of severe impairment of myocardial function that precedes lowered cardiac output, end-organ hypoperfusion, and global hypoxia [1]. Clinically, this presents as hypotension refractory to volume resuscitation with features of end-organ hypoperfusion requiring pharmacological or mechanical support [1]. Acute myocardial infarction (AMI) and its mechanical complications account for 81% of patients in CS [2]. Remaining causes may be cardiomyopathies, decompensated valvular heart diseases, cardiac tamponade, myocarditis and myocardial injury [3]. Heart surgery should be considered separately since postcardiotomy cardiogenic shock (PCS) may represent a combination of the above.

Exact definition of cardiogenic shock is not uniform neither in contemporary trials and guidelines, nor in clinical practice. In the SHOCK (Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock) and IABP-SHOCK II trials, cardiogenic shock was defined as systolic blood pressure (SBP) measurements of <90 mm Hg for ≥ 30 minutes or use of pharmacological and/or mechanical support to maintain an SBP ≥ 90 mm Hg [4,5]. Two large registries EHS-PCI (Euro Heart Survey Percutaneous Coronary Intervention Registry) [6] and KAMIR-NIH (Korean Acute Myocardial Infarction Registry-National Institutes of Health) [7] emphasized the role of collecting evidence of end-organ damage (altered mental status, urine output <30 mL/h, or cool extremities) before the diagnosis is done. The SHOCK Trial included cardiac index (CI) of ≤ 2.2 L/min per m^2 and a pulmonary capillary

wedge pressure (PCWP) of ≥ 15 mm Hg [4] An SBP < 90 mm Hg that is refractory to fluid resuscitation with clinical and laboratory evidence of end-organ dysfunction, in the setting of suspected cardiac dysfunction, is essential to the definition of CS. Latest European guidelines [8], in addition to the previous diagnostic criteria, look at clinical picture (cold extremities, oliguria, AMS, narrow pulse pressure) and laboratory tests (metabolic acidosis, elevated serum lactate, elevated serum creatinine) to define cardiogenic shock. Importantly, CS is a dynamic state extending from pre-shock to refractory shock states [9], which is influenced and potentially resolved by timely considerations of the required interventions.

Refractory cardiogenic shock (RCS) is a life-threatening condition often resulting from underlying cardiac or cardiopulmonary condition. Left untreated, it has an ominous prognosis. Since RCS is the leading cause of circulatory collapse, a circulatory support, and in particular, mechanical circulatory support (MCS), has been proposed as one modality of treatment. MCS encompasses a plethora of treatment approaches from short-term devices such as intra-aortic balloon-pump (IABP) or Impella® to long-term assistance such as ventricle assist devices (VADs). Somewhere in between short- and long-term support lies extracorporeal membrane oxygenation (ECMO). Due to many possible configurations of ECMO circuit and also because it can be used in synergy with other MCSs, often allowing for resolving RCS regardless of underlying cause, ECMO is becoming used more frequently worldwide.

However, certain complications have been unbreakably associated with ECMO therapy such as bleeding, cerebrovascular accidents and, as consequence, multiorgan failure together leading to high mortality rates in ECMO patients. However, ECMO is characterized by several major complications

such as bleeding, CVA, acidosis, vasoplegia and infection limiting its prolong use. On the other hand, patients with RCS and without MCS would inevitably die which puts ECMO therapy in an ethical dilemma context as well.

Refractory cardiogenic shock is a multilevel entity with heterogeneous etiology; therefore, varying mortality rates from report to report are not surprising. Due to a wide heterogeneity in the underlying pathology and comorbidity profile of the patients with RCS, the mortality and complications rate are widely ranging in the literature. However, the indications for ECMO have changed over time, and so have the patients' risk profiles with high risk patients being candidate for ECMO therapy and referred more willingly and more promptly by the physicians. This has led to the fact that mortality rates vary even more.

The aim of the current series of studies in this PhD dissertation was to identify the predictors of mortality and factors associated with improved and worsened results in adult patients undergoing contemporary ECMO therapy in complex clinical scenarios of refractory cardiogenic shock.

Mechanical circulatory support

While inotropic agents are the mainstay of therapy for hypotension and, thus, are widely used in cardiogenic shock, the mortality is higher with an increased number of prescribed inotropes/vasopressors [10,11]. The use of catecholamines in CS is further limited in arrhythmias, increased myocardial oxygen consumption, and inadequate circulatory support [12]. MCS devices

(Table 1) on the other hand offer significant advantages over vasopressor therapy, including substantial, often superior, cardiovascular support without increased risk of myocardial ischemia and possible decreased myocardial oxygen demand [13]. Some of them offer left ventricle (LV) unloading, lowering both the preload and afterload, particularly beneficial to impaired myocardium and reducing the risk of LV distension and thrombosis. Accordingly, large registry data have clearly demonstrated an association between early MCS application and improved survival [11]. Thus, prompt use of support devices remains an important therapeutic modality.

Types of MCS

Acute percutaneous MCS include intraaortic balloonpump (IABP), axial flow pumps (Impella®) left atrial-to-femoral arterial ventricular assist devices (Tandem Heart) and veno-arterial extracorporeal membrane oxygenation (V-A ECMO). Table 1.

Table 1. Mechanical Circulatory Support Devices and characteristics.

	Intra-aortic Balloon Pump	Impella®	TandemHeart®	V-A ECMO
Cardiac flow	0.3-0.5 L/min	1-5L/min	2.5-5L/min	3-7L/min
Flow direction	unchanged	LV->Ao	LA->Ao	RA->Ao
Synchronization with cardiac rhythm	Yes	No	No	No
Preload	unchanged	↓↓	↓↓	↓
Afterload	↓	↓	↑	↑↑↑
Coronary perfusion	↑	↑	unchanged	unchanged
MAP	↑	↑↑	↑↑	↑↑

Cardiac Flow	↑	↑↑	↑↑	↑↑
LVEDP	↓	↓↓	↓↓	unchanged
Oxygen demand	↓	↓↓	unchanged	unchanged
PCWP	↓	↓↓	↓↓	unchanged

V-A ECMO, veno-arterial extracorporeal membrane oxygenation; LV, left ventricle; Ao, aorta; MAP, mean arterial pressure; LVEDP, left ventricle end-diastolic pressure; PCWP, pulmonary capillary wedge pressure. Reproduced from: Atkinson TM, Ohman EM, O'Neill WW, Rab T, Cigarroa JE, Interventional Scientific Council of the American College of C. A practical approach to mechanical circulatory support in patients undergoing percutaneous coronary intervention: An interventional perspective. JACC Cardiovasc Interv. 2016;9:871-883.

There are 3 circuit configurations for MCS devices—pumping from the (1) right atrium/central vein to a systemic artery, (2) left atrium to a systemic artery or (3) left ventricle to a systemic artery. Peak flow rates of available devices range from 2.5 to 7 L/min [14].

IABP

Intra-aortic balloon pump (or contrapulsation balloon) was introduced over 50 years ago and remains most commonly employed support device used for therapy of cardiogenic shock. The IABP acts with several “indirect” mechanisms reducing both the LV afterload (enhanced systolic ejection) and the LV end-diastolic pressure (enhanced left atrial and pulmonary venous unloading). The IABP induces the aortic valve opening [15], improves coronary and abdominal circulation [16], allows pulsatility in end organ capillary bed [17] and modestly increase cardiac output (0.8–1 L/min).(ref) It is easy to implant and has contained costs. It is inserted via an 8Fr sheath in either the femoral or axillary artery [18]. The IABP Shock II Trial included 600 patients with CS from AMI undergoing early revascularization and randomized them to IABP or optimal medical therapy [5]. None of the assessed indices were anyhow altered with either approach; no mortality benefit was seen at 30 days, 6 and 12 months; neither the quality of life was improved [19]. The results were postulated to be driven by the fact that that the IABP plays no role in myocardium salvage [19,20]. Yet, certain limitations, among them a large proportion of

non-protocol cross-overs, operator dependent strategy of multivessel revascularization and not unified, often too late timing of MCS insertion must be acknowledged before interpreting these findings.

Impella

There are a number of devices designed to redirect the blood flow from LV to the aorta, of which most often employed during CS are different generations of Impella® devices (Table 1). These are axial flow pumps that are inserted to the common femoral artery and passed across the aortic valve into the LV. An axial rotor then ejects blood into the ascending aorta. Depending on the type, they achieve and maintain a cardiac output of 2.5 to 4 L/min for The Impella 2.5 and Impella CP. The Impella 5.0 is a larger device that can achieve a cardiac output of 5 L/min, however, unlike the smaller versions which can be inserted percutaneously, the latter often requires a surgical approach to the femoral artery for a 22-Fr sheath. Another device, Impella RP is a right-sided device introduced via an 11Fr catheter that pumps blood from the inferior vena cava to the pulmonary artery and delivers a flow rate >4 L/min for a right sided assist. Impella offers continuous, unsynchronized blood flow resulting in the loss of the normal isovolumic periods. With increasing the flow, it progressively unloads the LV. The LV stroke volume progressively decreases as pump flow increases, thereby increasing the systemic blood pressure and reducing the LA and pulmonary capillary wedge pressures. Despite the fact that the aortic valve does not open with the application of the Impella device, there is no risk of blood stasis in the LV and the aortic root. The uncoupling of LV and aortic pressure is a sign of an effective unloading of the ventricle. In this situation a flat systemic pressure line is a sign of maximal unloading. Secondary changes in myocardial contractility and peripheral resistance may further enhance the LV unloading

[14,21]. The Impella can also reduce RV afterload and facilitate RV output and pulmonary blood flow with improvement in gas exchange [23,24]. Impella use is contraindicated in moderate-to-severe aortic valve disease, mechanical aortic valve and severe peripheral arterial disease [13].

In the randomized PROTECT II Trial that focused on high-risk percutaneous coronary intervention (PCI) instead of cardiogenic shock, 452 symptomatic patients with complex 3-vessel disease or unprotected left main coronary artery disease and severely depressed left ventricular function were assigned to IABP or Impella 2.5 support during the procedure. Impella provided superior hemodynamic support compared with IABP as measured by cardiac power output (CPO).^(ref) Importantly, while the incidence of major adverse events at 30 days was not statistically different between the two groups, the use of Impella was associated with reduced rates of composite endpoint (all-cause death, MI, transient ischemic attack (TIA) or stroke, repeat revascularization procedure, need for a cardiac or a vascular operation, acute kidney failure (AKI), severe intraprocedural hypotension requiring therapy, cardiopulmonary resuscitation (CPR), ventricular tachycardia requiring cardioversion, aortic insufficiency and angiographic failure of PCI) at 90 days. Evidence on effectiveness of Impella devices in cardiogenic shock come from The IMPRESS in Severe Shock (IMPella versus IABP Reduces mortality in STEMI patients treated with primary PCI in Severe cardiogenic Shock) trial [24]. It randomized 48 patients suffering acute MI with CS to either Impella CP or IABP. Study was inconclusive due to relatively small sample and similar, close to 50%, mortality in both groups.

Regardless of the increasing use of MCS devices, The SHOCK [4], IABP-SHOCK II [5] and IMPRESS in Severe Shock [24] trials all showed 50% constant mortality over 6 to 12 months over last 20 years

of experience. On the contrary, one recent analysis of the cVAD (Catheter-based Ventricular Assist Device) Registry indicated that early implantation of a MCS device before PCI ($p = 0.04$) and before requiring inotropes and vasopressors ($p = 0.05$) was associated with increased survival in multivariate analysis. Indeed, survival was 66% when MCS was initiated <1.25 hours from shock onset, 37% when initiated within 1.25 to 4.25 hours, and 26% when initiated after 4.25 hours ($p = 0.017$) [11]. After the Detroit Cardiogenic Shock Initiative has proposed the use of standardized protocols emphasizing early Impella use, a pilot study by the same group reported 76% survival to discharge with this approach [25].

Tandem heart

The Tandem Heart is a device redirecting cardiac blood flow from LA to arterial system. Traditionally, a cannula is passed into LA through femoral vein, RA and atrial septal puncture; LA blood is aspirated and directed into one or both femoral arteries [13]. Because LA is drained directly, this unloads the LV, resulting in decreased pulmonary capillary wedge pressure (PCWP) and left ventricle end diastolic pressure (LVEDP) [14]. A previous randomized study, showed that as compared with IABP, the TandemHeart percutaneous VAD achieved significantly greater increases in cardiac index and mean arterial blood pressure and significantly greater decreases in pulmonary capillary wedge pressure. Overall 30-day survival and severe adverse events were not significantly different between the 2 groups [26]. However, the main limitation to the widespread use of the Tandem Heart is that it requires transseptal puncture which often translates into prolonged time from “door-to-LV unloading”.

Veno-arterial extracorporeal membrane oxygenation (V-A ECMO)

Veno-arterial extracorporeal membrane oxygenation (V-A ECMO) in its original configuration involves drainage of venous blood, passing it through an oxygenator membrane and returning the oxygenated blood to systemic circulation using a centrifugal pump. Its institution is achieved with cannulation of the right atrium and aorta in case of central cannulation as in post-cardiotomy setting. Alternatively, femoral vessels are cannulated to constitute peripheral ECMO. While peripheral ECMO can reduce LV preload, it increases afterload and this can cause increased ventricular wall tension due to retrograde flow [13]. ECMO has a complex and variable hemodynamic response. ECMO institution seemingly increases the left ventricle afterload with a rise in LV end-systolic volume and reduction in LV stroke volume. If peripheral resistance and LV contractility are fixed, increase in LV end-diastolic volume is the only way to overcome the afterload via the Frank–Starling mechanism. In this case, higher levels of VA-ECMO flow cause a progressive rise in LV end-diastolic pressure, LA pressure, PCWP, that are associated with a further reduced LV stroke volume [13,27,28]. High afterload situations with inability of LV to manage the transpulmonary blood flow, inadequate response to inotropes, complete cardiac arrest with incomplete venous drainage and aortic valve incompetenc is the common path towards LV distension and failure. Patients with severely impaired LV function and/or right ventricular dysfunction are more prone to develop an ineffective LV unloading [29].

LV overload increases wall stress, myocardial oxygen consumption and induces sub-endocardial ischemia and ventricular arrhythmias, jeopardizing ventricular recovery after entering this vicious circle. The consequence of the pressure overload may ultimately result in pulmonary congestion and edema.

Due its importance in the chain of support in the ardiogenic shock, ECMO runs have increased steadily in the past 5-10 years. Up till 2013, ECMO had been used in $\approx 13\,000$ patients and its rate of survival-to-discharge was 39% when used in cardiac support [30]. The counts are increasing each year; the latest report from the Extracorporeal Life Support Organization (ELSO) Registry (www.elseo.org) points to nearly 26.000 ECMO runs in adult cardiac setting with 59% survival. However, the disturbing absence of large RCTs of ECMO in patients with CS limits its use to refractory CS cases as a bridging therapy [13]. The bridging offered by ECMO are the following (Figure 1).

Figure 1. Decision flow diagram; ECMO, extracorporeal membrane oxygenation; HTx, heart transplantation; VAD, ventricle assist device.

Firstly, ECMO allows the vulnerable myocardium to recover in the setting of cardiogenic shock; if the time is enough, and the revascularization is performed either by PCI or coronary artery bypass grafting (CABG), ECMO may add to uneventful recovery. Even with limited resources and deteriorating patient, ECMO buys time to decision, whether to wait for recovery, bridge to more-durable support like VADs,

bridge directly to heart transplantation, or quickly declaring the futility of ECMO in complex patients with limited or no indication for more advanced treatment in a timely manner and withdrawing the therapy. Transitioning to VAD support or heart transplantation listing from ECMO appears to improve in-hospital survival, as shown by Smedira and coworkers [31]. They found a 75% early survival rate in ECMO patients bridged to a VAD after a short ECMO run. Despite this apparent effectiveness, only < 20% of patients supported with ECMO transition to other support, that is, VAD or heart transplantation (range 0%–20%) totally dependent upon the suitability of the candidate for more durable therapies and the availability of hub-and-spoke networks allowing patient transfers to centers capable of these advanced heart failure options.

Complications

ECMO remains amongst most invasive and intensive therapies; occurrence of complications in ECMO patients is common and they frequently determine the final outcome [32]. The complications may occur already at the time of ECMO institution but their extent and gravity depend highly on ECMO duration. ECMO as an accessory blood circuit deregulates the defense mechanisms in human body; the blood flow is continuous and retrograde instead of pulsatile and antegrade affecting brain-blood barrier and vasoactive properties of blood vessels. (ref) Exposure of blood to the artificial tubing system of ECMO circuit triggers a complex immune response affecting all metabolic pathways, and in particular, coagulation cascade. (ref) Therefore, to prevent clot formation in the tubing or oxygenator membrane, the ECMO necessitates systemic heparinization which adds to coagulopathies. Not surprising, bleeding represents the most frequent complication in ECMO, occurring in up to 90% of patients in some series

[33,34]. The high risk of bleeding is further aggravated in cases of post-AMI and post-cardiotomy cardiogenic shock, resulting from antiplatelet therapy in the former and surgery-related bleeding in the latter. While some investigators advocate the avoidance of heparin infusion for the first 12-48 hours in ECMO [35,36], heparin can be held for even longer periods [37,38], or alternative anticoagulation e.g. bivalirudin [NCT03707418] used in high-risk patients. (ref)

Along with bleeding, there are additional adverse events whose rates are similar across ECMO settings with the exception of AMI and post-cardiotomy. Indeed, higher risk of complications in post-AMI and PC-ECMO often is a result of acute onset of cardiogenic shock, underlying comorbidities in these patients and the preceding cardiopulmonary bypass (CPB) run and the cardiac surgery.

Central nervous system (CNS) complications in V-A and V-V ECMO have recently been shown to occur in 15% and 7% of adult patients, respectively [39,40]. Since clearly associated with ominous prognosis, they are most feared. Indeed, in an analysis of 4,500 patients from the ELSO registry undergoing ECMO for several indications [39], hospital mortality in patients with CNS complications was 89%, compared to 57% those without CNS ($p < 0.001$). In a multivariable model, age, pre-ECMO cardiac arrest, the use of inotropes on ECMO, and post-ECMO hypoglycemia were shown to be independently associated with CNS complications. In PC-ECMO, these rates appear to be much higher, accounting for up to 30% of cases [36,41-43] depending on pre-surgical condition, history of CNS accidents and surgical technique [44,45]. A high level of suspicion, appropriate and constant neuro-monitoring, and ECMO management modification [46] may influence the risk and rates of CNS complications.

Acute kidney failure with or without the need for continuous renal replacement therapy (CRRT) poses a transient threat to most ECMO cases. One meta-analysis demonstrated a higher mortality and a longer ECMO duration corresponding with CRRT although the authors rightly pointed out that these findings were not based on RCTs [47] and therefore reflected, a relatively higher severity of illness in patients who received ECMO plus CRRT. For early initiation of CRRT to balance the fluid overload rather than evening the metabolic acidosis, the results are ambiguous [48].

Lastly, limb complications are strongly associated with circulation centralization in cardiogenic shock. The use of ECMO is exacerbating this problem, particularly in peripheral configuration. Although the use of ipsilateral additional DPC (distal perfusion cannula) reduces the risk for leg ischemia [49], delay in DPC placement, often triggers late signs of ischemia and may lead to a reperfusion injury and, ultimately, poor outcome [50]. To mitigate potential issues with cannula access site, femoral- but also axillary or carotid artery in case of femoral artery stenosis, can all be achieved by cannulating a Dacron or Hemashield prosthetic graft (6–8 mm), anastomosed end-to-side onto the artery of interest thus maintaining unobstructed arterial flow in both directions [36]. Figure 2.

Configurations and hybrid cannulation

Besides traditional ECMO cannulation approaches, including, certain changes in patients' conditions or the occurrence of particular complications (i.e., cerebral hypoxia or left ventricular dilation) may require alterations in cannulation strategies. Additionally a combination of ECMO with additional invasive or minimally invasive procedures, to improve organ function, distal perfusion and, thus, ECMO efficacy may be warranted. Prolonged ECMO support duration, in particular, for patients on transplant

waiting lists but also those being bridged to long-term assist devices, has determined the need for technology development in order to ensure an adequate patient management and to reduce the risk of complications.

Figure 2. Cannulation of axillary artery for ECMO institution. Graft prosthesis is anastomosed end-to-side to the artery and cannulated to allow for unobstructed blood flow.

Notably, cannulation strategies evolved from original V-V and V-A configurations to so called “hybrid” ECMO configurations, employing third or fourth cannula to improve systemic oxygenation and/or cardiac unloading. ECMO configurations may further be expanded by adding percutaneous devices such as IABP, Impella or TandemHeart.

Epidemiology and outcomes

Temporary mechanical circulatory support is increasingly used in patients affected by acute heart failure [51]. In the analysis of the Nationwide Inpatient Sample from 2011 to 2014 including almost 12,000 patients undergoing short-term cardiocirculatory assistance, use of percutaneous device increased by 1,511%, whereas, non-percutaneous device by 101% [52]. More interestingly, the MCS implant moved from 39.6% to 47.2% of patients older than 65 years of age among the overall study population, underlining the higher consideration for MCS use also in this challenging patient population. Another recent analysis, this time including the 2004-2014 year-period, showed that among MCS types, ECMO had the highest growth (1,421%), followed by other types of short-term MCS (1,229.2%), percutaneous cardiocirculatory support (216.7%), and intra-aortic balloon pump (140%) [53]. The incidence of ECMO implementation in patients after open-heart surgery has been reported between 0.4% and 3.7% and has increased considerably over the past 2 decades [52] to the point that PC cardiogenic shock has become the most frequent indication for ECMO in the United States [54]. In fact, only between 2007 and 2011, non-percutaneous postcardiotomy ECMO cannulation increased 2-fold, while the use of percutaneous ECMO increased by more than 15-fold [52]. Maxwell et al. evaluated more than 9,000 ECMO patients from the Nationwide Inpatient Sample database in the United States from 1998 to 2009 and identified 4,493 (approx. 50%) patients cannulated for cardiogenic shock in the postoperative period [55]. Recently, data from ELSO Registry also confirmed a substantial increase in PC-ECMO use over the last 10 years [56].

The European and American Societies of Cardiology guideline recommendations assigned ECMO the class IIb recommendation, level of evidence C, for the management of cardiogenic shock in STEMI [57]. Despite the above recommendation, and also growing worldwide utilization and experience, in-hospital ECMO outcomes have not shown substantial improvement [56,58]. Little is still known of who benefits most from ECMO, or the cost-effectiveness of such a resource-intense therapy [52]. The inherent features of ECMO in terms of quick availability, relative ease of application in expert centers and reliability, have made it an attractive option, particularly in the post-cardiotomy setting [59,60].

Specific areas - PCS

Due to its inherent features, ECMO represents a more appealing approach compared to other implantable or para-corporeal VAD [61-66], and particularly for PCS [52-56]. While indeed PC cardiogenic shock has become the most frequent indication for ECMO in the United States [54] its exponential increase did not parallel improved clinical outcomes [56,67]. Reports addressing PC-ECMO are limited, with only a few single-centre experiences available in the literature [68-86] commonly including adult and pediatric populations in the same series, or combining the PC-ECMO cases with the institutional global ECMO experience [87-104]. The characteristics of ECMO implantation (patient profiles, surgical access or location of implantation, timing of application, and duration of support), complications, and outcomes in the post-cardiotomy ECMO setting are different than in other applications of ECMO [105-110]. In the largest study to date assessing in-hospital and long-term survival after ECMO for PCS [56], overall successful weaning from ECMO was possible for 63% of patients but survival to hospital discharge was only 25%. Figure 3.

Figure 3. Data abstracted from the ELSO database show the exponential increase in extracorporeal membrane oxygenation (ECMO) for PCS. Figure copied from: 56. Whitman GJR. Extracorporeal membrane oxygenation for the treatment of postcardiotomy shock. J Thorac Cardiovasc Surg 2017;153:95-101.

These findings were comparable to results of smaller series of patients with PCS undergoing ECMO for which early survival rates of between 16% and 41% have been reported [42,89].

Specific areas - Elderly

More advanced V-A ECMO technology, more experience in implant and management, as well as inclusion in resuscitation protocols, have been some of the factors which favored broader ECMO indications. Importantly, ECMO has now become a valid option also for patients previously not considered for temporary circulatory support, such as..., to promote organ recovery or transition to more advanced and durable therapies in case of failure to restore sufficient cardiac function. At the same time, however, V-A ECMO is well-known for being resource-intensive and often yielding a complicated post-implantation course. In older patients, in most scenarios, the only objective of V-A

ECMO is 'bridge to recovery', since more advanced treatment modalities such as heart transplantation or use of durable LVADs are either contra-indicated or considered futile as well as inappropriate. Nonetheless, as the population ages, proper understanding of the use and impact of V-A ECMO specifically in patients with advanced age referred for RCS, will become increasingly relevant to elucidate actual patient outcome and whether this type of treatment may play a role and should be considered in this setting. Concerning the patients' characteristics, although PC-ECMO candidates are predominantly young and undergoing emergency operations [31], elderly patients are increasingly considered candidates for ECMO. Age of >65 years has not been regarded as an absolute contraindication to V-A or V-V ECMO candidacy [111,112] although long- term outcomes remain unreported. Other clinical characteristics of today's ECMO candidates include renal insufficiency, AMI, presence of left-main disease, LV dysfunction, prolonged history of coronary artery disease with previous AMI, prior open-heart surgery, and urgent or emergent status. Therefore, selection of elderly patients for ECMO dependent on multiple factors. Decision to implant or continue such a temporary MCS, therefore, is often difficult and several clinicians may avoid or limit the indications in the elderly to reduce resource consumption in limitedly successful procedures. From a clinical perspective, the majority of centers look at physical and neurological status prior to the event necessitating ECMO, the severity of insult, duration/degree of shock, presence of prior arrest, and associated medical comorbidities when selecting potential candidates for ECMO therapy. The availability, therefore, of indicators for more favorable outcome are required to guide clinical management, either prior or during ECMO support. High lactates at ECMO implant and renal failure, particularly requiring dialysis, have

been shown to independently predict unfavorable results in all V-A ECMO patients, but particularly in the elderly.

Figure 4. Summary of pre-implant criteria to be considered in the ECMO decision making in the elderly patients according to the survival probability. ECMO, extracorporeal membrane oxygenation; PCI, percutaneous coronary intervention; TAVR, transcatheter aortic valve replacement; HTx, heart transplantation; APACHE II; acute physiology and chronic health evaluation II; SAPS II, simplified acute physiology score II; CABG, coronary artery bypass grafting.

As mentioned earlier, etiology of RCS may be also associated with more favorable conditions for recovery. For example, post-ACS patients have a considerable chance of surviving as compared to patients with acute decompensation of chronic heart failure as well as the presence of cardiac arrest or prolonged low-flow time during cardio-pulmonary resuscitation at ECMO implant, all of which are associated with almost no chance of survival [37,113]. Figure 4.

Specific areas - Bridge to VAD and bridge to HTx

Despite evolution and recent advancements, V-A ECLS still represents a resource-consuming modality and mostly last resort of treatment. In most cases, centres' protocols and resources limit ECMO implementation to highest risk patients which are, in fact, least likely to benefit from such therapies [52,56,58,114,115]. Since CS arises from a plethora of underlying impaired cardiovascular .... and since conducting a randomized controlled trial in this peculiar setting would raise ethical questions, V-A ECLS's optimal implementation and management in patients with CS has not been well studied or defined. Despite growing worldwide utilization and experience in MCS, outcomes of patients undergoing V-A ECLS, in particular in-hospital mortality, have not shown substantial progress [55,56]. Interestingly, outcomes are fairly different from centre to centre suggesting that variations in practice patterns in management of cardiogenic shock endure and may play a role in driving the above differences [116]. These might include different schemes of timing of cardiogenic shock recognition, tailored escalation to mechanical circulatory support, centralization of care and hemodynamic monitoring. Hypothetically, readability of well-experienced ECLS teams and potentially shorter bridging times in HTx/VAD units may contribute to improved results.

Aim and outline of the thesis

The purpose of this thesis was to analyze the in-hospital and remote outcomes of ECMO in the treatment of cardiogenic shock, including survival and complications. Additionally, complex clinical scenarios were addressed to evaluate and identify mortality predictors in these complex cases since these are most vulnerable to factors other than ECMO itself influencing the outcomes. For this purpose,

several investigations were performed, by means of original studies, meta-analysis and reviews. Two large registry analyses were performed; one assessing the in-hospital outcomes in adults undergoing V-A ECMO for postcardiotomy cardiogenic shock from ELSO registry database; the other addressed elderly patients (>70 y.o.) undergoing V-A ECMO for cardiogenic shock. Notably, survival and complications were analyzed in a meta-analysis of LV-unloading techniques; by means of meta-analyses of the baseline surgical status as potentially influencing the outcome. Similarly, meta-analyses allowed for detailed investigation of the role of centre's status (VAD/HTx vs non-VAD/HTx) on patient sequelae both in postcardiotomy CS and in general CS setting.

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CHAPTER 2

MORTALITY PREDICTORS IN THE ELDERLY WITH CARDIOGENIC SHOCK ON VENO- ARTERIAL EXTRACORPOREAL LIFE SUPPORT

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ABSTRACT

Objectives: Because significantly higher mortality is observed in the elderly patients undergoing veno-arterial extracorporeal membrane oxygenation (V-A ECMO) for refractory cardiogenic shock (RCS), making decision-making in this setting challenging, we aimed to elucidate predictors of unfavorable outcomes in these elderly patients (≥ 70 years).

Design: Multicentre registry.

Setting: Refractory cardiogenic shock due to various etiologies.

Patients: Elderly patients (≥ 70 years).

Interventions: Veno-Arterial Extracorporeal Membrane Oxygenation

Measurements and Main Results: Three age groups (70-74, 75-79, ≥ 80 years) were in-depth analyzed. Uni- and multi-variate analysis were performed. From 1998 to December 2018, 2,644 patients ≥ 70 years (1,395 [52.8%] 70-74 years of age, 858 [32.5%] 75-79 years, and 391 [14.8%] ≥ 80 y.o.) were submitted to V-A ECMO for RCS. Peripheral access was applied in majority of patients. ECMO support duration was 4.3 ± 5.5 days, (2.9 ± 3.7 days in patients ≥ 80 years) ($P < 0.001$). Weaning from ECMO was possible in 1,236 pts (46.7%). Overall in-hospital mortality was estimated at 68.3% (1,807/2,644 pts.) with highest crude mortality rates observed in 75-79 y.o. subgroup (70.1%). Complications were mostly cardiovascular and bleeding, without apparent differences between subgroups. Airway pressures, 24-hours pH after ECMO start, ECMO duration, and renal replacement therapy were associated with higher mortality.

Conclusions: This study confirmed the remarkable increase of V-A ECMO use in the elderly affected by RCS. Despite in-hospital mortality remains high, V-A ECMO should still be considered in such a setting even in very elderly patients, since age itself was not linked to increased mortality, whereas several predictors may guide indication and management.

Introduction

Veno-arterial extracorporeal membrane oxygenation (V-A ECMO) is an effective therapy and is increasingly used in adults with refractory cardiogenic shock (RCS) [1-6]. During last 20 years, increase of the number of ECMO cases in the elderly patients was higher by half than among younger patients, with a rise of 280% between years 2005-2010 and 2011-2015 [7]. More advanced V-A ECMO technology, more confidence in implant and management, as well as inclusion in resuscitation protocols, have been some of the factors which favored broader indications, also in patients previously not considered for such a type of temporary circulatory support, to promote organ recovery or transition to more advanced and durable therapies in case of failure to restore sufficient cardiac function. At the same time, however, V-A ECMO is well-known for being resource-intensive and often characterized by a complicated post-implantation course. In the very old patients, the only objective of V-A ECMO is 'bridge to recovery', since more advanced treatment modalities such as heart transplantation or use of durable left ventricular assist devices (LVAD) are either contra-indicated or considered futile as well as inappropriate. Nonetheless, as the population ages, proper understanding of the use and impact of V-A ECMO specifically in patients with advanced age referred for RCS, will become increasingly more

relevant to elucidate actual patient outcome and whether this type of treatment may play a role and should be considered in this setting.

Previous investigation comparing elderly versus younger patients undergoing V-A ECMO for RCS showed that in-hospital mortality is significantly higher in former group [7]. However, the overall outcome of elderly patient did not appear unacceptable, suggesting that V-A ECMO might be considered in RCS. Patient selection, however, may play an additional critical role in the light of optimizing resources and chances of favorable results. Paucity of data remains on involving the use of V-A ECMO in such a challenging setting and answering how the threshold of age among elderly patients (eg, >75 years or >80 years) affects the clinical outcome is crucial. Many programs entertain somewhat arbitrary upper age limits for ECMO use. Some investigators have even suggested that age >75 years should be a contraindication for ECMO support. As mentioned, however, growing number of elderly patients have been treated recently, and the trend seems to continue. It is becoming apparent that temporary cardiocirculatory support should not be denied solely only on the basis of patient age, but decision should be given to reversibility of cardiogenic shock with support and comorbid conditions likely to impact patient survival. Elderly patients in RCS often have significant and complex comorbidities that can affect outcomes. Defining better decision-making and optimal candidate selection of elderly patients eligible for V-A ECMO due to RCS, have been, till now, poorly investigated.

The primary aim of the present analysis, therefore, was to analyze data from the international worldwide Extracorporeal Life Support Organization (ELSO) Registry to investigate ECMO outcomes among the

elderly patients and hopefully define risk factors associated with in-hospital mortality specific to elderly patient group.

Methods

Data source and study population.

Patient data was extracted from the ELSO Registry which is a worldwide voluntary registry collecting data related to ECMO implant in all patient age and conditions, including cardiac, respiratory, or as part of cardio-pulmonary resuscitation [8]. Data are collected from the contributing centers with a standardized form containing patient demographics, diagnosis and procedure information, ECMO technique, complications during ECMO, and survival to hospital discharge. Currently, as for year 2018, 391 centers have provided adult and pediatric data to the registry with data on 19,627 V-A ECMO runs in adult (> 18 years of age) patients with cardiac etiology of RCS. Information from elderly patients alone (≥ 70 years of age) supported with a single run of V-A ECMO for RCS listed in the ELSO registry between 1997 and 2018 were extracted. Patients supported with ECMO for extracorporeal cardiopulmonary resuscitation (ECPR) or respiratory dysfunction, and those with multiple ECMO runs were excluded. No informed consent was obtained, because the data set was limited to non-identifiable elements of information. This study was approved by ELSO Registry Committee.

Main goals and definitions.

We aimed to describe the prevalence of complications following VA-ECMO in the elderly population and to identify factors associated with in-hospital mortality. To study the relation of more advanced age in the elderly population with outcomes, we examined 3 cohorts grouped according to the age at

diagnosis: patients aged 70-74 years, 75-79 years, and ≥ 80 years, respectively. The independent variables were grouped before analysis as follows: demographic data, International Classification of Diseases diagnosis codes (reviewed by two authors independently and disagreement resolved by consensus), pre-ECMO course variables, pre-ECMO therapies instituted, ECMO course data. Survival to hospital discharge was the primary end-point for the study. All complications were categorized using ELSO registry complication categorizations and included the following: 1) limb complications, 2) central nervous system complications, 3) bleeding complications, 4) kidney failure, 5) sepsis, and were further subdivided.

Statistical analysis.

Categorical data were compared with chi-square and presented were frequencies with proportions. Continuous variables were analyzed using the ANOVA analysis and were reported as means with standard deviations (SDs). To assess predictor variables and major morbidity, the chi2 was used for categorical variables. To address missing values for variables, we used fully conditional specification (Markov chain Monte Carlo) for missing data (1,000 iterations) [9]. Mortality, gender, primary diagnosis, pre-ECMO support, pre-ECMO cardiac arrest, age, PCO₂, pH at 24 hours, and year were employed as predictors. Variables with missing data in more than 5% of the patients were excluded from analysis.

The pre-ECMO variables included CPR, chronic renal failure, time between intensive care unit (ICU) admission and cannulation, systolic and diastolic blood pressure values (DBP) within 6 h of cannulation, blood gases, pre-ECMO support and ventilator settings.

The primary end-point was in-hospital mortality, and the primary predictor of interest was patient age at cannulation. A piecewise model was initially used to evaluate the association between age and in-hospital mortality. An age cut-off was identified by calculating the probabilities of 2x2 tables formed by the outcome and dichotomized age for all possible thresholds of age and calculating the associated χ^2 statistic. The age with the maximum χ^2 statistic was identified as the cut-off point. Simulation study has shown that if a cut-off point exists, maximizing the χ^2 statistic can recover a true threshold for a continuous random variable [10]. To evaluate independent risk factors of in-hospital mortality variables that achieved $P < 0.1$ in the univariate analysis were examined by using multivariate analysis with forward stepwise logistic regression. Previous studies suggested that factor which predominantly impact frequency of complication in the elderly population is shorter time of ECMO support we estimated odds ratios in multivariate model with duration of ECMO support. Complications occurring in both groups are reported as number (%) with corresponding odds ratios (OR) and 95% confidence intervals (95% CIs).

Results

Patient demographic characteristics.

The number of elderly VA-ECMO cases in the ELSO registry increased over the study time period (Figure 1).

FIGURE 1. The in-hospital mortality rates in the elderly patients admitted to VA-ECMO for RCS enrolled in the ELSO registry in proceeding time periods.

There is a steady increase in number of ECMO cases in the elderly in analyzed time periods with steady mortality rates ($p=NS$). A total of 2,644 elderly patients were included in this analysis. To establish an age cut-off, a distribution of the χ^2 statistics was calculated for all possible cut-offs of age. The maximum χ^2 was 4.834; with 52.8% ($n=1,395$) of these patients between 70 and 74 years of age, 32.5% ($n=858$) between 75 and 79 years, and 14.8% ($n=391$) of patients ≥ 80 years of age. Pre-ECMO patient profiles stratified according to age are presented in Table 1.

Table 1. Demographic and Clinical Characteristics along ECMO Support Details of Elderly Patients Stratified According to Age.

Variable	Overall (n = 2,644)	Age Group 70-74 (n = 1,395)	Age Group 75-79 (n = 858)	Age Group ≥80 Years (n = 391)	p Value
Male	1684 (63.7)	896 (64.2)	539 (62.8)	249 (63.7)	0.796
Weight, kg	81.0 ± 19.8	82.8 ± 20.3	80.6 ± 19.0	75.6 ± 18.8	<0.001
Cause of cardiogenic shock					
PCS	1087 (41.1)	541 (38.8)	375 (43.7)	171 (43.7)	0.036
CABG	340 (12.9)	170 (12.2)	134 (15.6)	36 (9.2)	0.004
Valve	271 (10.2)	123 (8.8)	86 (10.0)	62 (15.9)	<0.001
CABG+Valve	212 (8.0)	99 (7.1)	73 (8.5)	40 (10.2)	0.107
AMI	187 (7.1)	100 (7.2)	54 (6.3)	33 (8.4)	0.382
Hemodynamics before VA-ECMO					
SBP	85.5 ± 29.5	85.3 ± 27.8	85.6 ± 30.6	86.1 ± 32.9	0.928
DBP	49.3 ± 17.0	49.9 ± 15.9	48.8 ± 17.9	48.4 ± 19.0	0.358
Mean	61 ± 18.5	61.4 ± 17.7	60.2 ± 18.7	61.1 ± 20.6	0.476
Venous oxygen sat	61.1 ± 18.5	61.4 ± 18.3	59.2 ± 19.1	64.1 ± 18.0	0.267
Pre-ECMO blood gases					
Pre-ECMO pH	7.28 ± 0.15	7.28 ± 0.14	7.28 ± 0.15	7.29 ± 0.15	0.478
Pre-ECMO HCO ₃	19.9 ± 5.8	19.9 ± 5.9	19.8 ± 5.5	20.3 ± 6.1	0.443
Pre-ECMO pO ₂	164.5 ± 129.7	153.9 ± 121.2	171.9 ± 136.2	187.5 ± 141.1	<0.001
Pre-ECMO FiO ₂	83.1 ± 22.9	83.0 ± 22.7	82.5 ± 23.5	84.5 ± 22.4	0.552
Pre-ECMO SaO ₂	92.6 12.5	92.6 11.5	92.6 13.8	92.9 13.1	0.948
Pre-ECMO pCO ₂	41.8 17.2	41.7 16.2	42.6 19.8	40.5 13.7	0.232
Pre-ECMO support					
IABP	732 (27.7)	397 (28.5)	247 (28.8)	88 (22.5)	0.046
CPB	746 (28.2)	359 (25.7)	259 (30.2)	128 (32.7)	0.007
Nitrix oxide	149 (5.6)	83 (5.9)	56 (6.5)	10 (2.6)	0.014
Pacemaker	223 (8.4)	113 (8.1)	77 (9.0)	33 (8.4)	0.769
Inotropes	1538 (58.2)	821 (58.9)	503 (58.6)	214 (54.7)	0.326
LVAD	96 (3.6)	58 (4.2)	33 (3.8)	5 (1.3)	0.025
ECMO Support Details					
Peripheral cannulation	1565 (59.2)	850 (60.9)	478 (55.7)	237 (60.6)	0.041
Days on ECMO	4.3 ± 5.5	4.9 ± 6.4	4.0 ± 4.3	2.9 ± 3.7	<0.001

PCS, post-cardiotomy shock; CABG, coronary artery bypass grafting; AMI, acute myocardial infarction; SBP, systolic blood pressure; DBP, diastolic blood pressure; ECMO, extracorporeal membrane oxygenation; FiO₂, Fraction of inspired oxygen; IABP, intra-aortic balloon pump; CPB, cardiopulmonary bypass; LVAD, left ventricle assist device. Values are mean ± SD or n (%).

Most common origin of cardiogenic shock among elderly patients supported with ECMO remained undefined, post-cardiotomy shock was clearly mentioned in 41.1% of cases (among these post CABG-PCS followed in 12.9% and valve in 10.2%, 28.2% could not be weaned from CPB), AMI was diagnosed in 7.1%.

ECMO Management and Outcomes

Peripheral cannulation was preferred approach (59.2%). Average ECMO support duration was 4.3 ± 5.5 days in the overall population; with increasing age the ECMO support duration shortened from 4.9 ± 6.4 days in the age range of 70-74 years, 4.0 ± 4.3 in 75-79 y.o., and 2.9 ± 3.7 in patients ≥ 80 years ($P < 0.001$). Weaning from ECMO was possible in 1,236 pts (46.7%) with respective rates of 658 (47.2%), 387 (45.1%) and 191 (48.9%) in subgroups 70-74 years, 75-79 years, and ≥ 80 years. Overall in-hospital mortality was estimated at 68.3% (1,807/2,644 pts.) with highest crude mortality rates observed in 75-79 y.o. subgroup (70.1%); mortality in age groups 70-74 years and ≥ 80 years were 67.0% and 67.8% respectively. Figure 2.

FIGURE 2. The in-hospital weaning from ECMO support and mortality rates according to predefined age subgroups.

Table 2 lists univariate predictors of mortality in the elderly patients; among them, certain pre-ECMO variables and outcomes predicted mortality in multivariate analyses as well and are listed in Table 3.

Table 2. Univariate Predictors (p<0.1) of Mortality in the Elderly Patients

Variable	Univariate Analysis		
	HR	95% CI	p Value
Age groups			
70-74 y (reference)	1.00		
75-79 y	1.20	1.00-1.44	0.06
≥80 y	1.01	0.79-1.28	0.95
Other variables			
Days on ECMO	1.02	1.01-1.04	0.01
Pre-ECMO PEEP	1.03	1.00-1.06	0.07
Pre-ECMO pH	0.18	0.09-0.36	<0.01
Pre-ECMO HCO ₃	0.95	0.93-0.97	<0.01
pH at 24h	0.01	0.00-0.02	<0.01
PaO ₂ at 24h per 10 mmHg	1.02	1.01-1.03	<0.01
HCO ₃ at 24h	0.94	0.92-0.96	<0.01
Rate (24 hours)	1.02	1.00-1.05	0.07
FiO ₂ (24 hours)	1.00	1.00-1.01	0.08
PIP (24 hours)	1.06	1.04-1.08	<0.01
PEEP (24 hours)	1.03	1.00-1.06	0.05
Pre-ECMO SBP	0.99	0.99-1.00	<0.01
Pre-ECMO DBP	0.98	0.98-0.99	<0.01
Pre-ECMO mean BP	0.99	0.98-0.99	<0.01
Percutaneous access	0.78	0.66-0.93	<0.01
Post-CABG	1.24	0.97-1.60	0.09
Post-CABG+Valve	1.32	0.96-1.81	0.09
Post-HTx	0.42	0.18-0.96	0.04
Myocarditis	0.28	0.07-1.16	0.08
Pulmonary embolism	0.21	0.09-0.52	<0.01
Complications			
Cardiac arrhythmia	2.10	1.59-2.79	<0.01
CPR required	5.66	2.45-13.07	<0.01
Inotropes on ECLS	1.68	1.40-2.01	<0.01
Myocardial stun	3.39	1.84-6.24	<0.01
Tamponade (blood)	2.19	1.40-3.44	<0.01
Cannulation site bleeding	1.33	1.02-1.72	0.03
DIC	11.38	2.76-46.93	<0.01
GI hemorrhage	4.02	2.14-7.56	<0.01
Hemolysis	1.72	1.04-2.84	0.03
Surgical site bleeding	2.14	1.69-2.71	<0.01
Culture proven infection	1.43	1.04-1.99	0.03
WBC <1500	6.56	1.56-27.62	0.01
Limb complication	3.67	2.05-6.58	<0.01
ECMO-related mechanical complication	1.92	1.45-2.54	<0.01
Glucose <40	19.87	2.73-144.61	<0.01
Hyperbilirubinemia	2.90	1.95-4.31	<0.01
pH <7.2	3.91	2.44-6.27	<0.01
Cerebral hemorrhage	3.63	1.28-10.32	0.02
Cerebral infarction	4.23	2.03-8.83	<0.01
Seizures	2.71	1.05-7.03	0.04

Pulmonary hemorrhage	1.92	0.96-3.85	0.07
Creatinine >3.0	2.24	1.56-3.23	<0.01
Creatinine 1.5-3.0	1.53	1.22-1.91	<0.01
RRT as a complication	3.29	2.62-4.13	<0.01
Pre-ECMO support			
Inotropes	1.32	1.12-1.55	<0.01
Bicarbonates intravenous	1.51	1.18-1.92	<0.01
Cardiac pacemaker	1.35	0.99-1.84	0.06
Cardiopulmonary bypass	1.22	1.02-1.47	0.03
Hyperventilation	0.26	0.08-0.90	0.03
IABP	1.30	1.08-1.57	0.01
RRT	1.98	1.27-3.09	<0.01
RVAD	3.49	0.80-15.30	0.10

ECMO, extracorporeal membrane oxygenation; SBP, systolic blood pressure; DBP, diastolic blood pressure; CABG, coronary artery bypass grafting; HTx, heart transplantation; ECLS, extracorporeal life support; DIC, disseminated intravascular coagulation; GI, gastrointestinal; WBC, white blood cells; RRT, renal replacement therapy; IABP, intra-aortic balloon pump; RVAD, right ventricle assist device.

TABLE 3. Multivariate Predictors of Mortality in the Elderly Patients

Variable	Multivariate Analysis		
	HR	95% CI	p Value
Pre-ECMO variables			
70-74 y (reference)	1.00		
75-79 y	1.37	1.05-1.80	0.05
≥80 y	1.72	1.18-2.52	<0.01
Pre-ECMO MAP	0.99	0.98-1.00	<0.01
Pre-ECMO HCO ₃	0.94	0.92-0.97	<0.01
Pre-ECMO RRT	1.96	1.05-3.66	0.04
Pre-ECMO + 24 hours variables			
Pre-ECMO MAP	0.96	0.93-0.99	0.02
Pre-ECMO HCO ₃	0.99	0.98-1.00	0.02
Pre-ECMO RRT	3.25	1.56-6.78	<0.01
pH at 24h	0.01	0.00-0.13	<0.01
PaO ₂ at 24h per 10 mmHg	1.04	1.03-1.06	<0.01
HCO ₃ at 24h	0.95	0.90-1.00	0.03
PIP (24 hours)	1.04	1.01-1.08	0.01
24 hours variables + complications			
pH at 24h	0.02	0.00-0.18	<0.01
PaO ₂ at 24h per 10 mmHg	1.04	1.03-1.06	<0.01
HCO ₃ at 24h	0.94	0.90-0.98	<0.01
PIP (24 hours)	1.03	1.00-1.06	0.03
Myocardial stunning	4.49	1.31-15.38	0.02
Pulmonary hemorrhage	4.76	1.06-21.47	0.04
RRT as a complication	2.49	1.71-3.63	<0.01
CNS infarction	4.30	1.15-16.05	0.03
Surgical site bleeding	1.53	1.02-2.30	0.04
Days on ECMO	1.04	1.00-1.08	0.04

MAP, mean airway pressure; RRT, renal replacement therapy; PIP, peak inspiratory pressure; CNS, central nervous system; ECMO, extracorporeal membrane oxygenation.

Age of 75-79 years was found to be a mortality predictor in multivariate analysis with however borderline level of significance HR 1.37; 95% CIs: 1.05-1.80; P=0.05, as compared to age >80 years: HR 1.72; 95% CIs: 1.18-2.52; P<0.01. Among remaining mortality predictors, pre-ECMO mean airway pressure, pH at 24 hours, ECMO duration, and renal replacement therapy both before and during ECMO support, were independently associated with higher mortality.

Complications

Figure 3 graphically represents the percentage extent of complication occurring while on ECMO for RCS.

FIGURE 3. Overall complications rates in the ELSO registry analysis.

The most common complications were cardiovascular (25%), followed by bleeding (15%), renal (22%), mechanical (14%) and metabolic (11%) complications. Limb complications along with neurologic and

infectious sequelae were observed in 13% of cases. There were no marked differences between age subgroups and incidence of clinically relevant complications Exact complications percentage rates according to age subgroup and complications' categories are delineated in Figures 4-11.

FIGURE 4. Cardiovascular complications rates.

FIGURE 5. Bleeding complications rates.

FIGURE 6. Infectious complications rates.

FIGURE 7. Limb complications rates.

FIGURE 8. Mechanical complications rates.

FIGURE 9. Metabolic complications rates.

FIGURE 10. Neurologic complications rates.

FIGURE 11. Renal complications rates.

Sensitivity analysis

To corroborate the results on mortality beyond the multivariate analysis, subgroups comparison was performed opposing age subgroups 75-79 years and ≥ 80 years against 70-74 years (reference subgroup) and calculating again the odds ratio for in-hospital mortality in 3 different scenarios: male vs female, post-cardiotomy- vs non-post-cardiotomy shock and peripheral vs central cannulation. Figure 12. Again, there were no statistical differences in the subgroup analyses.

FIGURE 4. Subgroup analysis of in-hospital mortality among the age groups. Relative risks and 95% confidence intervals (CI) are presented for the cumulative 30-day mortality in patients 75 to 79 y.o. and ≥80 y.o. as compared to 70-74 y.o. (reference). OR, odds ratio.

Comment

Main Study Findings

1. Our study showed that, as already shown in the trend of the general use of temporary mechanical circulatory support in RCS, V-A ECMO use in the elderly patients is exponentially increasing,
2. A relevant number of patients undergo V-A ECMO placement because of post-cardiotomy RCS,
3. Overall in-hospital mortality in this challenging setting is not prohibitive and the trend is rather stable in the last years,

4. Most likely due to already careful patient selection, even observing the age-adjusted outcome, even the more advanced ages (> 80 y.o.) have in-hospital results which do not discourage or contraindicate the use of ECMO in these age categories for RCS,
5. ECMO duration is significantly shorter in the more advanced age most likely due to earlier death or ECMO withdrawal because of futility (complications incompatible with recovery and life, like neurologic, family request, or attending personnel decision),
6. Cardiovascular-related complications represented the most frequent adverse event, followed by bleeding and renal complications. Neurologic complications (as shown by previous studies on this issue from ELSO Registry on CNS adverse events and V-A ECMO [7]) confirm high morbidity burden and strong association between neurologic complications and death.
7. Pre-ECMO factors (pH at 24 hours), indication, and renal complication with dialysis, and ECMO duration were found as negative predictor regarding in-hospital survival.

Temporary mechanical circulatory support (MCS) is increasingly used in patients affected by acute heart failure. Stretch and associated have shown, through an analysis of the Nationwide Inpatient Sample from 2011 to 2014 including almost 12,000 patients undergoing short-term cardiocirculatory assistance, that the use of percutaneous device increased by 1,511%, whereas, non-percutaneous device by 101% [2]. More interestingly, this study has shown that the MCS implant moved from 39.6% to 47.2% of patients older than 65 years of age among the overall study population, underlining the higher consideration for MCS use also in this challenging patient setting. Another recent analysis, from the Nationwide Inpatient Sample including the 2004-2014 year-period, showed that, among MCS types,

ECMO had the highest growth (1,421.4%), followed by other types of short-term MCS (1,229.2%), percutaneous. Cardiocirculatory support (216.7%), and intra-aortic balloon pump (140%) [11] Despite increasing use and expertise, V-A ECMO represents an aggressive treatment in complex patients, thereby associated with high complication and mortality rates [7]. The search for predictors for unfavorable patient outcome is, therefore, critical in an attempt to improve results, resource utilization, and decision-making in challenging conditions [12]. Among several well-known factors, age has been accounted for less satisfactory in-hospital outcome [7,13-19]. Table 4.

Table 4. Summary of Favorable and Unfavorable Predictors for 30-Day/In-Hospital Mortality after Veno-Arterial Extracorporeal Membrane Oxygenation in the Elderly Patients Based on the Presented Study (text underlined> and Other Published Investigations [references].

Unfavorable Predictors	
	High Lactates [13, 14, 16, 17]
	Pre-ECMO Renal Failure [15, 17]
	Acute Decompensation of Chronic Heart Failure [14]
	Central Cannulation [14]
	Cardiac tamponade as a complication [15]
	Atrial fibrillation [17]
	Pre-ECMO complement C3 [17]
	Pre-ECMO C-reactive protein [17]
	Coagulopathy with transfusion of high volumes of fresh frozen plasma and platelets [17]
	Glasgow Coma Scale [18]
	APACHE II Score [17,18]
	SAPS II Score [17,18]
	Favorable Predictors
	Weight [13]
	Intra-aortic balloon pump support [13]
	Post-transcatheter aortic valve replacement [13]
	Post-AMI Cardiogenic Shock [14]
	Peripheral Cannulation [14]

ECMO: Extracorporeal Membrane Oxygenation; AMI: Acute Myocardial Infarction

Indeed, a recent ELSO Registry analysis comparing younger versus older (≥ 70 years of age) groups confirmed that elderly patients are exposed to higher rate of adverse results, either for complications or for in-hospital mortality [7]. However, in-hospital mortality rate was not discouraging, indicating that age per se' should not be considered an absolute contraindication for short-term use of V-A ECMO in RCS [7]. Our findings are relevant since, as mentioned above, indicate that although old age is linked

to limited success rate, age was not directly related to ominous prognosis. Indeed, the 75-79 age group had somehow a worse outcome than patients with more advanced age, suggesting that careful selection, although not standardized by evidence-based data, may provide still ultimate favorable results.

Elderly patients have somehow peculiar features with respect to ECMO indications. Indeed, the most frequent condition for ECMO implant is post-cardiotomy, as shown by several investigators [13,14,20]. Post-cardiotomy indication for V-A ECMO placement is indeed common in older patients as compared to younger subjects [7]. This aspect may indicate that clinicians are more incline to consider and accept the use of temporary support due to RCS in the elderly patients than in non-surgical environment.

Peripheral cannulation was used more frequently in our patient population. This is in accordance with the findings of Sertic et al. [14] who also showed that central cannulation is associated with worse outcome in older patients. This aspect, however, may be related to worse clinical conditions usually pertained by post-cardiotomy situation. The use of V-A ECMO for post-cardiotomy indication has been recently associated with poor results more likely because of pre-ECMO comorbidities, impact of pre-operative cardiac illnesses and complicated surgical procedures, as well as type of complications more frequently observed in such a setting (bleeding) [6]. Other etiologies might have better results, as recently shown by Sertic et al who showed that post-acute myocardial infarction ECMO placement has better outcome, which is confirmed also at post-discharge assessment [14].

Complications rate is high in V-A ECM [21-23]. Our study confirms the high incidence of major complications in the elderly patients. Cardiovascular and end-organ perfusion adverse events are the

most adverse events, followed by bleeding and renal complications, as shown by other investigators [13,14]. The shorter ECMO duration may derive from these dreadful complications which may impede acceptable cardio-circulatory support, or indicate extremely low chance of recovery, prompting the attending personnel to early interruption of ongoing mechanical assistance [14]. This attitude is also related to the almost unique bridge-to-recovery path which characterizes V-A ECMO in such patient category, being more advanced forms of therapy (left ventricular assist devices and heart transplant) almost inaccessible.

Decision to implant or continue such a temporary MCS, therefore, is often difficult and several clinicians may avoid or limit the indications in the elderly to reduce resource consumption in limitedly successful procedures. The availability, therefore, of indicators for more favorable outcome might be precious and guiding clinical management, either prior or during ECMO support. High lactates at ECMO implant and renal failure, particularly requiring dialysis, have been shown to independently predict unfavorable results in all V-A ECMO patients, but particularly in the elderly. Our data confirms such negative predictors, adding pre-ECMO circulatory state and ECMO duration as additional factors to consider. As mentioned, etiology of RCS may be also associated with more favorable conditions for recovery, being post-AMI as benign condition for positive outcome, whereas acute decompensation of chronic heart failure as well as the presence of cardiac arrest or prolonged low-flow time during cardio-pulmonary resuscitation at ECMO implant, are associated with almost no chance of survival [14,17]. Our analysis of the ELSO Registry addressed only RCS cases, and therefore, we could not confirm this aspect. However, previous investigation using the same database to assess the results of ECMO in patient older than 75 years and undergoing V-A ECMO for refractory cardiac arrest, did show a

reduced survival as compared to younger subjects (27% versus 40% of in-hospital survival), but, again, not so negative to contraindicates this kind of treatment, provided that underlying etiology and low-flow time are in accordance with the positive predictors of such variables [14,24]

Limitations

Data in the ELSO registry are submitted voluntarily and limited to in-hospital course with no follow-up information. Retrospectively collected data are subject to incomplete or missing reporting of events or patients. There were complete data for the outcome variable of death, but weight; arterial systolic, diastolic, and mean blood pressures; arterial oxygen saturation; pulmonary artery systolic, diastolic, and mean blood pressures; peak inflation pressure at 24 h on ECMO; and mean airway pressure at 24 h on ECMO all had some missing data. The size of the database and our use of multiple conditional specification method helped us to mitigate potential bias related to missing data. Nevertheless, it is possible that missing data might have biased the study findings. In addition, our data must be read with caution because the distribution of ages in the older cohort was narrow so there are few patients at the extreme ages. Indeed, limited access to elderly patients to ECMO should be taken into account, as many clinicians do not consider ECMO as an option in such patient settings also in the presence of RCS of various etiologies. Finally, patient survival and outcome are limited to in-hospital course because the ELSO registry does not include follow-up data collection after hospital discharge. Further clinical research about this aspect is therefore warranted.

Conclusions

The use of V-A ECMO for the treatment of RCS in the elderly patients is remarkably growing. In-hospital complication and mortality remain high, but not prohibitive to discourage ECMO use in such a challenging setting. Patient status at implant and etiology, complication type, ECMO duration, but not more advanced age, represent critical factor to take into consideration for V-A ECMO implant decision-making.

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CHAPTER 3

LEFT VENTRICLE UNLOADING WITH VENO-ARTERIAL EXTRACORPOREAL MEMBRANE OXYGENATION FOR CARDIOGENIC SHOCK. SYSTEMATIC REVIEW AND META-ANALYSIS

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Abstract: During veno-arterial extracorporeal membrane oxygenation (VA-ECMO), the increase of left ventricular (LV) afterload can potentially increase the LV stress, exacerbate myocardial ischemia and delay recovery from cardiogenic shock (CS). Several strategies of LV unloading have been proposed. Systematic review and meta-analysis in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement included adult patients from studies published between January 2000 and March 2019. The search was conducted through numerous databases. Overall, from 62 papers, 7581 patients were included, among whom 3337 (44.0%) received LV unloading concomitant to VA-ECMO. Overall, in-hospital mortality was 58.9% (4466/7581). A concomitant strategy of LV unloading as compared to ECMO alone was associated with 12% lower mortality risk (RR 0.88; 95% CI 0.82–0.93; $p < 0.0001$; $I^2 = 40\%$) and 35% higher probability of weaning from ECMO (RR 1.35; 95% CI 1.21–1.51; $p < 0.00001$; $I^2 = 38\%$). In an analysis stratified by setting, the highest mortality risk benefit was observed in case of acute myocardial infarction: RR 0.75; 95%CI 0.68–0.83; $p < 0.0001$; $I^2 = 0\%$. There were no apparent differences between two techniques in terms of complications. In heterogeneous populations of critically ill adults in CS and supported with VA-ECMO, the adjunct of LV unloading is associated with lower early mortality and higher rate of weaning.

1. Introduction

Veno-arterial extracorporeal membrane oxygenation (VA-ECMO) provides life support for patients with refractory cardiogenic shock and significantly improves their survival working as a bridge to either recovery or other long-term treatments [1–7].

A well recognized limitation of the retrograde aortic flow while on VA-ECMO is the increase of left ventricular (LV) afterload [8], which can potentially lead to high LV stress and may exacerbate myocardial ischemia thus delaying recovery from cardiogenic shock [9]. Elevated LV pressure can also promote LV dilatation and trigger ventricular arrhythmias, or, secondarily, increase left atrial pressure

causing pulmonary edema [10]. Ultimately, a reduced flow across the aortic valve can induce formation of thrombus in the LV or the aortic root [11].

Several LV unloading strategies have been described and proposed in order to minimize the risk of these complications [12], however, the available evidences are still conflicting whether these techniques are safe and useful adjuncts to VA-ECMO in patients with cardiogenic shock [13–15].

The aim of this study was to comprehensively assess the impact on early outcomes of different strategies of LV unloading in patients undergoing VA-ECMO and sustaining advanced cardiogenic shock by various etiologies.

2. Experimental Section

2.1 Data Sources and Search Strategy

This systematic review and meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [16]. Research of relevant studies was limited to the period January 2000–March 2019, through PubMed, EMBASE, CINAHL, the Cochrane Register of Controlled Clinical Trials (CENTRAL) and Google Scholar. Abstracts were eligible for detailed assessment if available online and reporting outcomes of interest. The search terms were: “extracorporeal membrane oxygenation” and “extracorporeal life support”. No language restrictions were imposed. References of original articles were reviewed manually and cross-checked for other relevant reports. Authors of individual studies were contacted for missing data.

2.2. Selection Criteria and Quality Assessment

Human studies were included if they assessed survival after VA-ECMO or weaning from VA-ECMO support instituted for refractory cardiogenic shock. Research centers were checked to avoid potential overlapping patients and those reporting on smaller samples of patients were excluded. Reviews and case reports were not considered. Two independent reviewers (M.K. and K.Z.) selected the studies for

inclusion, extracted studies, as well as patient characteristics of interest and relevant outcomes. Two authors (M.K. and K.Z.) independently assessed the trials' eligibility and risk of bias. Risk of bias at the individual study level was assessed using the Risk of Bias in Not-randomized Studies-of Interventions (ROBINS-I) tool [17]. Any divergences were resolved by a third reviewer (G.R.) and quantified using the approach of Cohen's kappa [18].

2.3. Endpoint Selection

The primary endpoints were in-hospital/30-day survival and weaning from VA-ECMO. Secondary endpoints were in-hospital cerebrovascular events (CVE), brain death, limb complications, reoperation for bleeding, sepsis and acute kidney failure w/wo continuous veno-venous hemofiltration (CVVH). Outcome definitions were the ones adopted by the investigators of the included studies.

2.4. Statistical Analysis

Statistical analyses were performed in Comprehensive Meta-Analysis, v. 2.0 (Biostat, Englewood, NJ, USA) and Review Manager 5.3 (The Nordic Cochrane Centre, Copenhagen, Denmark). The results are expressed as pooled untransformed proportion risk ratios (RR) with their 95% confidence intervals (CI). Heterogeneity across studies was evaluated using the I^2 test. To control for the anticipated heterogeneity among observational studies, absolute values and means were pooled using inverse variance random effects models. The primary endpoints were assessed in relation to the specific setting according to etiology of cardiogenic shock which included: (1) postcardiotomy shock (PCS), (2) acute myocardial infarction (AMI), (3) myocarditis and (4) mixed cohort of different etiologies including both postcardiotomy shock and AMI and other etiologies. Number needed to treat (NNT) was calculated for these subgroups. Secondary analysis focused on specific left ventricular unloading strategy: (1) intra-aortic balloon pump (IABP), (2) LV venting with cannula in left atrium or ventricle or (3) percutaneous ventricular assist device (Impella, Abiomed, Danvers, MA, USA). We performed separate analysis of studies with propensity score matching or presenting propensity score adjusted odds ratio (OR) of

primary endpoints. We investigated if use of different unloading strategies had influence on complication rates, ECMO duration and weaning rates by means of meta-regression analyses [19]. Similarly, we addressed the impact of hypertension, diabetes, age and gender on mortality outcome. Sensitivity analyses were performed by excluding from analyses single studies, one at a time, and repeating the calculations. Publication bias was assessed (1) by visual approach plotting log event rate against standard error in the funnel plot; and (2) by linear regression approach [20].

3. Results

3.1. Study Selection

The study selection process and reasons for exclusion of some studies are described in Figure 1. A systematic search of the online databases allowed us to screen based on title and collect 271 potentially eligible records that were retrieved for scrutiny. Of those, 204 were further excluded because they were not pertinent to the design of the meta-analysis or did not meet the explicit inclusion criteria based on their content. To avoid potential double inclusion of patients' populations, 5 studies were excluded (A1–A5) since they were conducted in the same institution in overlapping time frames. Sixty-three series of patients from 62 observational studies (Appendix [6–67]) that enrolled 7581 patients eventually were included in the analysis. Patients were divided into 2 groups: those undergoing LV unloading concomitant to VA-ECMO and those undergoing VA-ECMO alone; (3337; 44.0%) vs. (4244; 56.0%).

Patients undergoing VA-ECMO had a mean age of 57.8 years and 71.0% were male. Follow-up across the studies varied between 30-day and in-hospital survival. Table 1 details about studies and Table 2 about patients' characteristics. Risk of bias for each study across each of the seven risk of bias domains is presented in Table 3. Overall, the studies reported either moderate or serious risk of bias.

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram of study selection process. References of included and excluded studies are listed in the supplementary material.

Given the overall high risk of bias along with the limited number of studies, all articles were retained for the purposes of this review. Most commonly, biases arose from (1) selection of participants for the study, and (2) subjective distribution of the participants within the study arms.

Populations included patients on VA-ECMO support for cardiogenic shock secondary to mixed etiologies (23 series, 4204 patients), PCS (22 series, 2324 patients) and AMI (14 series, 950 patients); VA-ECMO was employed for myocarditis in 4 series enrolling 103 patients.

3.2. Primary Endpoints

3.2.1. Mortality

All 63 included series (7581) contributed to the analysis of overall mortality; constructed funnel plot did not reveal any signs of publication bias or big study effect (Figure 2).

Figure 2. Publication bias analysis (SE: standard error).

Overall in-hospital mortality was 58.9% (4466/7581). LV unloading as adjunct to ECMO support was associated with 12% lower risk of mortality compared to ECMO alone therapy: risk ratio (RR); 95% confidence intervals (CIs): 0.88 (0.82–0.93); $p < 0.0001$; $I^2 = 40\%$; Figure 3.

Table 1. Characteristics of included studies.

Study	Setting	Unloading Strategy	Unloading Strategy Usage (%)	N. of pts	Peripheral ECMO (%)	Distal Perfusion (n)	ECMO Duration	Flow Rate	Total Weaning Rate (%)	Bridge to VAD (n)	Bridge to HTx (n)
Acheampong 2016	PCS	IABP	58.3	24	NR	NR	8.4 (0.8–35.4) d	NR	75	1	0
Akanni 2018	mix	Impella	12.9	225	NR	NR	3.54 (1.64–5.97) d	NR	NR	63	NR
Aoyama 2013	AMI	IABP	92.1	38	100	NR	126.5 ± 146.4 h	NR	NR	NR	NR
Asaumi 2005	Other	IABP	42.9	14	100	NR	130 (42–171) h	NR	71.4	1	0
Aso 2016	mix	IABP	36.6	1650	100	NR	2.31 d	NR	65.5	NR	NR
Aziz 2010	mix	IABP	20	10	100	10	5.8 d	3.5 to 5.0 L/min	60	1	1
Beiras-Fernandez 2011	PCS	IABP	49.3	73	NR	NR	4.4 ± 4.0 d	NR	NR	NR	NR
Beurtheret 2013	mix	IABP	31	87	100	NR	NR	NR	44.8	4	5
Biancari 2017	PCS	IABP (47); vent (5)	25.7	148	60.1	66	6.4 ± 5.6 d	NR	48.6	6	0
Brechot 2018	mix	IABP	40.2	259	100	259	2.2 ± 4.3 d	3.5 to 4.5 L/min	55.2	34	21
Carroll 2015	mix	IABP+Impella	15.4	123	75	NR	NR	NR	56.1	2	29
Chen 2005	Other	IABP	60	10	100	NR	126.2 ± 56.3 h	NR	100	1	0
Chen 2006	AMI	IABP	86.1	36	100	NR	108.5 ± 77.5 h	NR	69.4	NR	NR
Chen 2018	PCS	IABP	63.3	60	100	100	5.3 ± 2.8 d	NR	48	NR	NR
Cho 2018	AMI	IABP	4.8	42	100	NR	NR	initial of 2.2 L/min/m ² , which was subsequently regulated to maintain a mean arterial pressure of 65 mmHg	29.3	NR	NR
Choi 2018	AMI	IABP	35.2	145	NR	21	2.0 d [IQR: 1.0–4.0]	3.3 L/min	62.8	NR	1
Chung 2011	AMI	IABP	70	20	NR	NR	3.8 ± 4.3 d	NR	70	NR	NR
Czobor 2016	mix	IABP (10); Impella (1)	44	25	100	25	NR	initiated at up to 4.5 L/min and adjusted	NR	NR	NR
Elsharkawy 2010	PCS	IABP	9.4	233	33	NR	NR	NR	NR	28	25
Formica 2010	PCS	IABP	69	42	64.3	10	7.9 ± 5.3 d	to maintain a cardiac index of 2.5 l/min/m ²	69	NR	NR
Gass 2014	mix	IABP	41.5	135	100	NR	8.5 ± 7.1 d	2.5 to 4.0 L/min	40.7	20	0
Guihaire 2017	PCS	IABP (25); vent (13)	27.2	92	84.8	NR	6 d	NR	48	2	2
Hei 2011	PCS	IABP	16.2	68	100	68	4.75 d	40–220 mL/kg/min	76.5	8	NR
Kagawa 2012	AMI	IABP	82.6	86	100	NR	24 (8–65) h	minimum flow of 2.0 L/min	50	NR	NR
Kim 2014	AMI	IABP	75.9	58	NR	NR	68.7 ± 17.4 h	NR	41.4	NR	NR

Lee 2016	mix	IABP	8.7	23	100	NR	98 (60–192) h	3.0 to 4.0 L/min	NR	NR	NR
Lee 2017	mx	IABP	16.3	135	100	NR	99.6 ± 103.23h	adjusted to maintain a cardiac index of 2.4 L/min/m ²	39.3	NR	NR
Li 2015	PCS	IABP	59.3	123	100	123	4.3 d	3.0 L/min	56.1	NR	NR
Lin 2016	mix	IABP	57.1	529	100	256	NR	NR	NR	2	29
Lorusso 2016	other	IABP (34); vent (13)	59.6	57	82.5	63.1	9.9 ± 19 d	NR	75.5	2	3
Luo 2009	mix	IABP	24.4	45	88.9	NR	5.48 d	Initially, 2.5 l/min/m ² with the condition improved, 40 mL/kg/min. adjusted the ECMO blood flow rate in time to maintain LVEF	60	5	NR
Mikus 2013	PCS	IABP	92.9	14	42.9	14	5 d	to maintain cardiac index of 2.6 l/min/m ²	50	0	0
Muller 2016	AMI	IABP (96); Impella (3)	69.6	138	NR	132	7 d	NR	35.5	13	18
Nakamura 2015	other	IABP	95.5	22	100	22	179 ± 25 h	initial flow rate was 3.0–3.5 L/min; According to the indicators of peripheral circulatory failure (e.g., arterial blood gas analysis, mixed venous oxygen saturation, lactic acid and urinary output), the flow rate of ECMO was decreased	NR	1	0
Negi 2016	AMI	IABP	60	15	100	NR	1.875 d	NR	53.3	NR	1
Overtchouk 2018	AMI	IABP	59.4	106	NR	106	NR	NR	NR	10	2
Papadopoulos 2015	PCS	IABP	21.9	360	90	NR	7 ± 1 d	50–70 mL/kg/min	58.1	6	2
Pappalardo 2016	mix	Impella	21.7	157	100	39	167 (72–286) h *	Maximal speed	36.3 *	8 *	0 *
Park 2014	AMI	IABP	42.7	96	100	NR	NR	initial of 2.2 L/min/m ² and adjusted to maintain a mean arterial	60.4	NR	NR

								pressure of 65 mm Hg			
Patel 2018	mix	Impella	45.5	66	100	NR	NR	NR	56.1	5	NR
Pokersnik 2012	PCS	IABP	59.2	49	65.3	32	3.8 ± 3.4 d	gradually increased to 2.0 L/min/m ² and adjusted as necessary to maintain adequate hemodynamics and oxygen delivery.	55.1	2	0
Poptsov 2014	PCS	vent	60.9	46	100	100	NR	NR	NR	NR	NR
Raffa 2017	PCS	IABP	26.7	86	34.9	NR	5 d	NR	49	NR	NR
Rastan 2010	PCS	IABP	74.1	517	39.3	121	3.28 ± 2.85 d	NR	63.3	15	5
Ro 2013	mix	IABP	23.7	253	96.4	NR	71.0 h	NR	46.6	NR	3
Russo 2010	mix	IABP	85.7	14	57.1	253	10.2 d	NR	78.6	2	6
Sakamoto 2012	AMI	IABP	95.9	98	100	NR	68.9 ± 62.7 h	NR	55.1	0	0
Santise 2014	PCS	IABP	72.2	18	17	NR	6.7 ± 3.2 d	4164 ± 679 mL/min	72.2	NR	NR
Shinn 2009	mix	IABP	33.7	92	100	24	90.9 ± 126.0 h	NR	64.1	NR	NR
Shmack 2017	mix	vent	41.7	48	20.1	NR	6.10 ± 3.81 d	2.6 L/min/m ²	NR	14	5
Slottosch 2012	PCS	IABP	93.5	77	100	77	79 ± 57 h	4-7 L/min	62.3	NR	NR
Slottosch 2017	mix	IABP	74.8	139	79.1	NR	4.9 d	4-7 L/min	43.2	NR	15
Smedira 2001	mix	IABP	54.5	202	75.7	NR	NR	NR	58.9	6	42
Tepper 2018	mix	IABP	50	60	0	NR	NR	5.2 L/min	60	10	NR
Unosawa 2012	PCS	IABP	83	47	68.1	NR	63.5 ± 61.5 h	2.34 L/min	61.7	0	0
van den Brink 2017	AMI	IABP	16.7	12	100	NR	5 (1–10) d	NR	66.7	1	NR
Wang 2013	PCS	IABP	47.1	87	NR	37	61 ± 37 h	calculated to supply at least adequate total systemic circulatory support (2.2 L/min) and to achieve a SvO ₂ of 70%	58.6	NR	NR
Weber 2017	mix	IABP	27.3	11	100	11	123.8 ± 120.9 h	NR	0	NR	NR
Wu 2012	mix	IABP	73.3	60	NR	NR	NR	NR	63.3	NR	NR
Xu 2016	mix	IABP	68.8	16	NR	NR	119.3 ± 114.8 h	NR	NR	NR	NR
Zhao 2015	PCS	IABP	66.7	24	95.8	NR	115.23 ± 70.17 h	49 mL/min/kg	66.7	1*	NR
Zhong 2017	PCS	IABP (9); vent (3)	33.3	36	80.6	NR	77.5 ± 34.5 h	NR	66.7	NR	NR

* concurrent use of LVAD and ECMO.

Table 2. Characteristics of patients.

Study	Setting	Unloading Strategy	Unloading Strategy Usage (%)	N. of pts	Age (Years)	Male (%)	Diabetes (%)	Hypertension (%)	PCI *	CABG **
Acheampong 2016	PCS	IABP	58.3	24	41 (IQR: 22–75)	58.3	NR	NR	NA	NA
Akanni 2018	mix	Impella	12.9	225	57 (46–67)	69.3	29	57	NR	NR
Aoyama 2013	AMI	IABP	92.1	38	59.9 ± 13.5	92.1	NR	NR	89	11
Asaumi 2005	Other	IABP	42.9	14	38.4 ± 15.8	50	NR	NR	NA	NA
Aso 2016	mix	IABP	36.6	1650	NR	69.4	NR	NR	NR	NR
Aziz 2010	mix	IABP	20	10	45.3 ± 18.9	50	10	40	NR	NR
Beiras-Fernandez 2011	PCS	IABP	49.3	73	49.3 ± 18.0	64.4	NR	NR	NA	NA
Beurtheret 2013	mix	IABP	31	87	46 ± 15	67.8	15	24	NR	NR
Biancari 2017	PCS	IABP (47); vent (5)	25.7	148	65.4 ± 9.4	78.4	40	NR	NA	NA
Brechot 2018	mix	IABP	40.2	259	50.2	69.9	NR	NR	NR	NR
Carroll 2015	mix	IABP+Impella	15.4	123	56 (41–65)	69	20	42	6	4
Chen 2005	Other	IABP	60	10	37.4 ± 14.7	NR	NR	NR	NA	NA
Chen 2006	AMI	IABP	86.1	36	57 ± 10	91.7	39	NR	19	78
Chen 2018	PCS	IABP	63.3	60	51.4 ± 12.7	75	17	33	NA	NA
Cho 2018	AMI	IABP	4.8	42	63.48 ± 11.46	66.7	41	48	100 [74]	0
Choi 2018	AMI	IABP	35.2	145	64.6 ± 11.7	75.9	54	53	90 [83]	NR
Chung 2011	AMI	IABP	70	20	67.7 ± 11.7	30	35	45	35	55
Czobor 2016	mix	IABP (10); Impella (1)	44	25	NR	80	44	52	NR	NR
Elsharkawy 2010	PCS	IABP	9.4	233	NR	67.4	21	NR	NA	NA
Formica 2010	PCS	IABP	69	42	64.3 ± 11.3	66.7	33	67	NA	NA
Gass 2014	mix	IABP	41.5	135	57.3 ± 15.3	64.4	31	48	NR	NR
Guihaire 2017	PCS	IABP (25); vent (13)	27.2	92	64.5 (18-83)	59	NR	NR	NA	NA
Hei 2011	PCS	IABP	16.2	68	49.2 ± 13.3	76.5	NR	NR	NA	NA
Kagawa 2012	AMI	IABP	82.6	86	63 (56–72)	81	31	63	71	0
Kim 2014	AMI	IABP	75.9	58	61.2 ± 11.3	82.8	NR	NR	NR	NR
Lee 2016	mix	IABP	8.7	23	55 (40, 68)	90	52	52	65	NR
Lee 2017	mx	IABP	16.3	135	59.44 ± 16.55	69.6	38	42	NR	NR
Li 2015	PCS	IABP	59.3	123	56.2 ± 11.8	65.9	NR	NR	NA	NA
Lin 2016	mix	IABP	57.1	529	55.1 ± 15.3	75.4	32	35	NR	NR
Lorusso 2016	other	IABP (34); vent (13)	59.6	57	37.6 ± 11.8	35.1	NR	NR	NR	NR
Luo 2009	mix	IABP	24.4	45	49.0 ± 14.1	76	NR	NR	NA	NA
Mikus 2013	PCS	IABP	92.9	14	53.1 ± 14.3	64.3	29	64	NA	NA
Muller 2016	AMI	IABP (96); Impella (3)	69.6	138	55 (46–63)	80	NR	NR	81 [72]	NR
Nakamura 2015	other	IABP	95.5	22	46.2 ± 18.7	45.5	NR	NR	NA	NA
Negi 2016	AMI	IABP	60	15	57 ± 13	60	20	87	NR	NR

Overtchouk 2018	AMI	IABP	59.4	106	52.7 ± 10.4	84	21	37	75 [72]	4
Papadopoulos 2015	PCS	IABP	21.9	360	62 ± 17	76.1	42	63	NA	NA
Pappalardo 2016	mix	Impella	21.7	157	53 (46–65)	83	NR	NR	36	NR
Park 2014	AMI	IABP	42.7	96	NR	77.1	61	48	81 [63]	10
Patel 2018	mix	Impella	45.5	66	NR	68.2	NR	NR	15	29
Pokersnik 2012	PCS	IABP	59.2	49	65 ± 13	67.3	39	90	NA	NA
Poptsov 2014	PCS	vent	60.9	46	42.1 ± 4.1	76.1	NR	NR	NA	NA
Raffa 2017	PCS	IABP	26.7	86	65 ± 11.2	65.1	17	94	NA	NA
Rastan 2010	PCS	IABP	74.1	517	63.5 ± 11.2	71.5	33	70	NA	NA
Ro 2013	mix	IABP	23.7	253	58.8 ± 15.3	60.9	23	39	NR	NR
Russo 2010	mix	IABP	85.7	14	47.8 ± 16.8	71.4	NR	NR	NR	NR
Sakamoto 2012	AMI	IABP	95.9	98	72 ± 12	66.3	35	45	94 [66]	2
Santise 2014	PCS	IABP	72.2	18	49 ± 11	77.8	17	22	NA	NA
Shinn 2009	mix	IABP	33.7	92	56 ± 18	64.1	24	29	NR	NR
Shmack 2017	mix	vent	41.7	48	49.7 ± 19.5	47.9	NR	NR	NR	NR
Slottosch 2012	PCS	IABP	93.5	77	60 ± 13	76.6	18	50	NA	NA
Slottosch 2017	mix	IABP	74.8	139	58 ± 15	76.3	27	NR	NR	NR
Smedira 2001	mix	IABP	54.5	202	55 ± 14	72	21	NR	NR	NR
Tepper 2018	mix	IABP	50	60	53.9 ± 14.9	53.3	38	53	NR	NR
Unosawa 2012	PCS	IABP	83	47	64.4 ± 12.5	74.4	38	43	NA	NA
van den Brink 2017	AMI	IABP	16.7	12	63 (47–75)	83	17	42	100	0
Wang 2013	PCS	IABP	47.1	87	65 ± 7	58.6	11	19	NA	NA
Weber 2017	mix	IABP	27.3	11	52.5 ± 16.4	81.8	NR	NR	NR	NR
Wu 2012	mix	IABP	73.3	60	49	66.7	43 ***	NR	48 ***	48 ***
Xu 2016	mix	IABP	68.8	16	62.3 ± 11.1	62.5	38	NR	NR	NR
Zhao 2015	PCS	IABP	66.7	24	59.3 ± 11.9	79.2	25	42	NA	NA
Zhong 2017	PCS	IABP (9); vent (3)	33.3	36	50.4 ± 12.2	91.7	25	81	NA	NA

* PCI as a part of managing strategy of cardiogenic shock; data presented for studies with population with acute myocardial infarction etiology; in square brackets reported is the rate of successful angioplasty. ** CABG as a part of managing strategy of cardiogenic shock; data presented for studies with population with acute myocardial infarction etiology. *** data for AMI patients only.

Table 3. ROBINS-I tool bias assessment.

Study	Bias Due to Confounding	Bias in Selection of Participants into the Study	Bias in Measurement of Interventions	Bias Due to Departures from Intended Interventions	Bias Due to Missing Data *	Bias in Measurement of Outcomes *	Bias in Selection of Reported Result *	Overall Bias	Cohen's Kappa
Acheampong 2016	Serious	Critical	Serious	NA	Moderate	Moderate	Low	Serious	0.83
Akanni 2018	Moderate	Low	Low	NA	Low	Moderate	Moderate	Moderate	1
Aoyama 2013	Serious	Low	Moderate	NA	Moderate	Serious	Serious	Serious	1
Asaumi 2005	Serious	Moderate	Serious	NA	Low	Critical	Critical	Critical	0.67
Aso 2016	Moderate	Low	Critical	NA	Low	Serious	Moderate	Moderate	0.83
Aziz 2010	Serious	Low	Low	NA	Low	Moderate	Moderate	Low	0.83
Beiras-Fernandez 2011	Moderate	Low	Low	NA	Moderate	Critical	Critical	Critical	0.83
Beurtheret 2013	Serious	Moderate	Low	NA	Moderate	Low	Low	Low	1
Biancari 2017	Low	Low	Serious	NA	Moderate	Low	Low	Low	0.83
Brechot 2018	Moderate	Low	Critical	NA	Low	Critical	Critical	Critical	1
Carroll 2015	Moderate	Low	Moderate	NA	Moderate	Moderate	Moderate	Moderate	1
Chen 2005	Moderate	Moderate	Low	NA	Low	Serious	Serious	Serious	0.83
Chen 2006	Serious	Low	Low	NA	Moderate	Serious	Serious	Serious	0.83
Chen 2018	Moderate	Low	Critical	NA	Moderate	Serious	Serious	Serious	0.67
Cho 2018	Serious	Moderate	Moderate	NA	Moderate	Serious	Serious	Serious	1
Choi 2018	Serious	Low	Serious	NA	Moderate	Serious	Serious	Serious	0.83
Chung 2011	Moderate	Low	Low	NA	Moderate	Moderate	Moderate	Moderate	1
Czobor 2016	Serious	Low	Moderate	NA	Moderate	Serious	Serious	Serious	1
Elsharkawy 2010	Serious	Low	Low	NA	Moderate	Moderate	Moderate	Moderate	0.83
Formica 2010	Moderate	Moderate	Serious	NA	Moderate	Moderate	Moderate	Moderate	0.67
Gass 2014	Moderate	Low	Critical	NA	Low	Moderate	Moderate	Moderate	1
Guihaire 2017	Low	Serious	Low	NA	Moderate	Moderate	Moderate	Moderate	1
Hei 2011	Serious	Low	Low	NA	Moderate	Moderate	Low	Low	0.83
Kagawa 2012	Moderate	Serious	Serious	NA	Moderate	Serious	Serious	Serious	0.83
Kim 2014	Moderate	Moderate	Critical	NA	Moderate	Critical	Critical	Critical	0.50
Lee 2016	Serious	Moderate	Serious	NA	Moderate	Moderate	Moderate	Moderate	1
Lee 2017	Moderate	Low	Moderate	NA	Moderate	Serious	Serious	Serious	1
Li 2015	Moderate	Low	Low	NA	Moderate	Moderate	Low	Moderate	0.83
Lin 2016	Moderate	Low	Critical	NA	Low	Serious	Serious	Serious	0.831
Lorusso 2016	Low	Moderate	Critical	NA	Moderate	Moderate	Low	Moderate	0.83
Luo 2009	Moderate	Low	Low	NA	Moderate	Moderate	Low	Moderate	0.67
Mikus 2013	Serious	Low	Low	NA	Low	Moderate	Moderate	Low	0.67
Muller 2016	Serious	Low	Low	NA	Moderate	Moderate	Moderate	Moderate	0.83
Nakamura 2015	Serious	Moderate	Serious	NA	Moderate	Moderate	Moderate	Moderate	1
Negi 2016	Moderate	Low	Low	NA	Low	Moderate	Moderate	Moderate	0.83
Overtchouk 2018	Moderate	Serious	Low	NA	Moderate	Critical	Critical	Critical	1
Papadopoulos 2015	Serious	Low	Low	NA	Moderate	Moderate	Moderate	Moderate	1
Pappalardo 2016	Moderate	Low	Critical	NA	Low	Serious	Serious	Serious	0.83
Park 2014	Moderate	Moderate	Low	NA	Moderate	Moderate	Moderate	Moderate	1
Patel 2018	Serious	Low	Low	NA	Low	Moderate	Moderate	Low	0.83
Pokersnik 2012	Serious	Serious	Critical	NA	Moderate	Moderate	Moderate	Moderate	1

Poptsov 2014	Moderate	Serious	Critical	NA	Moderate	Critical	Critical	Critical	1
Raffa 2017	Moderate	Low	Serious	NA	Moderate	Moderate	Low	Moderate	0.50
Rastan 2010	Moderate	Low	Low	NA	Moderate	Moderate	Moderate	Moderate	0.83
Ro 2013	Serious	Low	Critical	NA	Low	Critical	Critical	Critical	0.83
Russo 2010	Serious	Low	Low	NA	Low	Critical	Serious	Low	0.83
Sakamoto 2012	Moderate	Low	Moderate	NA	Moderate	Serious	Serious	Moderate	0.67
Santise 2014	Moderate	Serious	Serious	NA	Moderate	Moderate	Moderate	Moderate	0.83
Shinn 2009	Moderate	Low	Critical	NA	Moderate	Serious	Serious	Serious	0.83
Shmack 2017	Serious	Low	Serious	NA	Low	Critical	Critical	Critical	1
Slottosch 2012	Low	Low	Low	NA	Moderate	Low	Low	Low	1
Slottosch 2017	Low	Low	Low	NA	Moderate	Moderate	Low	Low	0.67
Smedira 2001	Moderate	Low	Serious	NA	Moderate	Serious	Moderate	Moderate	0.83
Tepper 2018	Moderate	Low	Critical	NA	Low	Moderate	Moderate	Moderate	1
Unosawa 2012	Serious	Low	Low	NA	Moderate	Moderate	Low	Low	1
van den Brink 2017	Moderate	Low	Critical	NA	Moderate	Serious	Serious	Serious	1
Wang 2013	Moderate	Critical	Low	NA	Moderate	Low	Low	Low	0.67
Weber 2017	Low	Critical	Critical	NA	Low	Critical	Critical	Critical	0.83
Wu 2012	Serious	Low	Moderate	NA	Moderate	Moderate	Moderate	Moderate	1
Xu 2016	Moderate	Low	Critical	NA	Moderate	Serious	Serious	Serious	0.83
Zhao 2015	Serious	Critical	Critical	NA	Moderate	Moderate	Moderate	Moderate	0.83
Zhong 2017	Low	Critical	Low	NA	Moderate	Serious	Low	Low	0.50

* When multiple outcomes were reported for a study, the highest level of bias at the outcome level is reported in the table. Bias reported for comparison of peripheral vs. central extracorporeal circulation and not for a study in general.

Figure 3. All-cause in-hospital mortality rate for patients receiving extracorporeal membrane oxygenation (ECMO) + left ventricular (LV) unloading versus ECMO alone treatment according to cardiogenic shock etiology.

The highest mortality risk benefit (25%) was observed in the subgroup of patients undergoing LV unloading + ECMO for AMI: RR (95%CI): 0.75 (0.67–0.83); $p < 0.00001$; $I^2 = 0\%$; NNT = 15. A mortality risk benefit of 11% was demonstrated in studies including mixed indication for LV unloading + ECMO: RR (95%CI): 0.90 (0.81–1.00); $p = 0.04$; $I^2 = 48\%$; NNT = 11; In patients with postcardiotomy cardiogenic shock, LV unloading on top of ECMO was associated with 7% non-significantly lower mortality risk; RR (95%CI): 0.93 (0.85–1.01); $p = 0.09$; $I^2 = 29\%$; NNT = 125. No differences were seen between LV-unloading + ECMO as compared to ECMO alone in patients with myocarditis; NNT = 9. Significant statistical differences as of extent of benefit were demonstrated between subgroups ($p_{\text{interaction}} = 0.01$). No impact on early mortality was found according to the type of cannulation, peripheral and central, in a meta-regression analysis, Figure 4. Similarly, these were unaffected by age, gender, diabetes and hypertension status (Figures 5-8).

Figure 4. Meta-regression: the impact of the rate of peripheral cannulation on Log odds ratio.

3.2.2. Weaning

Seventeen studies with nearly 3000 patients reported on weaning rates in subsets receiving LV unloading + ECMO as compared to ECMO therapy alone. In the overall analysis, LV unloading was associated with 35% higher probability of weaning from ECMO: RR (95%CI): 1.35 (1.21–1.51); $p < 0.00001$; $I^2 = 38\%$: weaning was possible in 60.4% (1789/2964) of included patients with corresponding rates of 75.3% (821/1090) and 51.7% (968/1874) for LV unloading + ECMO and ECMO alone; Figure 9.

Figure 5. Meta-regression showing the impact of age distribution on Log odds ratio.

Figure 6. Meta-regression showing the impact of gender distribution on Log odds ratio.

Figure 7. Meta-regression showing the impact of diabetes percentage distribution on Log odds ratio.

Figure 8. Meta-regression showing the impact of hypertension distribution on Log odds ratio

Figure 9. Weaning rate for patients receiving ECMO + LV unloading vs. ECMO alone treatment according to cardiogenic shock etiology.

LV unloading on top of ECMO was associated with a higher chance of weaning in postcardiotomy cardiogenic shock: RR (95%CI): 1.81 (0.99–3.29); $p = 0.05$; $I^2 = 0\%$. Differences between subgroups were not statistically significant.

3.3. Secondary Endpoints

There were no apparent differences between LV unloading + ECMO vs. ECMO alone treatment regarding the secondary endpoints (Figures 10-15). Neurologic complications incidence was reported in 6 studies (596 patients) with respective 8.5% (17/199) vs. 6.0% (24/397) for ECMO + LV unloading vs. ECMO alone (RR (95%CI): 1.03 (0.55–1.94); $p = 0.92$; $I^2 = 0\%$); Figure 10. Similarly, non-significant differences in terms of brain death was seen: (RR (95%CI): 0.82 (0.34–1.97); $p = 0.66$; $I^2 = 7\%$; Figure 11. ECMO + LV unloading was not

associated with any benefit nor harm in analysis of: limb complications (6 studies; 2695 patients): RR (95%CI): 1.06 (0.89–1.26); $p = 0.50$; $I^2 = 0\%$ (Figure 12); acute kidney injury (10 studies; 3178 patients): RR (95%CI): 1.03 (0.87–1.26); $p = 0.64$; $I^2 = 49\%$ (Figure 13); revision for bleeding: RR (95%CI): 0.81 (0.44–1.47); $p = 0.48$; $I^2 = 0\%$ (Figure 14); sepsis: RR (95%CI): 0.70 (0.31–1.57); $p = 0.38$; $I^2 = 0\%$ (Figure 15).

Figure 10. Neurologic complications.

Figure 11. Brain death.

Figure 12. Limb complications.

Figure 13. Acute kidney injury (AKI).

Figure 14. Revision for bleeding.

Figure 15. Sepsis.

3.3.1. Analysis Stratified by LV Unloading Technique

As secondary analysis, we assessed the impact of the different unloading techniques on mortality and weaning: 5 studies (382 patients) reported on LV unloading by direct LV venting catheters: a statistical trend of 32% reduced mortality risk was demonstrated for ECMO + LV venting as compared to ECMO alone: RR (95%CI): 0.68 (0.45–1.03); $p = 0.07$; $I^2 = 28\%$; Figure 16 and Table 4. Respective mortality rates were 30.4% (24/79) vs. 60.7% (184/303) for LV unloading + ECMO and ECMO alone. No data was available about the rate of weaning in the groups receiving an LV venting. Use of IABP as an adjunct ECMO was assessed in 56 studies (7015 patients): mortality rates were 56.4% (1791/3174) and 60.7% (2331/3841) for ECMO + IABP vs. ECMO alone; RR (95%CI): 0.89 (0.84–0.95); $p = 0.0004$; $I^2 = 39\%$. Intra-aortic balloon pump was further associated with significant increased chance of weaning from ECMO: RR (95%CI): 1.27 (0.14–1.42); $p < 0.0001$; $I^2 = 32\%$. Figure 16.

Table 4. LV unloading strategy.

	LA	RSPV	Direct LV Apex	LV by RSPV	PA
Guihaire 2017	13 patients				
Biancari 2017		3 patients	1 patient		1 patient
Poptsov 2014	19 patients (percutaneous)				
Shmack 2017				29 patients	
Lorusso 2016		4 patients	4 patients		2 patients

Lower, yet statistically non-significant mortality risk was found for ECMO + Impella as compared to ECMO alone (6 studies; 734 patients): RR (95%CI): 0.85 (0.67–1.09); $p = 0.20$; $I^2 = 41\%$. Additionally, Impella device was independently associated with higher chance of weaning from ECMO: RR (95%CI): 1.65 (1.05–2.59); $p = 0.03$; $I^2 = 74\%$ (Figure 17).

3.3.2. Sensitivity Analyses

Analyses were repeated as sensitivity for primary endpoints mortality and weaning from ECMO this time included only studies that reported effect estimates for propensity matched cohorts only: 5 studies (Appendix References [10,15,34,43,50]) provided propensity adjusted estimates of mortality; pooled together, LV unloading on top of ECMO was associated with over 25% statistically significant reduction in the odds of mortality as compared to ECMO alone: OR (95%CI): 0.74 (0.60–0.91); $p = 0.004$; $I^2 = 42\%$; Figure 18A.

Weaning rates for comparison LV unloading + ECMO and ECMO alone adjusted for propensity were reported in 4 studies (Appendix references [10,15,43,50]); again, LV unloading on top of ECMO was associated with over 75% significantly higher odds to wean from ECMO: OR (95%CI): 1.78 (1.40–2.28); $p < 0.001$; $I^2 = 0\%$; Figure 18B.

Figure 17. Weaning by device.

Figure 16. Mortality by device.

(A)

(B)

Figure 18. All-cause in-hospital mortality rate (A) and weaning rate (B) from studies reporting propensity adjusted results.

Sensitivity analyses performed by deleting each study, one at a time, and repeating the calculations did not change the direction nor magnitude of the treatment effect, suggesting absence of big-study effect.

4. Discussion

VA-ECMO is an established treatment able to provide a mechanical circulatory support for patients in cardiogenic shock, aiming a bridge to decision or to myocardial recovery [1–6]. Improvements in technology have mitigated the interaction between artificial surfaces of ECMO circuits and blood. However, other adverse

effects, known as “flow-related dynamic”, are strictly associated, both in central and peripheral ECMO configuration, with the retrograde direction of the flow towards a dysfunctional left ventricle. Two major issues have been longer debated by the scientific community: the first is the difference in outcomes and hemodynamic support between the central and peripheral cannulation; the second is the clinical impact of the left ventricle unloading and the strategy to achieve a safe and effective ventricular decompression. The first issue has been already addressed by our group [21]; aim of the current meta-analysis is to address the question whether myocardial unloading is beneficial or, by raising the complexity of ECMO management, futile or potentially detrimental to patients’ outcomes.

ECLS institution increases the left ventricle afterload with a rise in LV end-systolic volume and reduction in LV stroke volume. If peripheral resistance and LV contractility are fixed, increase in LV end-diastolic volume is the only way to overcome the afterload via the Frank–Starling mechanism. In this case, higher levels of VA-ECMO flow cause a progressive rise in LV end-diastolic pressure, LA pressure, pulmonary capillary wedge pressure, that are associated with a further reduced LV stroke volume [22–24]. High afterload situations with inability of LV to manage the transpulmonary blood flow, inadequate response to inotropes, complete cardiac arrest with incomplete venous drainage and aortic valve incompetence are the commonest risk factors for LV distension. Patients with severely impaired LV function and/or right ventricular dysfunction are more prone to develop an ineffective LV unloading [25]. LV overload increases wall stress, myocardial oxygen consumption and induce sub-endocardial ischemia and ventricular arrhythmias, jeopardizing ventricular recovery particularly in the presence of ischemia-induced myocardial impairment. The consequence of the pressure overload may ultimately account for pulmonary congestion and edema.

If the overload is extreme and LV contractile impairment significant, the LV is unable to provide a sufficient flow against the increased afterload and the aortic valve may remain closed even during systole, causing blood stasis in the left ventricle, left atrium and aorta, and accounting for intracardiac thrombosis which has been reported in up to 6% of the cases [26,27]. The LV dilatation may further induce annular dilatation and mitral valve leaflet tethering with severe functional regurgitation, thus, particularly in in patients with a history of chronic heart failure and LV dysfunction with a dilated LV, worsening the pulmonary congestion [28].

Definition of LV distension during VA-ECMO is lacking in the literature. Truby et al. [29] attempt to classify and grade the LVD according to the evidence of pulmonary edema on chest radiography and increased pulmonary artery diastolic blood pressure (> 25 mmHg). The latter was a surrogate of the wedge pressure evaluated in the “Should we emergently revascularize occluded coronaries for cardiogenic shock” (SHOCK) trial [30]. Clinical evidence of LV distension requiring immediate decompression was inversely related to the chance of myocardial recovery. Meani et al. [28] defined and graded the severity of LV loading during VA-ECMO according to hemodynamic parameters, chest X-ray and echocardiogram findings.

These differences in definitions and assessments may account for the high variability of LV distension rate in the literature. Camboni et al. [31] reported need for LV decompression in 2% of the cases in more than 600 patients. A strict and longer afterload reduction (> 24 hours), targeted lower ECMO flow and a restrictive fluid management were the strategy adopted in this large series. In Truby et al. [29] the clinical and subclinical (not warranting immediate decompression) LV distension occurred in 7% and 22% of patients, respectively. Among 184 peripheral VA ECMO in the series of Meani et al. [32], 5.4% required IABP placement because of a protracted closure of the aortic valve.

Drugs administration is the first line treatment of left ventricle distension. Inotropes can be administered to increase LV contractility while vasodilators may reduce the peripheral resistances and decrease left ventricle afterload. A careful fluid balance (diuretics/fluid restriction) avoiding fluid overload can reduce the risk of pulmonary edema. Ventilatory optimization, including higher PEEP, prolonged expiration time and lower tidal volume, may further improve the venous drainage.

When medical treatment is not successful, the non-pharmacological management of LV distension, acting with a “direct” or indirect” mechanism, can be obtained through a surgical or percutaneous strategy (Figure 19).

4.1. IABP

IABP has been the most used technique to unload the left ventricle during ECMO support [33]. The IABP acts with several “indirect” mechanisms reducing both the LV afterload (enhanced systolic ejection) and the LV end-diastolic pressure (enhanced left atrial and pulmonary venous unloading).

Figure 19. Left ventricle unloading strategies classified according to the direct or indirect, percutaneous or surgical strategies. The differences in arrows' width is intended suggesting the efficacy of left ventricle unloading (greater for direct surgical approach and Impella device). The color of the dash is intended suggesting blood oxygenation. Further techniques, not included in the picture, are the direct LV transaortic device by PulseCath device, percutaneous indirect LA drainage with TandemHeart transeptal cannula. PA: pulmonary artery; LA: left atrium; LV: left ventricle; RA: right atrium; * achieved through right superior pulmonary vein, left atrial roof, interatrial groove; ** simultaneous left and right atrial drainage with the multistage cannula coming from the femoral vein and positioned transeptally.

The IABP induces the aortic valve opening [32], improves coronary and abdominal circulation [34], allows pulsatility in end organ capillary bed [35], it is easy to implant and has contained costs. In animal studies the role of counterpulsation in VA-ECMO support seems controversial. Zobel [36] and Sauren [37] showed that IABP has beneficial effects on LV performance. Instead, Belohlávek et al. [38] showed that the combination of femoral VA-ECMO and IABP could impair coronary perfusion. In clinical practice the combination ECMO/IABP was associated with improvement in hemodynamics parameters [39,40], weaning rate [39,41] and survival [41,42].

4.2. ECPPELLA

The use of Impella in combination with VA-ECMO (also known as ECPPELLA/ECMELLA) has been shown to provide improved weaning and survival rates compared to ECMO alone strategy and to established risks scores [43–46]. The addition of a continuous flow vent reduces LV volumes and pressures. The LV stroke volume

progressively decreases as pump flow increases, with the raise of systemic blood pressure and reduction of LA and pulmonary capillary wedge pressures. Despite the aortic valve does not open, there is no risk of blood stasis in the LV and the aortic root. The uncoupling of LV and aortic pressure is a sign of an effective unloading of the ventricle. In this situation a flat systemic pressure line is a sign of maximal unloading. Secondary changes in myocardial contractility and peripheral resistance may further enhance the LV unloading [22,46]. The Impella can also reduce RV afterload and facilitate RV output and pulmonary blood flow with improvement in gas exchange [47,48]. Alongside these hemodynamic features, the use of an axial flow pump may provide a circulatory support while weaning from VA-ECMO. The possibility of reducing the duration of ECLS has been reported by Schrage et al. [46], however, in the experience of Pappalardo et al. [44], the association of Impella and VA-ECMO prolonged the time of support but provided a successful recovery of patients who might not have survived under VA-ECMO treatment alone. The use of Impella has been associated with a significant risk of severe bleeding, vascular complications and cerebral stroke [49,50]. In patients receiving the dual treatment with VA-ECMO, a higher occurrence of hemolysis has been reported [44], however, no difference was generally found in terms of risk of major and minor bleeding, and cerebral stroke compared to VA-ECMO alone [43,45]. These initial results seem to support an expanding use of Impella for LV unloading. Despite the evidences are still limited and coming from retrospective studies, most of the patients who underwent ECPELLA therapy were in cardiogenic shock with severely impaired LV function, were upgraded to VA-ECMO while on axial flow pump due to a progressive deterioration, or needed the implantation of Impella following significant and complicated LV distension.

4.3. Other Techniques

Other unloading strategies have been reported in the literature and address the endpoints of this meta-analysis (Table 4). Briefly, the left atrium can be drained surgically by a cannula in the left atrial roof or in the right superior pulmonary vein or percutaneously [28,51] by an interatrial septostomy (septostomy usually with ballooning or stent) or a cannula attached to the ECMO venous return or to device like TandemHeart®). Direct left ventricle unloading can be also achieved or by a surgical cannulation of the ventricle apex [52,53] and through the mitral

valve from the left atrium [52,54] or percutaneously by a catheter across the aortic valve. The surgical or percutaneous pulmonary artery cannulation [52,53], increasing the right-side blood drainage, will indirectly reduce the pulmonary venous return and left cardiac chamber loading. The experiences with these last unloading strategies include small populations, however, these studies found a positive impact of these adjuncts on patients' survival.

Hemodynamic responses to ECMO are different among patients and are affected by clinical presentation, associated comorbidities and the cardiovascular system coupling. This high variability may explain the difficulties in driving robust conclusions in terms of efficacy and safety of LV unloading during VA-ECMO.

Up to date and to the best of our knowledge other two meta-analysis have been published on LV unloading strategy [26,33]. In 2015, Cheng et al. [26] reported the impact of IABP on survival among 1517 patients (16 studies). The cumulative survival rate for patients on ECMO was 256/683 (37.5%) compared with 294/834 (35.3%) for patients with adjunctive IABP. Concomitant IABP was not associated with improved survival (RR: 1.143; 95% CI: 0.973 to 1.343; $p = 0.10$). IABP was not associated with improved survival in AMI patients (RR, 1.120; 95% CI, 0.772–1.624; $p = 0.55$), PCS (RR, 1.121; 95% CI, 0.826–1.520; $p = 0.46$) when placed prior to ECMO initiation (RR, 0.948; 95% CI, 0.718–1.252; $p = 0.71$), or when routinely inserted (RR, 1.102; 95% CI, 0.806–1.506; $p = 0.54$). Recently, Russo et al. [33] reviewed 17 observational studies including 3997 patients. A total of 1696 (42%) patients received a concomitant left ventricular unloading strategy while on VA-ECMO (IABP 91.7%, percutaneous ventricular assist device 5.5%, pulmonary vein or transseptal left atrial cannulation 2.8%). Mortality was lower in patients with (54%) versus without (65%) left ventricular unloading while on VA-ECMO (RR: 0.79; 95% confidence interval (CI): 0.72 to 0.87; $p < 0.00001$). Bleeding, limb ischemia, renal replacement therapy, multiorgan failure and stroke or transient ischemic attack were not demonstrably different in patients treated with VA-ECMO with versus without left ventricular unloading. Hemolysis was the only secondary outcome higher in patients who underwent VA-ECMO with left ventricular unloading (RR: 2.15; 95% CI: 1.49 to 3.11; $p < 0.0001$).

4.4. Limitations

As analysis of only non-randomized studies, our analysis shared similar limitations with these reports which included experiences with small populations and lacked some critical information about the timing of ECMO institution, the timing of LV unloading adjunct, or the weaning protocols. Most importantly, none of the studies report exact criteria for therapy escalation e.g., addition of IABP or Impella device to ECMO. In addition, observational nature of these studies promotes selection bias. However, compared to previous meta-analyses, that present certain methodological flaws (e.g., Russo by applying the very same search strategy included 17 studies and 3997 patients), the current study, including 62 studies and more than 7500 patients, represents the first comprehensive approach addressing LV unloading strategies during ECMO support.

We found that, regardless the strategy (IABP, Impella, others) and the etiology (PCS, AMI, other), LV unloading has a positive impact in patients' weaning, without adding any further risk of CVE, sepsis, acute renal injury requiring dialysis, limb complications and reoperation for bleeding. We have also provided a separate analysis of propensity-score matched and adjusted studies, trying, in the absence of prospective randomized data, to address the high heterogeneity of the included experiences due to different baseline populations' characteristics. This further analysis confirmed these findings favoring LV unloading techniques during VA-ECMO.

Despite the expected different flow patterns and afterload increase by central and peripheral cannulation, these two strategies were not significantly associated with a higher odds ratio risk of mortality considering the adjunct or the absence of LV unloading. However, we found a tendency in the association of higher odd ratio risk and progressively higher percentage of patients receiving peripheral cannulation, this finding couples the non-significant difference in outcomes in the PCS populations that have received a central VA-ECMO in almost 30% of the cases (less than 10% in the mixed populations, 0% in AMI patients), and suggests, within the limitations of this analysis, a more pronounced positive impact of LV unloading in the peripheral VA-ECMO setting.

The analysis of weaning, additionally included as a sensitivity analysis, might give presumptive underlying evidence of true reasons for improved survival after VA-ECMO support. The possibility of providing an adequate oxygen delivery associated with the reduction of myocardial injury and the relief of pulmonary congestion, thus enhancing arterial oxygenation and reducing pulmonary complications, may explain the higher rate of survival

in patients who received an adjunct treatment able to prevent or solve left ventricular distension during VA-ECMO support.

5. Conclusions

During veno-arterial extracorporeal membrane oxygenation, the increase of left ventricular afterload can negatively impact the recovery from cardiogenic shock. In this meta-analysis including 7581 patients on VA-ECMO support, the adjunct of left ventricular unloading was associated with 35% higher probability of weaning and 12% lower risk of mortality.

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CHAPTER 4

BASELINE SURGICAL STATUS AND SHORT-TERM MORTALITY AFTER EXTRACORPOREAL MEMBRANE OXYGENATION FOR POST-CARDIOTOMY SHOCK: A META-ANALYSIS.

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Objective: While reported mortality rates on post-cardiotomy extracorporeal membrane oxygenation (ECMO) vary from center to center, impact of baseline surgical status (elective/ urgent/ emergency/ salvage) on mortality is still unknown.

Methods: A systematic search was performed according to PRISMA statement using PubMed/Medline databases until March 2018 using the keywords "postcardiotomy", "cardiogenic shock", "extracorporeal membrane oxygenation", "extracorporeal life support". Relevant articles were scrutinized and included in the meta-analysis only if reporting in-hospital/30-day mortality and baseline surgical status. The correlations between mortality and percentage of elective/urgent/emergency cases were investigated. Inference analysis of baseline status and on-ECMO complications was conducted as well.

Results: Twenty-two studies (conducted between 1993-2017) enrolling N=2,235 post-cardiotomy ECMO patients were found. Patients were mostly of non-emergency status (65.2%). Overall in-hospital/30-day mortality Event Rate (95% Confidence Intervals) was 66.7% (63.3-69.9%). There were no differences in in-hospital/30-day mortality with respect to baseline surgical status in the subgroup analysis (test for subgroup differences; $p=0.406$). Similarly, no differences between mortality in studies enrolling <50 vs $\geq 50\%$ of emergency/salvage cases was found: respective event rates were 66.9% (63.1-70.4%) vs 64.4% (57.3-70.8%); $p=0.525$. Yet, there was a significant positive association between increasing percentage of emergency/salvage cases and rates of: neurological complications ($p<0.001$), limb complications ($p<0.001$) and bleeding ($p=0.051$). Incidence of brain death ($p=0.099$) and sepsis ($p=0.134$) was increased as well.

Conclusion: Other factors than baseline surgical status may, to a higher degree, influence the mortality in patients treated with ECMO for post-cardiotomy cardiogenic shock. Baseline status, however, strongly influences the complication occurrence while on ECMO.

Introduction

Extracorporeal membrane oxygenation (ECMO) is increasingly used in case of acute cardiac and lung compromise refractory to conventional treatment, when temporary support may allow the dysfunctional organs to recover, or to provide a "bridge-to-decision" approach for more advanced treatment [1-5]. The inherent

features of ECMO in terms of quick availability, relative ease of application, and improved as well as reliable performance have made it more and more attractive, particularly in post-cardiotomy (PC) setting. Post-cardiotomy ECMO has been shown to be the most frequent indication for ECMO implant in the United States until 2011 [3]; indeed, recent data from the Registry of the Extracorporeal Life Support Organization (ELSO), which includes almost 90.000 ECMO cases including both adults and children, have confirmed the substantial rise in PC-ECMO use along the time, with a remarkable increase during the last 2-3 years [5]. Unfortunately, the exponential increase in cases in the last years has paralleled a lack of substantial progress [6] or even a progressive worsening with regards to in-hospital patient outcome [5]. Despite a wide series of published experiences in ECMO, reports specifically addressing PC-ECMO are limited. These studies often include different surgical scenarios and baseline patients' surgical status (e.g. elective, urgent, emergency and salvage), making the conclusions even harder to draw. Aim of the current meta-analysis was to demonstrate whether baseline pre-ECMO surgical status has any influence on postoperative mortality and complications for PC-ECMO.

Material and methods

Data sources and search strategy

This systematic review and meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [7]. The PRISMA checklist is available as Appendix Table 1. Relevant studies to be included were searched until published in March 31st 2018, through PubMed, EMBASE, CINAHL, the Web of Science, the Cochrane Register of Controlled Clinical Trials (CENTRAL) and Google Scholar. The search term was: “extracorporeal membrane oxygenation” and “extracorporeal life support”. No language restrictions were imposed. References of original articles were reviewed manually and cross-checked for relevant reports.

Selection criteria and quality assessment

Studies were included if they met all of the following criteria: 1) study reporting baseline surgical status for at least 1 group of interest e.g. elective, urgent, emergency or salvage surgery; 2) studies assessing mortality after ECMO instituted for PC refractory cardiogenic shock; 3) study reporting institutional outcomes that for ECMO indication combined PC and non-PC cardiogenic shock, but PC comprised >70% of cases; 4) studies combining non-PC and PC cardiogenic shock patients but reporting mortality outcome separately for the latter. Studies were only excluded if: 1) paediatric and congenital heart surgery-related studies or mixed paediatric-adult populations; 2) animal studies; 3) conducted in the setting of veno-venous ECMO for respiratory distress following heart surgery; and 4) studies not reporting survival/mortality rates. Reviews and case reports were not considered.

Two independent reviewers (G.M.R and K.Z.) selected the studies for inclusion, extracted studies, as well as patient characteristics of interest and relevant outcomes. Two authors (G.M.R., and K.Z.,) independently assessed the trials' eligibility and risk of bias. Risk of bias at the individual study level was assessed using the ROBINS-I tool (Risk of Bias in Not-randomized Studies-of Interventions) [8]. Any divergences were resolved by two other authors (M.K. and R.L.) and quantified using the approach of Cohen's kappa [9].

Endpoint selection

The primary endpoint was in-hospital/30-day mortality. In-hospital mortality was preferred over 30-day mortality. The latter was pooled only in in-hospital rates were not available. Secondary endpoints were in-hospital neurological complications, limb complications, bleeding or reoperation for bleeding, sepsis and acute kidney injury (AKI) with/without continuous veno-venous hemofiltration (CVVH). Neurological complications encompassed cerebrovascular events, strokes, transient ischemic attacks etc. Separate analysis of brain death was conducted as well. Outcome definitions were the ones adopted by the investigators of the included studies.

Statistical analysis

Statistical analyses were performed in Comprehensive Meta-Analysis, v. 2 (Biostat,

Englewood, NJ). The results are expressed as pooled untransformed proportions (e.g. event rates (%)) and means with their 95% confidence intervals (CI). Heterogeneity across studies was evaluated using the I² test. To control for the anticipated heterogeneity among observational studies, absolute values and means were pooled using random effects models. Studies were stratified a priori based on the baseline surgical status: elective vs urgent vs emergency vs salvage; the interaction coefficient (Q-value) is provided for the respective comparisons along with P_{interaction}. Whenever a single study reported median values and interquartile ranges instead of mean±SD, the latter were approximated as described by Wan et al [10]. Additionally, we investigated if baseline surgical status had influence on mortality by means of meta-regression analyses [11]. Sensitivity analyses were performed by excluding from analyses single studies, one at a time, and repeating the calculations. Additionally, to best account for discrepancies across single studies, as a sensitivity analysis, all outcomes were analysed as stratified by emergency vs non-emergency baseline status; for this purpose, elective and urgent cases were pooled in non-emergency stratum; reported salvage cases or those undergoing cardiopulmonary resuscitation preoperatively were added to emergencies instead. Publication bias was assessed 1) by visual approach plotting log event rate against standard error in the funnel plot; and 2) by linear regression approach [12].

Results

Initial search process yielded 22,609 records; of these, 183 abstracts were retrieved for scrutiny based on the item's title. Following detailed assessment, 58 studies met all but 1st inclusion criteria and entered qualitative analyses. Of those, 22 (2,235 patients) [supplementary references 1-22] reported baseline surgical status and were included in the meta-analysis. The PRISMA flow chart is available as Figure 1.

Figure 1. PRISMA Flow Chart

Detailed characteristics of included studies as well as patients' baseline and surgical data are available in Table 1.

Table 1. Study baseline characteristics

Study (year) [reference]	N of PCS patients	Baseline status (elective/urgent/ emergency/salvage)	Age	Male (%)	Surgery type				ECMO duration	Weaning rates (%)
					CABG	Valve	Combined	Other		
Beckmann 2017 [e1]	8	NR/NR/3/NR	50.1 ± 15.8	62.5	0	4	1	3	12.0 ± 5.9 days	87.5
Biancari 2017 [e2]	148	19/34/80/15	65.4 ± 9.4	78.4	148	0	0	0	6.4 ± 5.6 days	48.6
Doll N 2003 [e3]	95	21/64/10/0	59.8 ± 13.3	69.5	63	18	8	6	2.8 ± 2.1 days	47.4

Elsharkawy 2010 [e4]	233	NR/NR/84/NR	NR	67.4			NR		NR	NR
Guihaire 2017 [e5]	92	NR/NR/33/NR	64.5 (18-83)	59	12	64	31*	16	6 days	48
Khorsandi 2016 [e6]	16	9/3/4/0	64.3 ± 14.5	73.3	3	4	5	3	5.5 ± 8.9 days	NR
Iazzara 1993 [e7]	11	1/6/4/0	NR	NR			NR		48 (22-93) hours	73
Magovern 1994 [e8]	21	0/11/10/0	61.6 ± 2.2	80.9	16	3	0	2	42.1 ± 3.9 hours	76.2
Mikus 2013 [e9]	14	6/2/6/0	53.1 ± 14.3	64.3	5	6	3	0	5 days	50
Muehrcke 1996 [e10]	23	6/0/17/0	47.3 ± 16.4	73.9	8	6	0	9	58.4 ± 35.1 hours	56.5
Papadopoulos 2015 [e11]	360	NR/NR/NR/50	62 ± 17	76.1	114	89	85	72	7 ± 1 days	58.1
Pokersnik 2012 [e12]	49	NR/NR/0/0	65 ± 13	67.3			NR		3.8 ± 3.4 days	55.1
Pontailier 2017 [e13]	127	NR/NR/49/NR	75.7 ± 4.7**	61.3**	42	36	18	18	5.6 ± 4.3 days**	41.1**
Raffa 2017 [e14]	86	NR/NR/33/NR	65 ± 11.2	65.1	19	14	29	24	5 days	49
Rastan 2010 [e15]	517	159/122/205/31	63.5 ± 11.2	71.5	193	96	72	156	3.28 ± 2.85 days	63.3
Santarpino 2015 [e16]	20	0/0/0/20	62.8 ± 8.8	80	20	0	0	0	107 ± 99 hours	NR
Saxena 2015 [e17]	45	35/6/4/0	76.8 ± 4.6	68.9			NR		103.8 ± 74.3 hours	53.3
Slottosch 2012 [e18]***	77	NR/NR/29/NR	60 ± 13	76.6	43	10	11	13	79 ± 57 hours	62.3
Slottosch 2017 [e19]***	100	NR/NR/37/0	58 ± 15*	76.3	45	19	24	12	117 ± 78 hours**	43.2**
Unosawa 2012 [e20]	47	NR/NR/22/NR	64.4 ± 12.5	74.4	19	8	6	14	63.5 ± 61.5 hours	61.7
Wu 2010 [e21]	110	NR/NR/31/NR	60 ± 14	70.9	31	42	19	18	143 ± 112 hours	60.9
Zhong 2017 [e22]	36	NR/NR/9/NR	50.4 ± 12.2	91.7			NR		77.5 ± 34.5 hours	66.7

* Multiple valve repair or valvular surgery combined with CABG; potential overlap.

** Reported for entire study population including non-PCS patients

*** Possible 2-year study period overlap.

Publication bias analysis along with reasons for bias risk increase is available as Table 2.

Table 2. ROBINS-I tool bias assessment.

Study	Bias due to confounding	Bias in selection of participants into the study	Bias in measurement of interventions	Bias due to departures from intended interventions	Bias due to missing data*	Bias in measurement of outcomes*	Bias in selection of reported result*	Overall bias	Cohen's Kappa
Beckmann 2017 [13]	Critical	Critical	Serious	NA	Low	Moderate	Moderate	Critical	71.4%

Biancari 2017 [14]	Critical	Low	Serious	NA	Low	Low	Low	Low	85.7%
Doll N 2003 [15]	Critical	Low	Low	NA	Moderate	Low	Low	Low	71.4%
Elsharkawy 2010 [16]	Critical	Low	Low	NA	Low	Moderate	Moderate	Low	85.7%
Guihaire 2017 [17]	Critical	Serious	Low	NA	Low	Moderate	Moderate	Moderate	85.7%
Khorsandi 2016 [18]	Critical	Low	Serious	NA	Low	Low	Low	Low	71.4%
Iazzara 1993 [19]	Critical	Low	Serious	NA	Moderate	Critical	Moderate	Moderate	71.4%
Magovern 1994 [20]	Critical	Low	Serious	NA	Moderate	Moderate	Critical	Moderate	71.4%
Mikus 2013 [21]	Critical	Low	Low	NA	Low	Moderate	Moderate	Low	85.7%
Muehrcke 1996 [22]	Critical	Moderate	Critical	NA	Serious	Low	Low	Moderate	85.7%
Papadopoulos 2015 [23]	Critical	Low	Low	NA	Low	Moderate	Moderate	Low	85.7%
Pokersnik 2012 [24]	Critical	Serious	Critical	NA	Low	Moderate	Moderate	Critical	71.4%
Pontailier 2017 [25]	Critical	Low	Serious	NA	Serious	Critical	Critical	Critical	71.4%
Raffa 2017 [26]	Critical	Low	Serious	NA	Low	Moderate	Low	Low	85.7%
Rastan 2010 [27]	Critical	Low	Low	NA	Low	Moderate	Moderate	Low	85.7%
Santarpino 2015 [28]	Critical	Low	Low	NA	Moderate	Low	Low	Low	71.4%
Saxena 2015 [29]	Critical	Low	Low	NA	Low	Moderate	Moderate	Low	71.4%
Slottosch 2012 [30]	Critical	Low	Low	NA	Low	Low	Moderate	Low	100%
Slottosch 2017 [31]	Critical	Low	Low	NA	Moderate	Moderate	Moderate	Moderate	71.4%
Unosawa 2012 [32]	Critical	Low	Low	NA	Low	Moderate	Moderate	Low	57.1%
Wu 2010 [33]	Critical	Low	Critical	NA	Low	Low	Low	Low	57.1%
Zhong 2017 [34]	Critical	Critical	Low	NA	Low	Serious	Moderate	Critical	71.4%

*When multiple outcomes were reported for a study, the highest level of bias at the outcome level is reported in the table. Bias reported for comparison of peripheral vs central extracorporeal circulation and not for a study in general.

Studies were judged to be moderate to severe risk of bias as none previously compared directly outcomes of patients in different surgical baseline status; no signs of small/big study effect was seen on visual inspection of funnel plot for primary endpoint (Figure 2) yet marked asymmetry was present later confirmed by linear regression approach in Egger's test: $p=0.023$

Figure 2. Publication bias

Mortality

Twenty-two studies contributed data for analysis of 30-day/in-hospital mortality; overall, 1,537 of 2,235 patients died during investigated follow-up which translated to estimated event rate of 66.7% (63.3-69.9%) in random effects model (Figure 3A). In a meta-regression there was no sign that percentage of emergency/salvage cases has had any influence on the estimate: $\beta_{\text{coef}} = -0.343$; $P_{\text{slope}} = 0.406$ (Figure 3B and Figure 3C).

A

Figure 1. Overall mortality analysis following ECMO institution (A); Meta-regression analysis of overall mortality plotted against increasing percentage of emergency/salvage cases (B); Summary analysis of mortality vs percentage of emergency/salvage cases (C). HTx, heart transplantation; VAD, ventricle assist device.

Nor evidence on any differences between mortality in studies enrolling <50 vs ≥50% of emergency/salvage cases was found: respective event rates were 66.9% (63.1-70.4%) vs 64.4 (57.3-70.8%); $p=0.525$ (Figure 4).

Figure 4. Sensitivity analysis <50% emergency vs >50% emergency cases

Whenever available, single study estimates for respective subgroups (elective vs urgent vs emergency vs salvage) were extracted. Accordingly, there was again no difference in mortality rates across these patients' strata ($P=0.398$): pooled mortality was 65.1% (59.2-70.6%) in emergency subgroup, followed by 70.9% (54.6-83.2%) in elective stratum. There was 73.8% (55.3-86.5%) mortality after ECMO in urgent surgeries and 79.4% (59.3-91.1%) mortality in baseline salvage cases (Figure 5).

Figure 5. Analysis of mortality stratified according to number of cases in each baseline surgical status subgroup.

Detailed interaction-P values for between single subgroups comparisons are displayed in Figure 6.

Figure 6. Network of interactions between the subgroups.

Complications while on ECMO

Table 3 lists complications occurring in the included studies and also transfusion statistics. In a meta-regression, there was a significant positive association between increasing percentage of emergency/salvage cases across single included studies and rates of complications: among them, neurological complications ($p < 0.001$) (Figure 7), limb complications ($p < 0.001$) (Figure 8) and bleeding ($p = 0.051$) (Figure 9), were strongly associated with increasing percentage of emergency/salvage surgeries. Non-significant associations, albeit signals of increased incidence, were found for brain death ($p = 0.099$) (Figure 10) and sepsis ($p = 0.134$) (Figure 11).

Regression of Percentage (%) of emergency/salvage cases on Logit event rate

Figure 7. Neurologic complications

Table 3. Complications

Study (year) [reference]	Baseline status (elective/urgent/ emergency/salvage)	Neurological complications. N (%)	Brain death. N (%)	Limb complications. N (%)	AKI. N (%)	Sepsis. N (%)	Bleeding. N (%)	MOF. N (%)	Transfusions		
									RBC	FFP	PLT
Beckmann 2017 [e1]	NR/NR/3/NR	1 (12.5)	1 (12.5)	NR	4 (50.0)	2 (25.0)	3 (37.5)	1 (12.5)		NR	
Biancari 2017 [e2]	19/34/80/15	35 (23.6)	14 (9.5)	18 (12.2)	67 (45.3)	36 (24.3)	62 (41.9)	54 (36.5)	17±17	14±21	28±72
Doll N 2003 [e3]	21/64/10/0	9 (9.5)	NR	15 (15.8)	64 (67.4)	7 (7.4)	59 (62.1)	12 (12.6)	30±20		NR
Elsharkawy 2010 [e4]	NR/NR/84/NR	23 (9.9)	NR	NR	101 (43.3)	48 (20.6)	15 (6.4)	75 (32.2)		NR	
Guihaire 2017 [e5]	NR/NR/33/NR	3 (3.3)	NR	9 (9.8)	NR	12 (12.6)	18 (19.6)	41 (70.7)	12±1		NR
Khorsandi 2016 [e6]*	9/3/4/0	3 (18.8)	NR	2 (12.5)	3 (18.8)	2 (12.5)	2 (12.5)	1 (6.3)		NR	
Iazzara 1993 [e7]	1/6/4/0	NR	NR	NR	1 (9.1)	3 (27.3)	10 (90.9)	5 (45.5)	25±9	21±7	41±10
Magovern 1994 [e8]	0/11/10/0	6 (28.6)	4 (19.0)	1 (4.8)	1 (4.8)	NR	20 (95.2)	NR	28±5	21±7	40±15
Mikus 2013 [e9]	6/2/6/0	2 (14.3)	NR	NR	7 (50.0)	6 (42.9)	9 (64.3)	6 (42.9)	54±36	NR	18±9
Muehrcke 1996 [e10]	6/0/17/0	3 (13.0)	NR	12 (52.2)	12 (52.2)	7 (30.4)	12 (52.2)	5 (21.7)	43±22	10±12	59±40
Papadopoulos 2015 [e11]	NR/NR/NR/50	43 (11.9)	NR	47 (13.1)	220 (61.1)	NR	148 (41.1)	248 (69.0)		NR	
Pokersnik 2012 [e12]	NR/NR/0/0	3 (6.1)	NR	NR	16 (32.7)	NR	35 (71.4)	NR		NR	
Pontailier 2017 [e13]*	NR/NR/49/NR	5 (3.9)	NR	7 (5.5)	NR	NR	7 (5.5)	NR	4±5	1±1	3±4
Raffa 2017 [e14]	NR/NR/33/NR	17 (19.8)	8 (9.3)	9 (10.5)	26 (30.2)	18 (20.9)	40 (46.5)	NR		NR	
Rastan 2010 [e15]	159/122/205/31	90 (17.4)	NR	141 (27.3)	336 (65.0)	NR	300 (58.0)	NR	14±12	14±13	2±NR
Santarpino 2015 [e16]	0/0/0/20	8 (40.0)	NR	NR	7 (35.0)	NR	12 (60.0)	NR	80%	54%	43%
Saxena 2015 [e17]	35/6/4/0	4 (8.9)	0	8 (17.8)	20 (44.4)	11 (24.4)	7 (15.6)	13 (38.2)		NR	
Slottosch 2012 [e18]	NR/NR/29/NR	17 (22.1)	NR	16 (20.8)	53 (68.8)	19 (24.7)	26 (33.8)	NR	29±16	18±13	4±3
Slottosch 2017 [e19]*	NR/NR/37/0	34 (24.5)	5 (3.6)	17 (12.2)	92 (66.2)	32 (23.0)	50 (36.0)	NR	38±12	21±22	5±6
Unosawa 2012 [e20]	NR/NR/22/NR	10 (21.3)	4 (8.5)	12 (25.5)	15 (31.9)	NR	33 (70.2)	18 (38.3)		NR	
Wu 2010 [e21]	NR/NR/31/NR	NR	7 (6.4)	11 (10.0)	46 (41.8)	28 (25.5)	31 (28.2)	28 (25.5)		NR	
Zhong 2017 [e22]	NR/NR/9/NR	4 (11.1)	2 (5.6)	5 (13.9)	NR	5 (13.9)	15 (41.7)	7 (19.4)	13±10	10±4	2±1
Regression complication rate (%) vs emergency/non-emergency ratio: coefficient and p-value		$\beta_{\text{coef}} = 1.721$ $P_{\text{slope}} < 0.001$	$\beta_{\text{coef}} = 1.958$ $P_{\text{slope}} = 0.099$	$\beta_{\text{coef}} = 1.711$ $P_{\text{slope}} < 0.001$	$\beta_{\text{coef}} = -0.428$ $P_{\text{slope}} = 0.526$	$\beta_{\text{coef}} = -0.732$ $P_{\text{slope}} = 0.134$	$\beta_{\text{coef}} = -0.507$ $P_{\text{slope}} = 0.051$	$\beta_{\text{coef}} = -0.201$ $P_{\text{slope}} = 0.886$	NA		

* Reported for entire study population including non-PCS patients

AKI, acute kidney injury; RBC, redo blood cells; FFP, fresh frozen plasma; PLT, platelets; MOF, multi-organ failure; NR, not reported.

Regression of Percentage (%) of emergency/salvage cases on Logit event rate

Figure 8. Limb complications

Regression of Percentage (%) of emergency/salvage cases on Logit event rate

Figure 9. Bleeding

Regression of Percentage (%) of emergency/salvage cases on Logit event rate

Figure 10. Brain death

Regression of Percentage (%) of emergency/salvage cases on Logit event rate

Figure 11. Sepsis

Sensitivity analyses

In an analysis performed by deleting single studies, one at a time and repeating the calculations, no evidence was found that single study has influenced the overall estimate (cumulative analysis – Figure 12). Similarly, after exclusion of studies reporting results for both post-cardiotomy and non-PC indications for ECMO, neither direction nor magnitude of the estimates was altered.

Figure 12. Cumulative analysis.

Discussion

Use of ECMO, as one of increasing varieties of mechanical circulatory support strategies, has gained worldwide recognition in the treatment of cardiopulmonary failure and its use has dramatically increased over last 20 years [6]. Veno-Arterial (V-A) ECMO has been increasingly used for PC shock that 1) often precludes weaning from CPB while in the operating room, 2) onset of refractory single-ventricle or biventricular failure in the operating room after CPB or in the perioperative phase in ICU, or 3) as salvage procedure in the presence of cardiac arrest while in the operating room or ICU after surgery. The reported definition of PC shock also includes the use of a mechanical circulatory support at any point during the initial hospital stay [13]. Patients with PC shock are typically characterised by high pre-operative serum creatinine levels, previous MI, presence of left-main disease, LV dysfunction, history of coronary artery disease, redo operations and unstable clinical status [14]. Despite plethora of applications, relative ease of handling, and technical advancements in cannulation techniques [15], improved outcomes are still hard to come by with still unsatisfactory mortality rates. Indeed, a trend toward worse survival rates, reaching a disappointing 15% of in-hospital survival in the most recent series, has been recently described through an analysis of the Extracorporeal Life Support Organization registry [5].

Cardiac surgical patients usually present with substantial pre-ECMO comorbidities and more advanced age [16]. All these factors, individually or in association, may influence the capability of the myocardium to recover or hamper favorable body response to prolonged extracorporeal mechanical assistance [17]. Another obvious factor potentially influencing the prognosis after implantation of ECMO in the setting of PC cardiogenic shock used to patients' baseline status and urgency of index cardiovascular procedure [13]. Surprisingly, in the current meta-analysis we were not able to demonstrate that with increasing percentage of emergency high risk interventions, the in-hospital mortality rates were any higher. Conversely, the principal finding of the current meta-analysis is the strikingly similar rates of in-hospital mortality between patients at opposite baseline surgical status (e.g. elective vs salvage cases: 71% vs 59% mortality). This, in turn, implies that ECMO implantation in an otherwise elective case yet complicated by cardiogenic shock dramatically increases the mortality risk, in our analysis well beyond the mortality threshold for ECMO salvage cases. These results, in practice, reflect the findings of the previous single reports that however did not address this issue directly. Santarpino et al. [18] reports a registry of 11 European Centres in which 85 patients underwent salvage CABG: 20 of those required V-A ECMO in early postoperative period, and 8 (40%) survived to discharge. On the other hand, Saxena et al. [19] reports a series of 45 mainly valvular surgery (80% elective cases) patients treated with ECMO: 11 patients only were discharged accounting for 24% survival rate. Lastly, in a study by Biancari et al. [20], mortality among elective cardiac surgery patients reached 74% (14/19) as compared 66% (10/15) in salvage setting. Current meta-analysis as well did not demonstrate that higher mortality rates were associated with emergency/salvage cases throughout included series. In contrast, these were strongly associated with complication rates. Indeed, in the analysis, more neurologic and limb complications as well as more bleeding were seen in the emergency/salvage scenarios. While excess of bleeding complications can easily be explained by different coagulation profiles of emergency/salvage coronary patients that indeed constituted more than 40% of entire analysis population (e.g. failed PCI, prior GP IIB/IIIA administration, high thrombotic burden requiring additional heparin for ECMO run etc.), increased rates of neurologic complications is presumably a multifactorial entity with pre-ECMO illness severity and treatments, ECMO management, and post-ECMO events all contributing to cerebral injury in these patients. Loss of cerebral autoregulation during severe arterial hypertension or hypotension,

thromboembolic events, haemorrhage related to anticoagulation use, cerebral vasospasm, and secondary brain injury from reactive tissue oedema around an area of focal cerebral insult have all been implicated in the genesis of brain injury in V-A ECMO patients. Although neurologic injury during V-A ECMO remains poorly defined in adult cohorts [21-24], prior investigations comprehensively report neurologic complications occurrence in 6–17% in adults supported with V-A ECMO for PC cardiorespiratory failure [21,25,26]. Yet, post-mortem examination in adults supported with V-A ECMO has shown that neurologic injury may be clinically undetected in 23–50% of cases [27,28]. In a multi-center study of V-A ECMO instituted in 3,005 patients [30], neurologic complications occurred in 15.1% and included brain death in 7.9%, cerebral infarction in 3.6%, seizures in 1.8% and cerebral haemorrhage in 1.8% respectively. These events had a significant impact on hospital mortality with survival rate being 11% for those with neurologic deficits, as compared with 57% among those without ($p < 0.001$). In the current analysis, unexpectedly, we did not observe that higher burden of neurologic complications translated to higher mortality: in fact, Santarpino et al. [18] reports overall 60% mortality and 40% neurologic complications while Guihaire et al. [29] had lowest neurologic complications incidence (3.3%) yet reported mortality reached 63%. In line with the current analysis are the findings from the ELSO registry [30] pointing to neurologic complications being most common in patients supported with ECMO during CPR that in our analysis was proxy for salvage cases. Cerebral hypo- perfusion, hypoxia, and post-resuscitation reperfusion injury are frequently observed after CPR, and can result in irreversible brain injury [21,25,e23].

Limb complications incidence ranged from 5.5 to 52.2% in the current series; finding attributable to heterogeneous definition of limb complication that in some studies was defined as ischemia requiring amputation, and in others fasciotomy, or groin infections. Said that, all these complications derive from continuous ischemia to the cannulated limb; large arterial cannulas can be more difficult to place during emergency settings or vascular complications (dissection or other kind of vascular damage) and may be associated with increased incidence of limb ischemia due to distal vessel occlusion or hypoperfusion [e24]. There is some evidence in the literature that smaller arterial cannulas (15 Fr) may result in adequate cardiac support as well; as assessed through hemodynamic and laboratory parameters with a significant decrease in bleeding at the cannulation site [e25]. In the current study, principally due to lack of reported data we could not

address the role of distal perfusion cannula in reducing the incidence of distal leg ischemia. Neither whether cannulation technique and/or cannula sizes influenced the results in surgical subgroups strata. Indirectly however this was assessed in a recent meta-analysis by Raffa et al. [15] that compared peripheral vs central cannulation for ECMO institution and found the estimated benefit of peripheral setting for endpoints of bleeding ($p=0.01$), continuous veno-venous hemofiltration ($p=0.03$) and transfusions ($p<0.001$) unrelated to baseline patients' status.

Limitations

Certain limitations to the current meta-analysis must be acknowledged. Firstly, data were pooled from observational case series with all underlying biases and limitations; for many reasons, among them lack of any adjustments done in single studies, we could not account for differences between patients' risk profiles, treatments received, baseline characteristics and underlying conditions. Secondly, studies are compared on a "study" and not on "patient level", therefore any conclusions regarding individualized treatments and benefits from ECMO for individual patient have to be drawn with caution. Thirdly, as for any single-arm comparisons, this meta-analysis does not compare outcomes of ECMO institution at different baseline surgical risk scenarios directly; conversely this analysis was designed to give indirect insight to differences between subgroups and to assess whether these differences were meaningful from a statistical standpoint. It must be as well acknowledged that several studies reported emergency percentages alone and did not report salvage, elective and urgent cases distribution; these for liability purpose, were therefore not included in the detailed analyses (Figure 2). On the other hand, both subgroup analyses and meta-regressions performed, represent most conservative approach for outcomes comparison, and because calculated in random effects model, accounting for between study variations, the results are robust and justified.

Conclusions:

Other factors than baseline surgical status may, to a higher degree, influence the mortality in patients treated with ECMO for PC cardiogenic shock. Baseline status, however, strongly influences the complications while on ECMO which, anyhow, apparently did not impact ultimate 30-day/in-hospital outcome.

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CHAPTER 5

VENO-ARTERIAL EXTRACORPOREAL MEMBRANE OXYGENATION FOR POST-CARDIOTOMY SHOCK

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Aims

Use of veno-arterial (V-A) extracorporeal membrane oxygenation (ECMO) for post-cardiotomy cardiogenic shock (PCS) has increased worldwide recently. The aim was to report on trends in use of V-A ECMO for PCS.

Methods and Results

We analysed data from the Extracorporeal Life Support Organization (ELSO) registry regarding outcomes of V-A ECMO for PCS in adult patients from 1995 through 2018. The analyses examined trends in use, patient profiles, and in-hospital outcomes including complications. Predictors of in-hospital mortality were assessed by multivariate logistic regression. During the study period, 8,053 patients submitted to V-A ECMO for PCS were found in the ELSO Registry. There was a significant trend toward more ECMO use in recent years (coef.: 0.009; $p<0.001$). Mean age was 56.3 ± 14.9 years and significantly increased over time (coef.: 0.513; $p<0.001$). Most commonly, V-A ECMO was instituted after coronary artery bypass surgery (CABG) (26.8%) and valvular surgery (25.6%), followed by heart transplantation (20.7%). Overall, successful ECMO weaning occurred in 4,520 cases (56.1%), and survival to hospital discharge was achieved in 41.4% of cases. In-hospital mortality rates remained constant over time (coef.: -8.775; $p=0.682$). Kidney injury (36.8%), surgical site bleeding (27.2%), cardiac arrhythmias (16.3%), sepsis (11.4%), metabolic disorders (12.9%) and neurologic complications (4.3%), were the most common adverse events. Reduced complication rates were observed in recent years (coef.: -0.009; $p=0.003$). Higher mortality was observed after CABG (53.8%), combined CABG with valve (59.0%), and vascular aortic (66.3%) procedures than other indications. Better survival rates were observed in heart transplantation recipients. Age, central cannulation and occurrence of complications while on ECMO were independently associated with poorer prognosis.

Conclusions

Analysis of adult patients supported on V-A ECMO for PCS reported to the ELSO registry demonstrated significantly increased use from 1995 through 2018. Mortality rates remained relatively constant over time despite a decrease in complications, in the setting of supporting older, higher risk patients.

Introduction

Veno-arterial extracorporeal membrane oxygenation (V-A ECMO) represents a well-established life-saving procedure for refractory acute cardiac or cardiorespiratory insufficiency [1,2]. Its use in the setting of post-cardiotomy cardiogenic shock (PCS) has increased in recent years, despite high associated mortality [3,4]. Severity of the patients' underlying disease together with extracorporeal circulation predisposes to complications, which combine to negatively impact survival. Indeed, recent reports have shown that V-A ECMO has increased exponentially for the treatment of PCS, yet survival rates to discharge have decreased [5]. Potential explanations for this include wider access to ECMO devices, expanded inclusion criteria, as well as offering ECMO as a last resort to patients who would have otherwise died due to postoperative complications.

Indeed, V-A ECMO for PCS has represented the main indication for ECMO use in many institutions and differs from other applications of ECMO in several respects. Patients managed with PCS V-A ECMO have different complexity of underlying diseases, severity of comorbidities, indication and type of surgical procedures, modality of access and timing of implantation, and complication types and rates, when compared with other indications for ECMO [6,7]. Limited experience in these procedures, particularly in centers without well-established ECMO programs, may impact patient outcomes. Together, these factors influence ECMO management and outcomes in PCS patients and make this particular indication at high risk for unfavorable results.

Due to the increased use, complex patient management and resource intensity of PCS-related ECMO, careful evaluation of patient attributes, complication rates and in-hospital outcomes across a large accumulated experience, should meaningfully inform the role of ECMO in this setting. Furthermore, trends in these outcomes assessed over the past 3 decades may also provide insights that could improve results, or suggest areas of focus for prospective research and clinical practice change to yield the greatest impact on patient outcomes. We utilized a robust patient registry reflecting the initial efforts at PCS V-A ECMO to the present day, focusing on patient characteristics and outcomes.

Methods

The ELSO registry is a voluntary registry with more than 420 centers worldwide contributing data, including information on pre-ECMO implant patient profile, use, complications, and in-hospital outcomes in adults and children undergoing temporary ECMO support [5,8]. Information present in the ELSO registry from January 1, 1995, through December 31, 2018 was analyzed. Data were collected using a standardized data reporting sheet, including patient demographics, pre-ECMO diagnoses and comorbidities, hemodynamic and laboratory information prior to and during ECMO, perioperative complications, and survival to hospital discharge. Patient diagnoses were reported using the International Classification of Diseases, 9th and 10th Edition codes. In this registry, indications for ECMO support are categorized as “cardiac,” “respiratory,” or “extracorporeal cardiopulmonary resuscitation” (ECPR).

Study Population

Data on patients more than 18 years old undergoing a single run V-A ECMO for refractory PCS were extracted. Indications for ECMO consisted of intra-operative failure to wean from cardiopulmonary bypass (CPB) due to right, left or biventricular failure, and post-operative refractory cardiogenic shock or cardiac arrest during the hospitalisation after the surgical procedure. Patients with pre-operative ECMO were excluded from the analysis, as were subsequent ECMO runs in patients undergoing more than one ECMO run. IRB approval was waived due to the retrospective design of the study and anonymous patient records in the registry. Informed consent was obtained as per regulations in the participating centers.

Main Goals and Definitions

We aimed to describe the trends of V-A ECMO for PCS, including perioperative morbidity as well as mortality, specifically attempting to identify factors associated with in-hospital mortality. All complications were categorized using ELSO registry complication codes and included the following: 1) limb complications, 2) central nervous system complications, 3) bleeding complications, 4) kidney injury, and 5) sepsis. These categories were then further subdivided, as appropriate. We declared post-operative: cardiopulmonary resuscitation, cardiac tamponade, disseminated intravascular coagulation, gastrointestinal bleeding, mediastinal bleeding, culture-proven sepsis, limb amputation or fasciotomy for ischemia, pump or oxygenator failure, severe hemolysis, brain

death, diffuse brain ischemia or hemorrhage, pulmonary hemorrhage and renal replacement therapy as major complications.

Statistical analysis

We compared in-hospital survivors and non-survivors and used the Shapiro–Wilk test for testing of normality of continuous variables. All variables were analyzed with descriptive and frequency analysis. Variables with missing data in more than 5% of the patients were excluded from analysis. The χ^2 and Fisher exact tests were used to compare group differences for categorical variables. Continuous variables were analyzed using the Mann–Whitney U test and were reported as means with standard deviations (SDs) or as medians with interquartile ranges (IQRs). Complications occurring in both groups are reported as number (%) with corresponding odds ratios (OR) and 95% confidence intervals (95%CI). $p < 0.05$ was considered a significant difference between the groups. The Storey–Tibshirani multiple testing correction was used [9]. Variables that achieved $p < 0.2$ in the univariate analysis were examined by using multivariate analysis with forward stepwise logistic regression to evaluate independent risk factors for hospital mortality. The performance of the multivariate model in predicting mortality was assessed by calculating a c-statistic for discrimination and by the Hosmer–Lemeshow goodness-of-fit statistics for calibration. Missing data were addressed with artificial neural networks up to 5%. All statistical tests were performed in STATA MP version 13.0 software (StataCorp, College Station, TX).

Results

During the study period, 8,053 patients received V-A ECMO for PCS. Figure 1 demonstrates the trend in the number of patients initiated on V-A ECMO for PCS from the ELSO database with corresponding annual mortality rates. While there was a significant increase in the number of ECMO for PCS cases in recent years (coef.: 0.009; $p < 0.001$), the mortality rate did not change significantly over time (coef.: -8.775; $p = 0.682$) (Figure 1). The mean age was 56.3 ± 14.9 years (range, 18–86 years); patient distribution across age strata was evenly maintained. Yet, a significant trend (coef.: 0.444; $p < 0.001$), for increasing average age was observed (Figure 2).

Figure 1. Annual trend in the number of patients undergoing V-A ECMO and in-hospital mortality.

Figure 2. Trends in average age and major complications during ECMO: cardiopulmonary resuscitation, cardiac tamponade, disseminated intravascular coagulation, gastrointestinal bleeding, mediastinal bleeding, culture-proven sepsis, limb amputation or fasciotomy for ischemia, pump or oxygenator failure, severe hemolysis, brain death, diffuse brain ischemia or hemorrhage, pulmonary hemorrhage and renal replacement therapy. ECMO, extracorporeal membrane oxygenation; SD, standard deviation.

All pre-operative patient characteristics and details about cardiac disease are shown in Table 1.

Table 1. Patient characteristics

Variable	Total (n=8,053)	In-hospital survivors (n=3,337)	In-hospital non-survivors (n=4,716)	p-value
Mean age, years				
18-38	1,169 (14.5)	638 (54.6)	531 (45.4)	<0.001
39-52	1,691 (21.0)	778 (46.0)	913 (54.0)	
53-62	2,194 (27.2)	917 (41.8)	1,277 (58.2)	
63-70	1,583 (19.7)	555 (35.1)	1,028 (64.9)	
>=71	1,416 (17.6)	449 (31.7)	967 (68.3)	
Gender				
Male	5,411 (67.2)	2,339 (43.2)	3,072 (56.8)	<0.001
Female	2,641 (32.8)	997 (37.8)	1,644 (62.2)	
Race				
White	4,797 (59.6)	1,973 (41.1)	2,824 (58.9)	0.039
Black	667 (8.3)	298 (44.7)	369 (55.3)	
Asian	1,335 (16.6)	580 (43.4)	755 (56.6)	
Hispanic	403 (5.0)	148 (36.7)	255 (63.3)	
Other	850 (10.6)	337 (39.6)	513 (60.4)	
Diabetes melitus	718 (8.9)	273 (38.0)	445 (62.0)	0.028
Dyslipidemia	495 (6.1)	168 (33.9)	327 (66.1)	<0.001
Chronic obstructive pulmonary disease	107 (1.3)	37 (34.6)	70 (65.4)	0.088
Obstructive sleep apnea	143 (1.8)	46 (32.2)	97 (67.8)	0.014
Chronic kidney disease	476 (5.9)	158 (33.2)	318 (66.8)	<0.001
Atrial fibrillation	706 (8.8)	309 (43.8)	397 (56.2)	0.101
STEMI*	460 (5.7)	189 (41.1)	271 (58.9)	0.459
Pulmonary hypertension	338 (4.2)	127 (37.6)	211 (62.4)	0.341
Previous heart surgery	339 (4.2)	147 (43.4)	192 (56.6)	0.247
Bacterial endocarditis	163 (2.0)	78 (47.9)	85 (52.1)	0.055
Cancer diagnosis	104 (1.3)	33 (31.7)	71 (68.3)	0.026

*Last 90 days

STEMI, ST-segment elevation myocardial infarction

Most commonly, patients were managed on ECMO for PCS after coronary artery bypass surgery (CABG) (26.8%) and valvular surgery (25.6%), followed by heart transplantation (20.7%), combination surgeries, such as CABG with valve (13.4%), and ventricular assist devices (8.5%).

ECMO implantation and weaning details are shown in Table 2. Table 2 also lists blood gases and hemodynamic variables at ECMO implantation and 24-hours following implantation. The most frequent indication for V-A ECMO in this cohort was failure to wean from cardiopulmonary bypass. Most ECMO access was achieved by peripheral cannulation (53.5%) followed by central cannulation (46.5%); the combination of central arterial and peripheral venous cannulation were pooled as central cannulation strategies. Concomitant intra-aortic balloon pumps (IABP) were used in 31.8% of the patients.

Table 2. Pre-ECMO information and support details

Variable	Total (n=8,053)	In-hospital survivors (n=3,337)	In-hospital non-survivors (n=4,716)	p-value
Pre-ECMO suport				
IABP	2,563 (31.8)	1,031 (40.2)	1,532 (59.8)	0.070
CPB	3,757 (46.7)	1,487 (39.6)	2,270 (60.4)	0.001
Nitric oxide	899 (11.2)	372 (41.4)	527 (58.6)	0.502
Pacemaker	840 (10.4)	293 (34.9)	547 (65.1)	<0.001
Inotropes	3,882 (48.2)	1,496 (38.5)	2,386 (61.5)	<0.001
LVAD	537 (6.7)	236 (43.9)	301 (56.1)	0.119
Pre-ECMO arterial blood gases				
pH	7.3 ± 0.1	7.31 ± 0.13	7.28 ± 0.15	<0.001
PCO ₂ (mmHg)	42.5 ± 20.2	41.9 ± 19.4	42.9 ± 20.7	0.078
Oxygen partial pressure (mmHg)	170.5 ± 135.2	173.7 ± 136.7	168.2 ± 134.1	0.123
Bicarbonate levels mEq/L	20.5 ± 5.8	21.2 ± 5.6	20 ± 5.9	<0.001
SaO ₂ (%)	92.8 ± 12.1	93.6 ± 10.7	92.2 ± 13.1	<0.001
Ventilator settings (pre-ECMO)				
Respiratory rate (/min)	16.1 ± 6.2	15.8 ± 6.0	16.4 ± 6.4	0.003
FiO ₂ (%)	81.62 ± 23.44	81 ± 23.8	82.1 ± 23.2	0.107
PIP (cm H ₂ O)	25.86 ± 8.27	24.7 ± 8	26.7 ± 8.4	<0.001
PEEP (cm H ₂ O)	7 ± 4.2	6.8 ± 3.6	7.2 ± 4.6	0.002
Mean AP	15.9 ± 11.6	15.5 ± 11.8	16.2 ± 11.5	0.135
Ventilator settings (24 hours)				
Respiratory rate (/min)	12.5 ± 4.6	12.2 ± 3.9	12.7 ± 5	<0.001
FiO ₂ (%)	50.1 ± 18.9	48.6 ± 17.4	51.4 ± 20	<0.001
PIP (cm H ₂ O)	24 ± 6.5	22.8 ± 5.7	24.8 ± 6.9	<0.001
PEEP (cm H ₂ O)	7.5 ± 3.4	7.4 ± 3.3	7.6 ± 3.4	0.032
Mean AP	14.3 ± 12.1	14.1 ± 12.5	14.5 ± 11.8	0.344
Pre-ECMO hemodynamics				
SBP (mmHg)	81.6 ± 26.5	83.4 ± 24.9	80.2 ± 27.6	<0.001
DBP (mmHg)	50.0 ± 17.0	51.8 ± 15.9	48.6 ± 17.6	<0.001
Mean arterial pressure (mmHg)	60.3 ± 18.5	62.6 ± 17.3	58.6 ± 19.2	<0.001
Venous oxygen saturation (%)	60.5 ± 17.3	60.8 ± 17.1	60.3 ± 17.5	0.597
Hours on ECMO				
Mean (hours)	140.9 ± 158.2	134.9 ± 143.7	145.1 ± 167.7	0.003
0-41	1,654 (20.5)	488 (29.5)	1,166 (70.5)	<0.001
42-88	1,831 (22.7)	872 (47.6)	959 (52.4)	
89-161	2,270 (28.2)	1,111 (48.9)	1,159 (51.1)	
>161	2,297 (28.5)	865 (37.7)	1,432 (62.3)	
Cannulation				
Peripheral	4,307 (53.5)	1,942 (45.1)	2,365 (54.9)	<0.001
Central	3,745 (46.5)	1,394 (37.2)	2,351 (62.8)	

ECMO, extracorporeal membrane oxygenation; IABP, intra-aortic balloon pump; CPB, cardiopulmonary bypass; LVAD, left ventricle assist device; PCO₂, partial pressure of carbon dioxide; SaO₂, oxygen saturation; FiO₂, fraction of inspired oxygen; PiP, peak inspiratory pressure; PEEP, positive end-expiratory pressure; AP, airway pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure.

Patients were maintained on ECLS for a median duration of 140.9±158.2 hours, with 134.9±143.7 hours for in-hospital survivors, and 145.1±167.7 hours for non-survivors (p=0.003). Overall, successful ECMO weaning was possible in 4,520 cases (56.1%). However, survival to hospital discharge was achieved in 41.4% of cases.

The use of PCS-ECMO was associated with numerous complications (Table 3).

Table 3. Complications during ECMO

Complications*	Total (n=8,053)	In-hospital survivors (n=3,337)	In-hospital non-survivors (n=4,716)	p-value
Limb complications				
Ischemia	312 (3.9)	88 (28.2)	224 (71.8)	<0.001
Limb compartment syndrome	106 (1.3)	24 (22.6)	82 (77.4)	<0.001
Fasciotomy**	143 (1.8)	37 (25.9)	106 (74.1)	<0.001
Amputation**	44 (0.5)	22 (50.0)	22 (50.0)	0.158
Hematologic/bleeding				
DIC**	238 (3.0)	42 (17.6)	196 (82.4)	<0.001
Hemolysis**	382 (4.7)	109 (28.5)	273 (71.5)	<0.001
Surgical site bleeding	2,187 (27.2)	733 (33.5)	1,454 (66.5)	<0.001
Cannulation site bleeding	130 (1.6)	38 (29.2)	92 (70.8)	0.003
Cardiac tamponade**	653 (8.1)	220 (33.7)	433 (66.3)	<0.001
GI bleeding**	322 (4.0)	79 (24.5)	243 (75.5)	<0.001
Neurologic				
Diffuse ischemia** confirmed by US/CT/MRI	7 (0.1)	1 (14.3)	6 (85.7)	0.141
Hemorrhage** confirmed by US/CT/MRI	129 (1.6)	13 (10.1)	116 (89.9)	<0.001
Infarction confirmed by US/CT/MRI	350 (4.3)	83 (23.7)	267 (76.3)	<0.001
Intra/extra parenchymal Hemorrhage** confirmed by US/CT/MRI	19 (0.2)		19 (100.0)	<0.001
Intraventricular hemorrhage ** confirmed by US/CT/MRI	7 (0.1)		7 (100.0)	0.024
Neurosurgical intervention performed	1 (0.0)		1 (100.0)	0.586
Seizures: confirmed by EEG	38 (0.5)	9 (23.7)	29 (76.3)	0.017
Seizures: clinically determined	98 (1.2)	26 (26.5)	72 (73.5)	0.001
Brain death**	239 (3.0)		239 (100.0)	<0.001
Sepsis				
Culture-proven infection**	918 (11.4)	349 (38.0)	569 (62.0)	0.014
Kidney failure				
sCr 1.5-3	1,834 (22.8)	661 (36.0)	1,173 (64.0)	<0.001
sCr >3	857 (10.6)	234 (27.3)	623 (72.7)	<0.001
CRRT**	2,965 (36.8)	816 (27.5)	2,149 (72.5)	<0.001
Cardiovascular				
Cardiac arrhythmia	1,311 (16.3)	438 (33.4)	873 (66.6)	<0.001
CPR required**	253 (3.1)	42 (16.6)	211 (83.4)	<0.001
Hypertension requiring vasodilators	271 (3.4)	137 (50.6)	134 (49.4)	0.001
Inotropes on ECMO	3,859 (47.9)	1,471 (38.1)	2,388 (61.9)	<0.001
Metabolic				
Glucose < 40	125 (1.6)	4 (3.2)	121 (96.8)	<0.001
Glucose > 240	950 (11.8)	407 (42.8)	543 (57.2)	0.183
Hyperbilirubinemia	1,040 (12.9)	275 (26.4)	765 (73.6)	<0.001
pH < 7.20	692 (8.6)	117 (16.9)	575 (83.1)	<0.001
pH > 7.60	279 (3.5)	134 (48.0)	145 (52.0)	0.014
Pulmonary				
Pulmonary hemorrhage**	210 (2.6)	56 (26.7)	154 (73.3)	<0.001

*Complications with their pertinent definitions are listed in the supplement

**Declared as major complications

DIC, disseminated intravascular coagulation; GI, gastrointestinal; US, ultrasound; CT, computed tomography; MRI, magnetic resonance imaging; EEG, electroencephalogram; sCr, serum creatinine; CRRT, continuous renal replacement therapy; CPR, cardiopulmonary resuscitation; ECMO, extracorporeal membrane oxygenation.

Notwithstanding, the number of patients with major complications decreased in recent years (coef.: -0.009; $p=0.003$; Figure 2). Overall, surgical site bleeding, sepsis, cardiac arrhythmias, kidney injury with or without the need for renal replacement therapy, metabolic disorders and neurologic complications were the most common.

When stratified by the type of primary surgery, a higher mortality was observed after CABG (53.8%), combined CABG with valve (59.0%), and vascular aortic (66.3%) procedures than other indications. (Figure 3).

Figure 3. Analysis of in-hospital mortality stratified by the type of primary surgery. CABG, coronary artery bypass grafting; HTx, heart transplantation; VAD, ventricle assist device.

Conversely, survival rates among patients requiring V-A ECMO following heart transplantation were nearly twice as high as non-survival accounting for a crude rate of 64.4%. Multivariate logistic regression analysis demonstrated that older age was significantly associated with in-hospital mortality (Table 4).

Table 4. Multivariate predictors of death at discharge (binary logistic regression)

Variable	OR	Lower CI	Upper CI	P-value
Age	1.020	1.017	1.024	<0.001
Weight	1.005	1.003	1.007	<0.001
Gender (male)	0.681	0.610	0.761	<0.001
Peripheral cannulation	0.729	0.660	0.806	<0.001
Arrhythmias	1.151	1.002	1.320	0.046
DIC	2.534	1.767	3.635	<0.001
GI bleeding	1.650	1.254	2.173	<0.001
Hemolysis	1.335	1.043	1.706	0.022
Surgical site bleeding	1.308	1.167	1.465	<0.001
Limb ischemia	1.657	1.260	2.180	<0.001
Hypoglycemia (<40mg/dL)	13.327	4.833	36.750	<0.001
Pulmonary hemorrhage	1.695	1.217	2.359	0.002
sCr >3	1.430	1.199	1.706	<0.001
CRRT	2.289	2.052	2.554	<0.001
Bicarbonate	1.361	1.188	1.560	<0.001
Dobutamine	0.859	0.752	0.982	0.026
Levosimendan	3.292	1.185	9.147	0.022
Vasopressors	1.106	1.003	1.220	0.044
CABG	1.170	1.040	1.317	0.009
Heart transplantation	0.626	0.539	0.727	<0.001
Aortic surgery	1.363	1.083	1.715	0.008

OR, odds ratio; CI, confidence interval; DIC, disseminated intravascular coagulation; GI, gastrointestinal; sCr, serum creatinine; CRRT, continuous renal replacement therapy; CABG, coronary artery bypass grafting.

In particular, of 1,416 patients over 70 years of age, 68.3% (967) did not survive to discharge ($p<0.001$; Table 1). Additionally, malignant arrhythmias, cardiac tamponade, disseminated intravascular coagulation, gastrointestinal bleeding, hemolysis, and surgical complications, were all associated with worse prognosis. Interestingly, peripheral cannulation was shown in the multivariate model to be associated with lower in-hospital mortality (Table 4 and Figure 4) and lower rates of surgical site bleeding complications (Figure 5). Hosmer-Lemeshow of the constructed multivariate model with $p=0.678$ with a c-statistic of 0.703 (95% CI, 0.692-0.715).

Discussion

Change in trends of V-A ECMO use

The use of temporary mechanical circulatory support including V-A ECMO is increasing but is often used as a last resort for patients who might otherwise die [3,4]. In United States, PCS and shock complicating ST-elevation myocardial infarction (MI) were the two most frequent indications for V-A ECMO implantation until 2012 [10].

The European and American Societies of Cardiology guideline recommendations assigned ECMO the class recommendation IIb, level of evidence C, for the management of cardiogenic shock in STEMI [11].

Figure 4. Analysis of trends in institution of V-A ECMO via peripheral cannulation and annual mortality rates.

Figure 5. Analysis of trends in institution of V-A ECMO via peripheral cannulation and rates of bleeding complications

Despite the above, and also growing worldwide utilization and experience, in-hospital ECMO outcomes have not shown substantial improvement [6,10]. Little is still known of who benefits most from ECMO, not to mention the cost-effectiveness of such a resource-intense therapy [4]. The inherent features of ECMO in terms of quick availability, relative ease of application in expert centers and reliability, have made it an attractive option, particularly in the post-cardiotomy setting [1,2]. In contrast, although the use of implantable or para-corporeal ventricular assist devices (VAD), either uni- or biventricular, has been applied in these circumstances, their complexity, lack of associated lung support, cost, and limited availability, have hampered their wider application, making V-A ECMO the most frequent temporary mechanical circulatory support in these circumstances [12].

Numerous publications have shown ECMO-related short- and medium-term outcomes [2,3]. However, specific reports about post-cardiotomy ECMO in acquired and congenital cardiac surgery patients, have been limited and usually report single center results only [13-15]. The characteristics of ECMO implantation (patient profiles, surgical access or location of implantation, timing of application, and duration of support), complications, and outcomes in the post-cardiotomy ECMO setting are different than in other applications of ECMO [16-21].

Change in patients risk profile

In addition, cardiac surgical patients are often characterized by substantial pre-ECMO comorbidities and more advanced age than in other ECMO populations [22,23]. Each of these factors, either individually or collectively, may influence the capability of the myocardium to recover from prolonged extracorporeal mechanical assistance. In some patients, the mechanical support does not facilitate improved cardiac function or organ integrity, and clinicians may therefore be forced to bridge the patient toward more advanced treatments, such as heart transplantation or long-term ventricular assist devices (VADs). The insights from important recently available studies are that prolonging V-A ECMO duration is associated with an increased mortality at early and later stages [24]. In fact, lack of cardiac function improvement within 7 days post-operatively may indicate reduced likelihood of recovery and prolonged support might favour the occurrence of complications with ominous prognosis. Notably, a trend towards worsened survival rates, reaching a low of 15% in 2016 was recently reported in another analysis of the ELSO registry, including both adult and pediatric patients [6]. Similarly, the largest report to date

on MCS use after cardiac surgery demonstrated a steadily increasing trend in non-intra-aortic balloon pump mechanical circulatory support use. However, the mortality rates were higher in recent years [4]. According to Flecher et al, [25] who included post-cardiotomy patients in their analysis, worse outcomes among post-cardiotomy ECMO patients was clearly demonstrated. Although this may be due, at least in part, to more widespread application of this technology to higher risk patients, this underlines the high complexity of PCS-ECMO patients.

Change in mortality

Our study demonstrates a trend toward an increasing number of ECMO procedures in recent years (coef.: 0.009; $p < 0.001$), yet no signs of increased mortality rates over time (coef.: -8.775; $p = 0.682$) were observed when looking only at the adult population. In the largest study to date assessing in-hospital and long-term survival after ECMO for PCS [14], overall successful weaning from ECMO was possible for 63.3% of the patients, but more than 50% of the weaned patients died during their hospital stay, with in-hospital survival ~~was~~ therefore limited to 25%. This findings was comparable to results of smaller series of patients with PCS undergoing ECMO for which early survival rates of between 16% and 41% have been reported [26,27]. In line with previous reports, in the current analysis, overall successful ECMO weaning was possible in 4,520 cases (56.1%), yet survival to hospital discharge was achieved in 41.4% of cases. The trend suggesting overall unchanging mortality over time might be surprising in the face of improvements in intensive care unit management, more advanced ECMO circuit components and novel technologies, as well as increased experience. On the other hand, these improvements may not directly translate to mortality reduction if they are being offset by the application of V-A ECMO for PCS in older and sicker patients. This hypothesis is supported by our finding that nearly two-thirds of patients included in the ELSO registry could be successfully weaned from ECMO despite increases in risk scores, patient age, and the complexity of the cardiac procedures.

Change in survival prediction

Prediction of post-cardiotomy ECMO weaning and survival has been addressed by numerous investigators [1,2,24-27]. Pre-implantation and intra-operative factors, as well as post-ECMO events and the patient's physiologic response to circulatory support, all play a critical role. Among pre-ECMO factors, ECPR, that is, ECMO institution during a cardiac arrest, was a strong negative predictor in several series [28-33]. Nevertheless, some investigators found that neither the occurrence of cardiopulmonary resuscitation nor the time spent in resuscitation had a significant effect on survival. The current analysis, which employed logistic regression to search for mortality predictors, demonstrated that age, duration of support, pH, and ventilation parameters, were all significantly associated with poor prognosis. Additionally, so were malignant arrhythmias, cardiac tamponade, disseminated intravascular coagulation, gastrointestinal bleeding, hemolysis and surgical complications. The impact of patient age on survival requires a distinct discussion in the context of post-cardiotomy ECMO, as many patients eligible for such support are elderly. Narotsky et al. [34], in an analysis of patients older than 65, all with refractory cardiopulmonary failure supported by ECMO, found survival to discharge and at one year, to be 30%. When the analysis was adjusted for confounders, however, age turned out not to be statistically significant as a predictor for in-hospital death, although a trend for increased risk was present. In this analysis of the ELSO registry, of 1,416 patients over age 70, 68.3% (967) did not survive to discharge ($p < 0.001$).

Benefits of peripheral access

Interestingly, the current report is the first to demonstrate the protective effect of peripheral cannulation for ECMO on survival. Patients undergoing ECMO for PCS had over 25% higher odds of survival compared to their centrally cannulated counterparts. This finding is partially in accordance with one recent meta-analysis [20] that analyzed 1,691 patients for direct comparison of peripheral and central cannulation in PCS and non-PCS patients. While all-cause mortality was unaltered with either technique, the risk of serious complications, that is bleeding, continuous veno-venous hemofiltration, and blood product transfusion, was significantly lower with the peripheral cannulation strategy. With a nearly five-fold higher number of patients in the current single report and focusing exclusively on PCS, the finding of significantly lower mortality rates with peripheral cannulation appears to be a robust finding.

Limitations

We analysed data from the ELSO Registry, an international collaboration with more than 400 contributing centers. The size of the dataset and inclusion of all PCS-ECMO criteria support the concept that generalizable conclusions may be inferred. The current analysis is, however, limited by the inherent shortcomings of registry data. Gathered data are of retrospective nature; selection criteria, V-A ECMO protocols, patient management and also skills, education and centers' ECMO experience and volume could not be accounted for in the analysis. The registry collects in-hospital data only, therefore long-term follow-up data and in particular survival and neurological sequelae were not available. The registry does not collect data on surgical and procedural characteristics other than the type of surgery. Whether the surgery was elective or emergent, the duration of cross-clamp and cardiopulmonary bypass, episodes of hypotension or arrhythmias during the surgery, could all impact the postoperative course. Finally, the current ELSO definitions were implemented recently and older data did not adhere to strict data definitions. Since mechanical circulatory support was earlier demonstrated to reduce the mortality rates in PCS to 50% (58.6% in the current series), equipoise to conduct a randomized trial in this setting would be lacking. In absence of randomized evidence, the current analysis represents the largest to date for heart surgery patients requiring postoperative V-A ECMO.

Conclusions

Analysis of patients managed on V-A ECMO for PCS reported to the ELSO registry demonstrated significantly increased use from 1995 through 2018. Mortality rates remained relatively constant over time despite a decrease in complications, in the setting of supporting older, higher risk patients. Further studies are needed to elucidate factors that might optimize patient selection and improve the outcomes of this very complex cohort of ECMO patients.

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CHAPTER 6

THE IMPACT OF CENTRE'S HEART TRANSPLANT STATUS AND VOLUME ON IN-HOSPITAL OUTCOMES FOLLOWING EXTRACORPOREAL MEMBRANE OXYGENATION FOR REFRACTORY POST-CARDIOTOMY CARDIOGENIC SHOCK: A META-ANALYSIS

Kowalewski M, Raffa GM, Zieliński K, Pilato M, Alanazi M, Gilbers M, Heuts S, Natour E, Bidar E, Schreurs R, Delnoij T, Driessen R, Sels JW, van de Poll M, Roekaerts P, Meani P, Suwalski P, Lorusso R.

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Background: Postcardiotomy cardiogenic shock (PCS) that is refractory to inotropic support remains a major concern in cardiac surgery and is almost universally fatal unless treated with mechanical support. While reported mortality rates on ECMO vary from center to center, aim of the current report is assess if the outcomes differ between centres according to volume and heart transplantation status.

Methods: A systematic search was performed according to PRISMA statement using PubMed/Medline databases between 2010 and 2018. Relevant articles were scrutinized and included in the meta-analysis only if reporting in-hospital/30-day mortality and heart transplantation status of the centre. Paediatric and congenital heart surgery-related studies along with those conducted in the setting of veno-venous ECMO for respiratory distress syndrome were excluded. Differences were assessed by means of subgroup meta-analysis and meta-regression.

Results: Fifty-four studies enrolling N=4,421 ECMO patients were included. Of those, 6 series were performed in non-HTx centres (204 pts;4.6%). Overall 30-day survival (95% Confidence Intervals) was 35.3% (32.5-38.2%) and did not statistically differ between non-HTx: 33.3% (26.8-40.4%) and HTx centres: 35.7% (32.7-38.8%); $P_{\text{interaction}}=0.531$. There was no impact of centre volume on survival as well: $\beta_{\text{coef}}=0.0006$; $P=0.833$. No statistical differences were seen between HTx and non-HTx with respect to ECMO duration, limb complications, reoperations for bleeding, kidney injury and sepsis. There were however significantly less neurological complications in the HTx as compared to non-HTx centres: 11.9% vs 19.5% respectively; $P=0.009$; an inverse relationship was seen for neurologic complications in centres performing more ECMOs annually $\beta_{\text{coef}}=-0.0066$; $P=0.031$. Weaning rates and bridging to HTx and/or VADs were higher in HTx facilities.

Conclusions: There was no apparent difference in survival after ECMO implantation for refractory PCS according to centre's ECMO volume and transplantation status. Potentially different risk profiles of patients in these centres must be taken account for before definite conclusions are drawn.

Background

Extracorporeal Membrane Oxygenation (ECMO) use is increasing; yet, it still does represent a resource-consuming modality of treatment and, in majority of cases, is seen as a last resort for patients who, otherwise, would inevitably die [1-5]. Postcardiotomy- and ST-elevation myocardial infarction (MI) complicating- cardiogenic shock (CS) were two most frequent indications for VA-ECMO implantation in the United States until 2011 [3-5]. Despite growing worldwide utilization and experience in mechanical circulatory support (MCS), in particular, in-hospital outcomes while on ECMO have not shown substantial progress [6]. While little is still known on who benefits most from ECMO support which is a long and advanced therapy [7], European Society of Cardiology guidelines cautiously assigned ECMO class of recommendation IIb, level of evidence C for the management of cardiogenic shock in STEMI [8].

Unlike STEMIs, cardiac surgical patients are usually characterized by substantial pre-ECMO comorbidities and more advanced age [9]. All these factors, individually or in association, may inhibit the potential of myocardium to recover after the surgery and/or hamper favorable body response to prolonged MCS. Indeed, in some patients, prolonged MCS does not lead to improved cardiac function or organ integrity; clinicians are therefore forced to bridge the patient; since bridge to recovery is no longer an option, more advanced treatments, such as heart transplantation (HTx) or long-lasting ventricular assist devices (VADs) remain. Not all heart surgery centres perform HTx, and not all of them perform VADs.

We therefore, undertook systematic review and meta-analysis to assess to which extent do the in-hospital outcomes differ across PCS-ECMO recipients in heart transplantation- as compared to non-transplant units to which could be attributed to readability of ECMO teams and potentially shorter bridging times in HTx/VAD units. To assess the impact of possible differences in experience between centres, we analyzed how the in-hospital outcomes are affected by centre's volume and annual ECMO institution rates.

Methods

Data sources and search strategy

This systematic review and meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic Reviews and meta-analyses (PRISMA) statement [10]. The PRISMA checklist is available as Appendix. To best reflect current clinical practice, relevant studies to be included were searched for between year 2000 until March 31st 2018, through PubMed, EMBASE, CINAHL, the Web of Science, the Cochrane Register of Controlled Clinical Trials (CENTRAL) and Google Scholar. Abstracts were eligible for detailed assessment if available online and reporting outcomes of interest. The search term was: “extracorporeal membrane oxygenation” and “extracorporeal life support”. No language restrictions were imposed. References of original articles were reviewed manually and cross-checked for other relevant reports.

Selection criteria and quality assessment

Studies were included if they met all of the following criteria: 1) human study; 2) studies assessing survival after ECMO instituted for postcardiotomy refractory cardiogenic shock; 3) study reporting institutional outcomes that for ECMO indication combined postcardiotomy and non-postcardiotomy cardiogenic shock but reporting outcomes of interest separately for the groups. Studies were excluded if: 1) paediatric and congenital heart surgery-related studies; 2) animal studies; 3) conducted in the setting of veno-venous ECMO for respiratory distress syndrome; and 4) studies not reporting survival/mortality rates. Studies were only eligible if reporting the transplant status of the centre; whenever this was not retrievable from the individual study, institutional website was searched for information regarding range of procedures performed. Lack of clear indication whether the centre performs heart transplantation led to exclusion of the study. Similarly, registries incorporating multiple centres but not reporting the status for single facilities were not considered. Reviews and case reports were not considered.

Two independent reviewers (P.M. and K.Z.) selected the studies for inclusion, extracted studies, as well as patient characteristics of interest and relevant outcomes. Two authors (P.M. and K.Z.) independently assessed the trials' eligibility and risk of bias. Risk of bias at the individual study level was assessed using the ROBINS-I tool (Risk of Bias in Not-randomized Studies-of Interventions) [11]. Any divergences were resolved by a third reviewer (R.L.) and quantified using the approach of Cohen's kappa [12].

Endpoint selection

The primary endpoint was in-hospital survival. Secondary endpoints were in-hospital cerebrovascular events (CVE), limb complications, bleeding or reoperation for bleeding, sepsis and acute kidney failure with or without continuous veno-venous hemofiltration (CVVH). Bridging to VAD and/or HTx was analysed as well. Outcome definitions were the ones adopted by the investigators of the included studies.

Statistical analysis

Statistical analyses were performed in Comprehensive Meta-Analysis, v. 2 (Biostat, Englewood, NJ). The results are expressed as pooled untransformed proportions (e.g. event rates (%)) and means with their 95% confidence intervals (CI). Heterogeneity across studies was evaluated using the I^2 test. Where available, we digitised Kaplan-Meier curves using Engauge Digitizer 9.5 (Mark Mitchell, Torrance, CA) and reconstructed time-to-event data using the algorithm specified by Guyot et al. [13]. To control for the anticipated heterogeneity among observational studies, absolute values and means were pooled using random effects models. Studies were stratified a priori based on the centre status (HTx vs non-HTx performing centre); the interaction coefficient (Q-value) is provided for the comparison HTx vs non-HTx along with respective $P_{\text{interaction}}$. Additionally, we investigated if HTx and non-HTx status had influence on ECMO duration, weaning rates, bridging to HTx/VAD rates; and further if ECMO duration and weaning rates in these centres correlated with bridging to HTx/VAD by means of meta-regression analyses [14]. Similarly meta-regression approach was used to determine whether annual ECMO institution rate for centre reporting such, affects the survival and remaining in-hospital outcomes. Annual ECMO institution rate was calculated by dividing number of study subjects by study duration period. Sensitivity analyses were performed by excluding from analyses single studies, one at a time, and repeating the calculations. Subgroup analyses were performed for survival endpoint by dividing the studies into distinctive strata (by mean and median annual ECMO institution rate as well as in tertiles and quartiles) and reporting respective $P_{\text{interaction}}$ for between subgroup comparison. Publication bias was assessed 1) by visual approach plotting log event rate against standard error in the funnel plot; and 2) by linear regression approach [15].

Results

Initial search process yielded 22,609 records; of these, 183 abstracts were retrieved for scrutiny based on the item's title. Registries were excluded since they incorporated both HTx and non-HTx centres [16-18]. Following detailed assessment, 54 studies (N=4,421 patients) [list of references to included studies] met inclusion criteria and entered quantitative analyses. PRISMA flow chart is available as Figure 1.

Figure 1. PRISMA Flow-chart.

Included studies were divided into HTx vs non-HTx centres subgroups: 48 studies including 4,217 (95.4%) patients were conducted in HTx- whereas 6 studies (N=204) in non-HTx centres. Prevalence of ECMO ranged

from 0.26% [70] to 3.35% [28]. Patients receiving ECMO at HTx centres were significantly younger than their non-HTx counterparts 57.2 ± 1.6 vs 64.2 ± 1.6 $P < 0.001$. CABG was most frequent procedure in both HTx and non-HTx centres 33.7% and 30.9% followed by valvular (25.1% and 21.1%) and combined surgeries (16.5% and 26.5%). Detailed characteristics of included studies as well as patients' baseline and surgical data are available in Table 1. Publication bias analysis along with reasons for bias risk increase is available as Table 2; studies were judged to be moderate to severe risk of bias as none previously compared directly HTx vs non-HTx centre performance; no signs of asymmetry were seen on visual inspection of funnel plot for primary endpoint (Figure 2).

Figure 2. Funnel plot for publication bias analysis.

ECMO strategy

In the studies that reported procedural details, ECMO was established during the initial cardiac surgery in 42.7% of cases because of circulatory instability during or immediately after weaning from cardiopulmonary bypass. ECMO was initiated in the OR in 56.5% of patients (50.1-62.7%), followed by ICU, cardiac catheterization laboratory, telemetry floor and emergency department. There was no significant difference in the rate of

placement of ECMO in the OR in non-HTx - as compared to HTx centres with respective rates of 64.5% (52.9-74.6%) vs 53.2% (45.6-60.7%); $P=0.108$. Peripheral cannulation was preferred approach (69.0%) for ECMO institution. Median ECMO duration in the entire series was 5 days (IQR: 3.3-6.0); without apparent differences between HTx (mean weighted average= 4.92 days) vs non-HTx- (5.04 days) centres. The details of procedural characteristics are available as Table 3. Successful weaning from ECMO was most often defined as decannulation after >48 hours. Overall, estimated 55.3% patients were weaned from ECMO with the weaning rates ranging from 31.4-100% in the entire series. No difference was noted regarding weaning rates between HTx vs non-HTx centres (56.6% vs 50.4%; $P=0.118$).

Survival and complications while on ECMO

Reported causes of death were divided into “while on-ECMO” and “after weaning” and are available in Table 4. Fifty-three studies (4,367 patients) contributed to the analysis of survival: Overall, 1,527 patients survived to hospital discharge which translated to estimated overall survival of 35.3% (32.5-38.2%). There was no difference between HTx - (35.7% [32.7-38.8%]) and non-HTx centres (33.3% [26.8-40.4%]) $p=0.531$ in random effects model. Figure 3. In meta-regression, there was no impact of centre volume on survival: $\beta_{\text{coef}}=0.0006$; $P=0.833$ (Figure 4). Limb complications incidence was reported in 30 studies (2,766 pts). Overall, 424 patients (13.0% [10.5-16.0%]) had limb complications; Figure 5; in the analysis stratified by centre status there was no difference between HTx - (13.0% [10.4-16.1%]) and non-HTx centres (13.35 [6.4-26.1%]) $P=0.919$. In meta-regression, there was no impact of centre volume on incidence of limb complications: $\beta_{\text{coef}}=0.0043$; $P=0.342$ (Figure 6). There were significantly less neurological complications in the HTx as compared to non-HTx centres: overall 385 patients (33 studies) experienced neurological complications (14.1% [11.8-16.8%]) Figure 7; among those 88 brain deaths (7.9% [5.6-11.0%]) occurred. Figure 8. Neurologic complications in non-HTx centres followed in 19.5% (14.5-25.8%) as compared to 11.9% (9.5-14.8%) in HTx centres; $P=0.009$. In meta-regression, less neurologic complications and brain deaths were seen in centres with higher annual ECMO institution rate: $\beta_{\text{coef}}=-0.0066$; $P=0.031$ (Figure 9) and $\beta_{\text{coef}}=-0.0515$; $P=0.071$ (Figure 10) respectively for neurologic complications and brain deaths

Table 1. Study characteristics.

Study	Study time frames	Prevalence (%)	N. of pts	Age (years)	Male (%)	LVEF (%)	Baseline sCr (mg/dL)	Status elective/ urgent/ emergency/ salvage (n)	Surgery (n)					
									CABG	Valve	Combined	Other	CPB	X-clamp
HTx/VAD centres														
Acheampong 2016	2001-2013	1.06	24	41 (IQR: 22–75)	58.3	47 (10-66)	NR	NR	0	14	3	7	NR	NR
Bakhtiary 2008	2003-2006	0.78	45	60.1 ± 13.6	77.8	25.8 ± 10	NR	NR	20	2	11	12	NR	NR
Beckmann 2017	1997-2011	NR	8	50.1 ± 15.8	62.5	NR	NR	NR/NR/3/NR	0	4	1	3	NR	NR
Beiras-Fernandez 2011	1996-2006	NR	73	49.3 ± 18.0	64.4	NR	1.8 ± 1.1	NR	14	13	6	40	254.3	110.9
Biancari 2017	2005-2016	0.60	148	65.4 ± 9.4	78.4	NR	NR	19/34/80/15	148	0	0	0	146	68
Burrell 2015	2007-2013	NR	54	48 (IQR: 34-58)	68.5	NR	1.2 (0.9-1.6)	NR			NR		NR	NR
Carroll 2015	2009-2014	NR	26	56 (IQR: 41-65)*	69.1*	30 (17-57)*	NR	NR			NR		NR	NR
Chen 2011*	2002-2008	NR	60	47 ± 2	60.8	NR	1.3 ± 0.1	NR			NR		NR	NR
Combes 2008	2003-2006	NR	16	46 ± 16*	56.8*	NR	NR	NR			NR		NR	NR
Distelmeier 2016	2003-2014	3.35	354	65 (IQR: 55-73)	68.6	NR	1.3 (1.1–1.8)	NR	48	110	84	111	NR	NR
Doll 2003	1997-2000	1.20	95	59.8 ± 13.3	69.5	46 ± 17.4	NR	21/64/10/0	63	18	8	6	NR	NR
Elsharkawy 2010	1995-2005	0.58	233	NR	67.4	NR	NR	NR/NR/84/NR			NR		NR	NR
Fiser 2001	1993-2000	0.91	51	61.0 ± 1.7	56.9	NR	NR	NR	34	5	5	7	172.3	68.6
Guihaire 2017	2005-2014	0.70	92	64.5 (18-83)	59	47.2 ± 17.4	1.16 ± 0.58	NR/NR/33/NR	12	64	31**	16	173.3	109.5

Hsu 2009	2002-2006	2.89	51	63.0 ± 15.7	70.6	40.1 ± 17.9	NR	NR	27	11	7	6	188	32
Kanji 2010*	2002-2006	NR	50	49.36	72	23.0	NR	NR			NR		NR	NR
Ko 2002	1994-2000	2.61	76	56.8 ± 15.9	63.2	NR	NR	NR	37	14	6	19	NR	NR
Lamarche 2010	2000-2008	0.30	24	54.6 ± 21	63	20 ± 25	NR	NR			NR		NR	NR
Li 2015	2011-2012	0.91	123	56.2 ± 11.8	65.9	54.6 ± 13.6	NR	NR	44	40	15	24	NR	NR
Liden 2009	2000-2007	NR	33	52.4 ± 12.7	93.9	NR	NR	NR	10	0	0	23	NR	NR
Liu 2009	2002-2005	0.58	14	55.7 ± 15.4	50	52.9 ± 21.4	1.3 ± 1.1	NR	1	7	2	4	247	132
Loforte 2014	2006-2012	1.27	155	58.2 (23–84)*	65.8*	48.2 (33–75)*	NR	NR	28	43	32	52	214.5	NR
Luo 2009	2005-2008	NR	36	49.7	72.2	NR	NR	NR	15	8	0	13	NR	NR
Mazzeffi 2016	2010-2015	0.42	23	57 ± 15	60.9	50 (40-55)	1.2 (0.9-2.0)	NR	7	6	0	10	160	NR
Meyer 2009	2007-2007	1.23	18	50 ± 15	72.2	NR	NR	NR	5	2	0	10	237	NR
Musial 2017	2009-2016	NR	27	45 ± 16	70.4	33.1 ± 22.3	NR	NR	0	16	0	11	NR	NR
Papadopoulos 2015	2001-2013	NR	360	62 ± 17	76.1	35	NR	NR/NR/NR/50	114	89	85	72	160	71
Park 2014	2005-2012	NR	115	61.7 ± 13.4	48.7	57.1 ± 14.3	NR	NR	25	31	33	26	232.4	104.7
Peigh 2015	2010-2014	NR	13	48 ± 14*	64.4*	NR	1.5 ± 0.8*	NR			NR		NR	NR
Pokersnik 2012	2005-2010	NR	49	65 ± 13	67.3	NR	NR	NR/NR/0/0			NR		239	110

Pontailier 2017	2004-2014	NR	127	75.7 ± 4.7*	61.3*	23 ± 12	1.9 ± 1.0	NR/NR/49/NR	42	36	18	18	NR	NR
Ranucci 2011	2008-2011	NR	11	NR	NR	NR	NR	NR			NR		283.1	NR
Rastan 2010	1996-2008	1.28	517	63.5 ± 11.2	71.5	19.9	NR	159/122/205/31	193	96	72	156	179	84.6
Rousse 2015	NR	NR	29	50.6 ± 15.4	65.5	NR	NR	NR			NR		NR	NR
Rubino 2017	2008-2016	NR	101	57.1 ± 15.8	63.4	NR	NR	NR	0	12	29	60	278.2	NR
Russo 2010	2005-2009	NR	3	63.3 ± 14.5	66.7	NR	1,3 ± 0.1	NR	1	1	0	1	NR	NR
Saxena 2015†	2003-2013	NR	45	76.8 ± 4.6	68.9	48.5	1.4 ± 0.5	35/6/4/0			NR		NR	NR
Slottosch 2012	2006-2010	NR	77	60 ± 13	76.6	42 ± 19	NR	NR/NR/29/NR	43	10	11	13	173	69
Slottosch 2017	2008-2016	NR	100	58 ± 15*	76.3	NR	NR	NR/NR/37/0	45	19	24	12	170	68
Truby 2015 *	2007-2013	NR	70	56.9 ± 16.1	67.6	NR	1.83 ± 1.09	NR	11	21	NR	8	NR	NR
Tsai 2016	2002-2011	NR	67	57 ± 14*	66.7*	NR	1.71 ± 2.17*	NR			NR		NR	NR
Wang 2009	2004-2008	0.49	62	51 ± 15	51.6	50 ± 16	NR	NR	13	39	4	6	NR	NR
Wang 2013	2004-2011	1.79	87	65 ± 7	58.6	46 ± 12	NR	NR			NR		182	94
Wu 2010	2003-2009	2.63	110	60 ± 14	70.9	43.4 ± 19.2	NR	NR/NR/31/NR	31	42	19	18	224	126
Xie 2017***	2011-2015	NR	273	NR	NR	NR	NR	NR			NR		NR	NR
Zhang 2006	1996-2004	NR	32	55.4 ± 11.9	56.3	55.3 ± 14.8	NR	NR	5	10	12	5	237	98.7
Zhao 2015	2004-2012	NR	24	59.3 ± 11.9	79.2	51.8 ± 14.2	NR	NR	20	2	0	2	NR	NR
Zhong 2017	2009-2016	0.64	36	50.4 ± 12.2	91.7	60.6 ± 7.86	NR	NR/NR/9/NR			NR		279	113

Non-HTx/VAD centres

Ariyaratnam 2014	2003-2013	NR	14	65.6 ± 10.5	57.1	NR	NR	NR	0	0	11	3	205.6	109.6
Deschka 2013	2008-2011	NR	28	66.6 ± 5.3	92.9	37.2 ± 13.0	NR	NR	17	11	0	0	NR	NR
Khorsandi 2016	1995-2015	NR	15	64.3 ± 14.5	73.3	NR	NR	9/3/4/0	3	4	5	3	NR	NR
Mikus 2013	2007-2011	0.26	14	53.1 ± 14.3	64.3	46.1 ± 13.9	NR	6/2/6/0	5	6	3	0	240.5	98.4
Raffa 2017	2007-2017	NR	86	65 ± 11.2	65.1	NR	NR	NR/NR/33/NR	19	14	29	24	197	104
Unosawa 2012	1992-2007	NR	47	64.4 ± 12.5	74.4	47.8 ± 19.1	NR	NR/NR/22/NR	19	8	6	14	217	81.2

* Reported for entire study population including non-PCS patients

** Multiple valve repair or valvular surgery combined with CABG; potential overlap.

*** Article in Chinese – data from English abstract

†One patient had transfemoral transcatheter aortic valve replacement.

Values are reported as mean ± SD, unless reported otherwise in the original manuscript. Numbers of patients in single studies do not always match the total n. of patients in the original manuscripts since only PCS subgroups were considered. Slottosch 2012 and Slottosch 2017 are studies from the same group; first [Appendix reference 39] describes ECMO support after surgery for acquired heart disease from 2006 to 2010, the second [Appendix reference 40] reports all patients receiving ECMO support longer than 48 h for cardiogenic shock from 01/2008 to 12/2016 therefore, there exists a potential overlap of included patients. LVEF, left ventricle ejection fraction; sCr, serum creatinine; CABG, coronary artery bypass grafting; CPB, cardiopulmonary bypass; IQR, interquartile range; NR, not reported.

Table 2. ROBINS-I tool bias assessment.

Study	Bias due to confounding	Bias in selection of participants into the study	Bias in measurement of interventions	Bias due to departures from intended interventions	Bias due to missing data*	Bias in measurement of outcomes*	Bias in selection of reported result*	Overall bias	Cohen's Kappa
Acheampong 2016 [19]	Critical	Critical	Serious	NA	Moderate	Moderate	Moderate	Moderate	0.57
Bakhtiary 2008 [20]	Critical	Low	Serious	NA	Moderate	Low	Low	Low	0.71
Beckmann 2017 [21]	Critical	Critical	Serious	NA	Low	Moderate	Moderate	Critical	0.71
Beiras-Fernandez 2011 [22]	Critical	Low	Low	NA	Low	Critical	Critical	Critical	0.71
Biancari 2017 [23]	Critical	Low	Serious	NA	Low	Low	Low	Low	0.86
Burrell 2015 [24]	Critical	Critical	Low	NA	Moderate	Moderate	Moderate	Moderate	0.86
Carroll 2015 [25]	Critical	Low	Moderate	NA	Serious	Critical	Serious	Critical	0.57
Chen 2011 [26]	Critical	Critical	Critical	NA	Serious	Critical	Critical	Critical	0.86
Combes 2008 [27]	Critical	Low	Low	NA	Serious	Critical	Critical	Critical	0.86
Distelmeier 2016 [28,29]	Critical	Low	Low	NA	Moderate	Critical	Serious	Critical	0.86
Doll 2003 [30]	Critical	Low	Low	NA	Moderate	Low	Low	Low	0.71
Elsharkawy 2010 [31]	Critical	Low	Low	NA	Low	Moderate	Moderate	Low	0.71
Fiser 2001 [32]	Critical	Low	Critical	NA	Moderate	Moderate	Moderate	Moderate	0.86
Guihaire 2017 [33]	Critical	Serious	Low	NA	Low	Moderate	Moderate	Moderate	0.86
Hsu 2009 [34]	Critical	Low	Low	NA	Moderate	Moderate	Moderate	Moderate	0.86
Kanji 2010 [35]	Critical	Low	Serious	NA	Serious	Moderate	Moderate	Serious	1
Ko 2002 [36]	Critical	Low	Critical	NA	Low	Moderate	Moderate	Critical	0.86
Lamarche 2010 [37]	Critical	Low	Moderate	NA	Moderate	Moderate	Moderate	Moderate	0.57
Li 2015 [38]	Critical	Low	Low	NA	Low	Moderate	Moderate	Low	0.86
Liden 2009 [39]	Critical	Moderate	Critical	NA	Moderate	Moderate	Moderate	Moderate	0.57
Liu 2009 [40]	Critical	Critical	Moderate	NA	Low	Moderate	Moderate	Moderate	0.71
Loforte 2014 [41]	Critical	Low	Critical	NA	Moderate	Moderate	Low	Critical	0.71
Luo 2009 [42]	Critical	Low	Low	NA	Moderate	Moderate	Low	Low	1
Mazeffi 2016 [43]	Critical	Low	Moderate	NA	Low	Moderate	Moderate	Moderate	1

Meyer 2009 [44]	Critical	Low	Low	NA	Moderate	Moderate	Moderate	Moderate	0.86
Musial 2017 [45]	Critical	Low	Critical	NA	Low	Serious	Moderate	Critical	0.71
Papadopoulos 2015 [46]	Critical	Low	Low	NA	Low	Moderate	Moderate	Low	0.86
Park 2014 [47]	Critical	Moderate	Low	NA	Low	Moderate	Moderate	Moderate	0.86
Peigh 2015 [48]	Critical	Low	Critical	NA	Serious	Critical	Critical	Critical	0.57
Pokersnik 2012 [49]	Critical	Serious	Critical	NA	Low	Moderate	Moderate	Critical	0.71
Pontailier 2017 [50]	Critical	Low	Serious	NA	Serious	Critical	Critical	Critical	0.86
Ranucci 2011 [51]	Critical	Critical	Critical	NA	Critical	Critical	Critical	Critical	0.86
Rastan 2010 [52]	Critical	Low	Low	NA	Low	Moderate	Moderate	Low	0.71
Rousse 2015 [53]	Critical	Low	Serious	NA	Moderate	Critical	Serious	Critical	0.71
Rubino 2017 [54]	Critical	Low	Critical	NA	Low	Moderate	Moderate	Critical	0.71
Russo 2010 [55]	Critical	Low	Low	NA	Low	Critical	Serious	Low	0.71
Saxena 2015 [9]	Critical	Low	Low	NA	Low	Moderate	Moderate	Low	0.86
Slottosch 2012 [56]	Critical	Low	Low	NA	Low	Low	Moderate	Low	0.86
Slottosch 2017 [57]	Critical	Low	Low	NA	Moderate	Moderate	Moderate	Moderate	0.86
Truby 2015 [58]	Critical	Low	Serious	NA	Moderate	Critical	Serious	Critical	0.86
Tsai 2016 [59]	Critical	Critical	Critical	NA	Serious	Critical	Critical	Critical	0.57
Wang 2009 [60]	Critical	Low	Low	NA	Moderate	Low	Moderate	Low	0.71
Wang 2013 [61]	Critical	Critical	Low	NA	Low	Low	Moderate	Low	0.86
Wu 2010 [62]	Critical	Low	Critical	NA	Low	Low	Low	Low	1
Xie 2017 [63]	Critical	Low	Critical	NA	Critical	Critical	Critical	Critical	0.86
Zhang 2006 [64]	Critical	Low	Critical	NA	Low	Serious	Moderate	Critical	0.86
Zhao 2015 [65]	Critical	Critical	Critical	NA	Low	Moderate	Moderate		0.71
Zhong 2017 [66]	Critical	Critical	Low	NA	Low	Serious	Moderate	Critical	0.57
Ariyaratnam 2014 [67]	Critical	Low	Critical	NA	Low	Critical	Serious	Critical	1
Deschka 2013 [68]	Critical	Low	Serious	NA	Moderate	Low	Low	Low	0.86
Khorsandi 2016 [69]	Critical	Low	Serious	NA	Low	Low	Low	Low	0.86

Mikus 2013 [70]	Critical	Low	Low	NA	Low	Moderate	Moderate	Low	0.71
Raffa 2017 [71]	Critical	Low	Serious	NA	Low	Moderate	Low	Low	0.71
Unosawa 2012 [72]	Critical	Low	Low	NA	Low	Moderate	Moderate	Low	0.86

*When multiple outcomes were reported for a study, the highest level of bias at the outcome level is reported in the table.

Table 3. Procedural characteristics

Study	Post-op IABP (n)	Peripheral cannulation (n)	ECMO at index procedure (n)	ECMO at OR/ICU	Distal perfusion (n)	LV venting (n)	ECMO			
							Duration	weaning (%)	Bridge to VAD (n)	Bridge to HTx (n)
HTx/VAD centres										
Acheampong 2016	14	NR	NR	20/4	NR	NR	8.4 (0.8–35.4) days	75.0	1	0
Bakhtiyary 2008	30	37	NR	30/15	NR	NR	6.4 ± 4.5 days	55.6	5	2
Beckmann 2017	NR	8	NR	NR	8	NR	12.0 ± 5.9 days	87.5	1	0
Beiras-Fernandez 2011	36	NR	NR	NR	NR	NR	4.4 ± 4.0 days	NR	NR	NR
Biancari 2017	47	89	76	NR	66	5	6.4 ± 5.6 days	48.6	6	0
Burrell 2015	NR	NR	NR	NR	NR	NR	7 (IQR: 5-8) days	100	NR	NR
Carroll 2015	13	92	NR	61/31**	NR	NR	94 (IQR: 43-172) hours	69	29	2
Chen 2011*	NR	NR	NR	NR	NR	NR	133 ± 12 hours	54.9	NR	NR
Combes 2008	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Distelmeier 2016/2017	44	347	NR	NR	NR	NR	4 (IQR: 2–7) days	NR	4	3
Doll 2003	95	26	NR	70/25	NR	NR	2.8 ± 2.1 days	47.4	8	3†
Elsharkawy 2010	22	77	NR	NR	NR	NR	NR	NR	28	25
Fiser 2001	NR	NR	NR	22/29	NR	NR	67.5 hours	31.4	NR	NR
Guihaire 2017	25	78	43	80/12	NR	13	6 days	48	2	2
Hsu 2009	51	51	NR	NR	NR	NR	7.5 ± 6.7 days	52.9	0	3
Kanji 2010	36	22	NR	NR	NR	NR	2.5 (IQR: 1.0-4.8) days	NR	NR	23
Ko 2002	54	61	39	23/30	20	NR	NR	60.5	2	2
Lamarche 2010	NR	8	NR	16/8	NR	NR	48 ± 65.5 hours	58.3	3	3
Li 2015	73	123	61	NR	123	NR	4.3 days	56.1	NR	NR
Liden 2009	14	NR	NR	NR	NR	NR	5.5 ± 4.9 days	NR	2	2
Liu 2009	10	14	9	NR	NR	NR	71 ± 52 hours	64.3	NR	NR
Loforte 2014	155	79	NR	NR	NR	NR	9.56 (2–43) days	56.8	1	4
Luo 2009	11	NR	NR	15/30	NR	0	131.6 hours	66.7	NR	2
Mazeffi 2016	3	9	3	NR	NR	0	3 (IQR: 1-8) days	100	2	NR
Meyer 2009	NR	18	NR	NR	18	NR	4 ± 4 days	66.7	NR	NR

Musial 2017	NR	27	27	NR	NR	NR	8.89 days	NR	NR	NR
Papadopoulos 2015	NR	324	NR	NR	NR	NR	7 ± 1 days	58.1	6	2
Park 2014	NR	115	41	NR	115	NR	71.3 (0.5-713) hours	40.8	NR	2
Peigh 2015	NR	NR	NR	NR	NR	NR	9.2 ± 6.1 days	NR	NR	NR
Pokersnik 2012	29	32	NR	NR	32	NR	3.8 ± 3.4 days	55.1	2	0
Pontailier 2017	NR	NR	NR	NR	NR	NR	5.6 ± 4.3 days*	41.1*	NR	NR
Ranucci 2011	NR	0	9/2	NR	NR	NR	122.1 ± 80.5 hours	63.6	NR	NR
Rastan 2010	383	203	NR	NR	121	NR	3.28 ± 2.85 days	63.3	15	5
Rousse 2015	5	25	NR	NR	29	29	8 (1-86) days	50.0	7	13
Rubino 2017	NR	NR	63	NR	NR	NR	5 (IQR: 3-8) days	57.4	3	3
Russo 2010	3	1	NR	NR	NR	NR	7.0 ± 5.2 days	66.7	0	1
Saxena 2015†	NR	15	NR	NR	NR	NR	103.8 ± 74.3 hours	53.3	NR	NR
Slottosch 2012	72	77	34	34/43	77	NR	79 ± 57 hours	62.3	NR	NR
Slottosch 2017	83	72	40	NR	NR	NR	117 ± 78 hours	43.2*	NR	NR
Truby 2015	NR	45	NR	71/108	9	NR	3.58 (IQR: 1.6 –5.9) days	NR	52	NR
Tsai 2016	NR	NR	NR	NR	NR	NR	7 ± 5 days*	70.5*	NR	NR
Wang 2009	19	NR	NR	36/26	NR	0	61 ± 37 hours	64.5	NR	NR
Wang 2013	41	NR	37	37/50	37	NR	61 ± 37 hours	58.6	NR	NR
Wu 2010	NR	NR	NR	98/12	NR	NR	143 ± 112 hours	60.9	2	0
Xie 2017***	NR	NR	NR	NR	NR	NR	NR	64.8	NR	NR
Zhang 2006	10	19	NR	NR	NR	NR	2.7 ± 1.7 days	43.8	NR	NR
Zhao 2015	16	23	9	NR	NR	NR	115.23 ± 70.17 hours	66.7	1**	NR
Zhong 2017	9	29	24	24/12	NR	NR	77.5 ± 34.5 hours	66.7	NR	NR
Non-HTx/VAD centres										
Ariyaratnam 2014	NR	0	NR	NR	NR	NR	5.6 ± 3.4 days	50.0	NR	NR
Deschka 2013	25	0***	NR	NR	NR	NR	8.7 ± 3.9 days	42.9	NR	NR
Khorsandi 2016	NR	5	NR	NR	NR	NR	5.5 ± 8.9 days	NR	NR	NR
Mikus 2013	13	6	12	NR	14	14	5 days	50	0	0
Raffa 2017	23	30	48	48/38	NR	NR	5 days	49	NR	NR
Unosawa 2012	39	32	33	33/14	NR	NR	63.5 ± 61.5 hours	61.7	0	0

* Reported for entire study population including non-PCS patients

** 24 (23%) in the cardiac catheterization laboratory, 16 (16%) at the bedside, and 1 (1%) in the emergency department

*** Central cannulation cohort alone; peripheral venous cannulation in 28 patients

†VAD and subsequent heart transplantation

Values are reported as mean ± SD, unless reported otherwise in the original manuscript. HTx, heart transplantation; VAD, ventricular assist device; IQR, interquartile range; NR, not reported.

Numbers of patients in single studies do not always match the total n. of patients in the original manuscripts since only PCS subgroups were considered.

Table 4. Reported causes of in-hospital/30-day death

Study	On ECMO only	After weaning/in-hospital/30-day death
HTx/VAD centres		
Acheampong 2016	NR	1 sepsis, 1 massive bleeding, 2 pulmonary; remaining: multiorgan failure or cardiac related
Bakhtiary 2008	18 persistent heart failure	12 multiorgan failure
Beckmann 2017	1 sepsis	1 biventricular failure, 1 low cardiac output, 1 cerebral haemorrhage, 1 multiorgan failure
Beiras-Fernandez 2011	refractory ventricular failure 40.6%, bleeding 23.2%, isolated persistent low cardiac output 21.7%, thromboembolism 8.7%, allograft failure 5.8%	NR
Biancari 2017	NR	NR
Burrell 2015	NR	NR
Carroll 2015	NR	multiorgan failure in 52 patients, neurologic injury in 9 patients, bleeding in 7 patients, hypoxemic respiratory failure in 2 patients, and other etiologies in the remaining 5 patients
Chen 2011*	NR	NR
Combes 2008	mainly due to refractory multiorgan failure with 14 within 24 hrs of onset	NR
Distelmeier 2016/2017	NR	NR
Doll 2003	NR	refractory myocardial failure in 71%, multisystem organ failure in 13%, sepsis in 7%, and other causes in 9%
Elsharkawy 2010	NR	NR
Fiser 2001	27 cardiac failures, 12 strokes, 3 multisystem organ failures, 1 respiratory insufficiency	NR
Guihaire 2017	NR	NR
Hsu 2009	NR	main causes were pulmonary infections
Kanji 2010	NR	NR
Ko 2002	16 multiple organ failure, 5 uncontrolled bleedings, 3 brain deaths, 2 circulatory shocks, 1 refractory ventricular arrhythmia, 1 myocardial infarction, 1 acute rejection, 1 graft failure	17 multiple organ failure, 3 persistent heart failure, 1 ventricular fibrillation
Lamarche 2010	NR	NR
Li 2015	NR	NR
Liden 2009	8 multiorgan failure, 6 poor cardiac function, 1 brain damage, 1 retroperitoneal bleeding, 1 fungal sepsis, 1 vasoplegia, 1 unknown	NR
Liu 2009	NR	4 haemodynamic unstable, 1 multiorgan failure, 1 sepsis, 1 other
Loforte 2014	mostly associated with sepsis and brain death	NR
Luo 2009	6 persistent heart failure without improvement, 4 multiorgan failure and others	5 sepsis and other
Mazeffi 2016	NR	7 multiple organ failure, 4 brain injury, 3 sepsis, 1 hemorrhage, 1 repeat arrest

Meyer 2009	NR	5 multiorgan failure, 4 non-recoverable myocardial failure, 3 sepsis, 1 intracerebral bleeding
Musial 2017	NR	NR
Papadopoulos 2015	NR	the main cause of death was sepsis (69%)
Park 2014	NR	6 multiorgan failure, 3 profound cardiac failure, 2 sepsis, 2 pan-peritonitis, 2 aortic ruptures, 1 intracerebral haemorrhage, 1 gastrointestinal bleeding
Peigh 2015	8 anoxic brain injuries, 8 strokes, 3 irreversible cardiac dysfunctions, 3 sepsis, 2 irreversible lung diseases, 1 abdominal compartment syndrome with hepatorenal syndrome, 1 failure to control bleeding	5 sepsis, 4 neurologic injuries, 2 acute myocardial infarction because of stent thrombosis, 1 family's withdrawal because of failure to thrive, and one case of each of the following: pulseless electric activity after internal defibrillator placement, persistent loss of cardiac activity despite biventricular assist device placement, acute failure of left ventricular assist device placement with persistent low flow and malperfusion, nonresectable cardiac metastasis (adenocarcinoma), and severe coagulopathy and multiple bleeding
Pokersnik 2012	NR	NR
Pontailier 2017	multiorgan failure for all patients	NR
Ranucci 2011	NR	NR
Rastan 2010	NR	the main reason for death was cardiac
Rousse 2015	21 multiple organ failures, 12 intra-abdominal bleeding, 4 strokes, 3 non-beating hearts, 7 haemorrhage or sepsis, 2 mesenteric ischemias (for entire study population of 124 patients)	NR
Rubino 2017	NR	causes of death were mostly related to cardiac disease
Russo 2010	NR	6 multiorgan failures, 1 pulmonary artery thrombosis, 1 thoracic bleeding
Saxena 2015†	NR	30 cardiac causes, 13 multiorgan failures, 6 septicemias
Slottosch 2012	NR	cardiac causes (50.9%), sepsis (29.1%), cerebrovascular complications (1.8%), bleeding (10.9%), gastrointestinal complications (7.3%)
Slottosch 2017	NR	60 cardiac deaths, 22 sepsis, 6 mesenteric ischemias, 5 cerebral deaths, 5 untreatable bleedings and 4 others (for entire cohort of 139 patients)
Truby 2015	NR	NR
Tsai 2016	NR	NR
Wang 2009	11 persistent heart failures, 7 sepsis with consecutive multiorgan failure, 2 cerebral infarction and bleeding, 2 disseminated intravascular coagulation	main cause was sepsis with consecutive multiorgan failure
Wang 2013	22 persistent heart failure without any improvement in cardiac function, 10 sepsis, 3 disseminated intravascular coagulation, 1 cerebral infarction and bleeding	sepsis with consecutive multiorgan failure for all weaned
Wu 2010	NR	8 excessive mediastinal bleeding, 15 profound cardiac failure, 6 severe brain damage, 3 bowel infarction, 2 massive air embolism, 28 sepsis with multiple organ failure
Xie 2017***	NR	NR
Zhang 2006	NR	NR
Zhao 2015	NR	the main cause of mortality was multiple system organ failure (50.0 %)

Zhong 2017

NR

7 sepsis with subsequent multi-organ failure, 6 persistent heart failures, 3 disseminated intravascular coagulation, 2 cerebral infarction

Non-HTx/VAD centres

Ariyaratnam
2014

NR

NR

Deschka 2013

NR

NR

Khorsandi
2016

NR

6 biventricular failures, 2 septic shocks, 1 major cardiovascular incident, 1 major haemorrhage, 1 respiratory failure, 1 multiorgan failure

Mikus 2013

multiple organ failure for all

NR

Raffa 2017

NR

the main reason for death was a cardiac event, followed by multiorgan failure and neurological complications

Unosawa 2012

7 intractable heart failure, 5 multiorgan failure, 4 brain death, 2 severe coagulopathic bleeding

8 multiorgan failures, 2 heart failures, 2 cardiac ruptures, 2 brain deaths, 1 pneumonia

Figure 3. Analysis of survival after following ECMO institution in HTx/VAD vs non-HTx/VAD centres. Squares represent point estimates of single studies; horizontal lines are respective 95% confidence intervals. Diamonds are indicative of subtotal and total pooled estimate. HTx, heart transplantation; VAD, ventricle assist device.

Figure 4. Meta-regression analysis of number of ECMOs per year on logit survival rate.

Figure 5. Analysis of limb complications following ECMO institution in HTx/VAD vs non-HTx/VAD centres.

Figure 6. Meta-regression analysis of number of ECMOs per year on logit limb complications event rate.

Figure 7. Analysis of neurologic complications following ECMO institution in HTx/VAD vs non-HTx/VAD centres.

Figure 8. Analysis of brain death following ECMO institution in HTx/VAD vs non-HTx/VAD centres. Squares represent point estimates of single studies; horizontal lines are respective 95% confidence intervals. Diamonds are indicative of subtotal and total pooled estimate.

Figure 9. Meta-regression analysis of number of ECMOs per year on logit neurologic complications event rate.

Figure 10. Meta-regression analysis of number of ECMOs per year on logit brain death event rate

Thirty-three studies enrolling 2,832 patients reported reoperations for bleeding; these were necessary in 1,232 cases (41.2% [35.6-47.1%]) in the entire series without statistical differences between HTx: 39.5% (33.6-45.8%); and non-HTx centres: 52.6% (36.6-68.0%); $P=0.139$. Figure 11. In meta-regression, there was no impact of centre volume on incidence of reoperation for bleeding: $\beta_{\text{coef}}=-0.0012$; $P=0.489$ (Figure 12). Sepsis has complicated 385 ECMO cases 20.7% (17.0-24.9%) but there were again no differences between HTx - (19.5% [15.5-24.1%]) and non-HTx centres (25.2% [16.9-36.0%]); $P=0.259$ in the meta-analysis (Figure 13) nor in meta-regression of centre's volume impact (Figure 14) ($\beta_{\text{coef}}=-0.0040$; $P=0.692$). In the analysis of AKI with or without CVVH (Table 5 lists AKI definitions across included studies) less AKIs in non-HTx centres were seen but the difference was not significant ($p=0.220$) Figure 15: Total incidence of AKI was 47.3% (41.5-53.1%) – 1,513 reported cases; in non-HTx centres AKI estimated rate was 38.7% (25.5-53.7%) as compared to 48.8% (42.5-55.1%) as observed in HTx centres; no effect of centre's annual ECMO institution rate on AKI incidence was demonstrated in meta-regression ($\beta_{\text{coef}}=-0.0012$; $P=0.488$) Figure 16.

Figure 11. Analysis of reoperations for bleeding following ECMO institution in HTx/VAD vs non-HTx/VAD centres.

Figure 12. Meta-regression analysis of number of ECMOs per year on logit reoperations for bleeding event rate.

Figure 13. Analysis of sepsis following ECMO institution in HTx/VAD vs non-HTx/VAD centres.

Figure 14. Meta-regression analysis of number of ECMOs per year on logit sepsis event rate.

Table 5. AKI definitions

Study	AKI definition
HTx/VAD centres	
Acheampong 2016	Renal insufficiency requiring hemodialysis
Bakhtiary 2008	Renal failure requiring continuous venovenous hemofiltration

Beckmann 2017	N/A
Beiras-Fernandez 2011	N/A
Biancari 2017	Renal replacement therapy
Burrell 2015	N/A
Carroll 2015	N/A
Chen 2011*	N/A
Combes 2008	N/A
Distelmeier 2016/2017	N/A
Doll 2003	Renal failure requiring hemofiltration
Elsharkawy 2010	Acute renal failure requiring dialysis
Fiser 2001	Renal failure requiring dialysis
Guihaire 2017	N/A
Hsu 2009	Renal failure requiring continuous venovenous hemofiltration
Kanji 2010	N/A
Ko 2002	Acute renal failure requiring dialysis
Lamarche 2010	N/A
Li 2015	Postoperative continuous renal replacement therapy
Liden 2009	Postoperative dialysis
Liu 2009	Acute renal failure requiring hemodialysis
Loforte 2014	Continuous veno-venous hemofiltration on ECMO
Luo 2009	Acute renal failure treated by continuous renal replacement therapy
Mazeffi 2016	Acute renal failure requiring renal replacement therapy
Meyer 2009	Renal failure requiring hemodialysis
Musial 2017	Acute renal failure requiring continuous renal replacement therapy
Papadopoulos 2015	Acute renal failure requiring continuous venovenous hemofiltration
Park 2014	N/A
Peigh 2015	N/A
Pokersnik 2012	An increase in serum creatinine to >2.0, and two times the most recent preoperative creatinine level or a new requirement for dialysis postoperatively
Pontailier 2017	N/A
Ranucci 2011	N/A
Rastan 2010	N/A
Rousse 2015	N/A
Rubino 2017	Renal impairment requiring continuous veno-venous hemofiltration
Russo 2010	N/A
Saxena 2015†	N/A
Slottosch 2012	Oliguria (less than 0.5 mL/kg/h) and a doubling of postoperative creatinine values with the need for hemodialysis
Slottosch 2017	Oliguria (<0.5 ml/kg/h) and a doubling of postoperative creatinine values with need for hemodialysis
Truby 2015	N/A
Tsai 2016	N/A
Wang 2009	Renal failure requiring continuous venovenous hemofiltration
Wang 2013	PCS-related renal failure requiring continuous venovenous hemofiltration (e.g. renal replacement therapy)
Wu 2010	Renal failure requiring continuous arteriovenous hemofiltration
Xie 2017***	N/A
Zhang 2006	N/A
Zhao 2015	Hemodialysis on ECMO
Zhong 2017	N/A
Non-HTx/VAD centres	
Ariyaratnam 2014	N/A
Deschka 2013	Acute renal failure requiring continuous veno-venous hemodiafiltration
Khorsandi 2016	Renal failure requiring renal replacement therapy
Mikus 2013	Renal failure requiring continuous venovenous hemofiltration
Raffa 2017	N/A

N/A, not available, ECMO, extracorporeal membrane oxygenation; PCS, postcardiotomy shock.

Figure 15. Analysis of acute kidney injury following ECMO institution in HTx/VAD vs non-HTx/VAD centres.

Figure 16. Meta-regression analysis of number of ECMOs per year on logit acute kidney injury event rate.

ECMO as bridging therapy

Eighty-six (estimated rate 3.5% [1.8-6.6%]) patients were bridged to heart transplantation. Of those, all were bridged to HTx in HTx centres. Of note, one reported patient died on ECMO after transfer from non-HTx centre to the referral hub centre while waiting for heart transplantation [70]. ECMO bridging to short- or long-term VAD ensued in 99 patients (4.3% [2.8-6.5%]); there were again no instance of reported bridging to VADs in non-HTx centres.

Additional analyses:

In several conducted meta-regressions, no impact of centre status on survival ($\beta_{\text{coef}} = 0.1418$; $P_{\text{slope}} = 0.555$) or ECMO duration ($\beta_{\text{coef}} = 0.0052$; $P_{\text{slope}} = 0.833$) could be demonstrated. Centre status positively, yet non-significantly, correlated with higher weaning rates ($\beta_{\text{coef}} = 0.2651$; $P_{\text{slope}} = 0.601$). Figure 17 and 18 summarize subgroup analyses performed for survival rates as divided by annual number of ECMOs performed. In sensitivity analysis for survival performed deleting single studies, one at a time, and repeating the calculations, no single study effect was seen changing neither direction nor the magnitude of the estimates.

Figure 17. Subgroup analysis to assess impact of centre volume on survival: arbitrary thresholds.

Figure 18. Subgroup analysis to assess impact of centre volume on survival: thresholds divided by mean and median number of ECMOs per year and divided in tertiles and quartiles.

Discussion

The current meta-analysis represents the first attempt to compare, although in indirect fashion, in-hospital outcomes of patients supported with VA-ECMO for refractory PCS between HTx and non-HTx centres. This research was aimed to investigate further factors other than the well-known patients' clinical status and procedure type that may affect the final outcome in PCS-ECMO patient. The care center with experience in dealing with acute and chronic end stage heart failure with expertise and prompt resources availability (medium and long term mechanical circulatory support and heart transplantation) as factor potentially affecting this outcome was the primary hypothesis of our study.

VA-ECMO is increasingly used for cardiorespiratory support in patients affected by refractory cardiogenic shock or cardiac arrest after cardiac surgery. [2] Despite that growing worldwide utilization and experience, ECMO in-hospital outcomes have not shown substantial progress. Conversely, a trend towards worse survival rates, reaching a disappointing 15% has been recently reported in another analysis of the Extracorporeal Life Support Organization registry [2]. Patients undergoing heart surgery usually present with substantial pre-ECMO comorbidities, more advanced age and above all different stages of developed heart failure. All these factors, individually or in association influence the capability of the myocardium to recover after the surgery and thus preclude favorable body response to prolonged MCS. Unfortunately, in a considerable proportion of patients, the MCS regardless of its duration, does not prompt to improved cardiac function or organ integrity; in turn, clinicians are forced to bridging the patient to more advanced treatments, such as HTx or VADs. The insights from important recently available study by Distelmeier [20] are that prolonging of VA-ECMO duration is associated with a disproportionate mortality at early and later stages. In fact, lack of cardiac function improvement within 7 days post-op. was indicative of futile support in the analysis. Consequently, this leads to conclusion that perhaps HTx or VADs in such ECMO-supported patients should be used much sooner, just in time to prevent life-threatening complications

Such hypothesis led to conception of the current study which is the first to compare, although in indirect fashion, the outcomes between HTx and non-HTx performing centres in patients undergoing ECMO treatment for refractory PCS. The first consideration come from the study population of this meta-analysis: The majority of patients (4,217 out of 4,421) and number of reports (48 out of 54) come from HTx centres which might suggest that 1) cardiac surgery population in HTx performing centres are of an increased risk for developing PCS, therefore higher operative risk burden in a first place; 2) ECMO represents a tool more routinely used for the treatment of refractory PCS in the HTx units; 3) there exists an unexplained underreporting from non-HTx centres of patients undergoing ECMO treatment and their perioperative outcomes. Regardless, our main findings were that among patients with PCS no differences in 30 day/in-hospital mortality were observed between heart transplantation centres as compared to non-transplant units. This was also confirmed in a subgroup analysis. While neutral, this finding implies similar mortality rates among patients operated on in HTx and long-term

assistance facilities as compared to patients operated in non-transplant units, given their respective potentially higher and lower baseline risk.

Second, there was no difference between the centres type with respect to limb complications, reoperation for bleeding, sepsis and acute renal injury with or without dialysis, yet neurological complications occurred less frequently in HTx centres. Neurologic complications are presumably a multifactorial entity with pre-ECMO illness severity and treatments, ECMO management, and post-ECMO events all contributing to CNS injury rates in these patients. Loss of cerebral autoregulation during severe arterial hypertension or hypotension, thromboembolic events, haemorrhage related to anticoagulation use, cerebral vasospasm, and secondary brain injury from reactive tissue oedema around an area of focal CNS injury have all been implicated in the genesis of brain injury in VA-ECMO patients. Although neurologic injury during VA-ECMO remains poorly defined in adult cohorts [16,21-23], prior investigations comprehensively report neurologic complications occurrence in 6–17% in adults supported with VA-ECMO for postcardiotomy cardiorespiratory failure [21,24,25]. What seems even more illustrative, postmortem examination in adults supported with VA-ECMO has shown that neurologic injury may be clinically undetected in 23–50% of cases [26,27]. In the current analysis, we saw neurologic complications more frequent in non-HTx centres. While this could not be accounted for in that type of analyses, the “over-delay” to ECMO commencement in the institutions with lower experience with circulatory support systems (be that ECMO or VADs) may have played a role in the excess of strokes in this population.

Finally, patients on ECMO bridged to HTx or mechanical circulatory support are reported only in the HTx units. Single patients in non-HTx institutions died while waiting for referral to HTx hub after the decision to transplant was met. From the technical standpoint, is noteworthy to underline that there were no differences in the ECMO duration between the two centres, yet notice must be made of statistical trend for the different ECMO location placement and weaning rate; that is, ECMO was instituted in the OR more frequently in non-HTx centres but again since delay to ECMO was seldom reported, we cannot address the issue whether this might have affected patient outcome. On the other hand, this may further suggest an easier applicability of ECMO in locations other than OR in HTx-centres with possibly prompt ECMO team availability as compared to the non-HTx units.

Limitations

Current meta-analysis is based on observational, one-arm comparisons and because of that is more prone to confounding as compared to head-to-head comparisons. On the other hand, no RCT exist regarding analyzed topic and presumably will not be organized due to ethical issues. One limitation of the study may be underrepresentation of patients treated in non-HTx institutions. Random effect meta-analysis and inverse variance analysis was used to account for that fact. These methods appoint random weights also in a subgroup analysis which could overcome discrepancies between population sizes. There was no standard definition for secondary endpoints or risk of bias of the included studies. Conducting detailed subgroup analyses was precluded by not sufficient data on timing and location of implantation, type, status and duration of surgical procedure likewise other baseline characteristic.

Conclusions

There was no apparent difference in survival after ECMO implantation for refractory PCS between centres which perform heart transplantations and those which do not. Potentially different risk profiles of patients in these centres must be taken account for before definite conclusions are drawn.

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CHAPTER 7

CARDIOGENIC SHOCK AND VENO-ARTERIAL ECLS IN HEART TRANSPLANTATION/VAD CENTRES AS COMPARED TO NON-TRANSPLANT/VAD UNITS. META-ANALYSIS.

Kowalewski M*, Zieliński K*, Gozdek M, Raffa GM, Pilato M, Alanazi M, Gilbers M, Heuts S, Natour E, Bidar E, Schreurs R, Delnoij T, Driessen R, Sels JW, van de Poll M, Roekaerts P, Meani P, Pasierski M, Suwalski P, Lorusso R.

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Objectives: Since reported mortality on veno-arterial (V-A) extracorporeal life support (ECLS) substantially vary between centers, aim of the current analysis was to assess the outcomes between units performing heart transplantation and/or implanting ventricular assist device (HTx/VAD) versus non-HTx/VAD units in patients undergoing V-A ECLS for cardiogenic shock.

Methods: Systematic search according to PRISMA was performed using PubMed/Medline databases between 2010 and 2019. Articles reporting in-hospital/30-day mortality and centre's HTx/VAD status were included. In-hospital outcomes and long-term survival were analysed in subgroup meta-analysis.

Results: 174 studies enrolling N = 13,308 patients were included with 20 series performed in non-HTx/VAD centres (1,016 patients, 7.8%). Majority of patients underwent V-A ECLS for postcardiotomy shock (44.2%) and acute myocardial infarction (20.7%). Estimated overall in-hospital mortality was 57.2% (54.9-59.4%). Mortality rates were higher in non-HTx/VAD (65.5% [59.8-70.8%]) as compared to HTx/VAD centres (55.8% [53.3-58.2%]); $P < 0.001$. Estimated late survival was 61.8% (55.7-67.9%) without differences between non-HTx/VAD and HTx/VAD centres: 66.5% (30.3-1.02%) vs 61.7% (55.5-67.8%), respectively ($p = 0.797$). No differences were seen with respect to ECLS duration, limb complications, reoperations for bleeding, kidney injury and sepsis. Yet, weaning rates were higher in HTx/VAD vs non-HTx/VAD centres 58.7% (56.2-61.1%) vs 48.9% (42.0-55.9%): $p = 0.010$. Estimated rate of bridge to heart transplant was 6.6% (5.2-8.3%) with numerical, yet not statistically significant difference between non-HTx/VAD (2.7% [0.8-8.3%]) as compared to HTx/VAD (6.7% [5.3-8.6%]) ($p = 0.131$).

Conclusions: Survival after V-A ECLS differed according to centre's HTx/VAD status. Potentially different risk profiles of patients must be taken account for before definite conclusions are drawn.

Introduction

Despite advances in revascularization strategies, operative techniques and management, as well as heart failure therapy, cardiogenic shock (CS), regardless whether resulting from acute, chronic or end-stage heart condition,

continues to be associated with significant morbidity and mortality [1]. Nowadays, veno-arterial (V-A) extracorporeal life support (ECLS) is widely recognized as an efficient and easy to implant mechanical support system (MCS), providing efficient, both hemodynamic and respiratory support. It safeguards end-organ perfusion during the shock state, thereby, serves as a bridge to recovery of cardiac function, heart transplantation (HTx) or more durable ventricle assist device (VAD) [2,3,4,5]. Despite that, V-A ECLS still represents a resource-consuming modality and mostly last resort of treatment. In most cases, centres' protocols and resources limit ECLS implementation to highest risk patients which are least likely to benefit from such therapies [4,6,7,8,9]. Since CS arises from a plethora of underlying impaired cardiovascular and since conducting a randomized controlled trial in this peculiar setting would raise ethical questions, V-A ECLS's optimal implementation and management in patients with CS has not been well studied or defined. Despite growing worldwide utilization and experience in MCS, outcomes of patients undergoing V-A ECLS, in particular in-hospital mortality, have not shown substantial progress [4,10]. Interestingly, they are fairly different from centre to centre suggesting that variations in practice patterns in management of cardiogenic shock endure and may play a role in driving the above differences [11, 39]. These might include different schemes of timing of cardiogenic shock recognition, tailored escalation to mechanical circulatory support, centralization of care and hemodynamic monitoring. We hypothesized that readability of well-experienced ECLS teams and potentially shorter bridging times in HTx/VAD units may contribute to improved results. Therefore, we undertook a systematic review and meta-analysis to assess to which extent do the in-hospital and remote outcomes differ across patients in cardiogenic shock and receiving V-A ECLS treatment in HTx/VAD as compared to non-HTx/VAD facilities.

Methods

Data sources and search strategy

This systematic review and meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic Reviews and meta-analyses (PRISMA) statement [12]. Relevant studies to be included were searched for until November 30th 2019, through PubMed, EMBASE, CINAHL, the Web of Science, the Cochrane

Register of Controlled Clinical Trials (CENTRAL) and Google Scholar. Abstracts were eligible for detailed assessment if available online and reporting outcomes of interest. The search term was: “extracorporeal membrane oxygenation”, “extracorporeal life support” and “cardiogenic shock”. No language restrictions were imposed. References of original articles were reviewed manually and cross-checked for other relevant reports.

Selection criteria and quality assessment

Studies were included if they met all of the following criteria: 1) human study; 2) studies assessing survival after ECLS instituted for refractory CS regardless of underlying conditions; 3) studies conducted in the setting of V-A ECLS or studies conducted in combined setting of veno-arterial and veno-venous (V-V) ECLS, but reporting at least one of the outcomes of interest for the former group. Studies were only excluded if: 1) paediatric and congenital heart surgery-related studies; 2) animal studies; 3) conducted entirely in the setting of V-V ECLS regardless of underlying conditions; and 4) studies not reporting survival/mortality rates. Studies were only eligible if reporting the transplant status of the centre; whenever this was not retrievable from the individual study, institutional website was searched for information regarding range of procedures performed. Lack of clear indication whether the centre performs heart transplantation led to exclusion of the study. Similarly, registries incorporating multiple centres but not reporting the status for single facilities were not considered. Studies reporting in both paediatric and adult population were considered only if pertinent data was available for adult subset or in case paediatric population was <15% of the study. Mixed V-A ECLS configurations were also eligible such as standard V-A ECLS, veno-veno-arterial (V-VA) and/or veno-arterial-venous (V-AV) setting. Studies conducted in centres performing VAD only were pooled with those performing HTx and VADs. Reviews and case reports were not considered.

Two independent reviewers (G.M.R and K.Z.) selected the studies for inclusion, extracted studies, as well as patient characteristics of interest and relevant outcomes. Two authors (G.M.R. and K.Z.) independently assessed the trials' eligibility and risk of bias. Risk of bias at the individual study level was assessed using the ROBINS-I tool (Risk of Bias in Not-randomized Studies-of Interventions) [13]. Any divergences were resolved by a third reviewer (M.K.) and quantified using the approach of Cohen's kappa [14].

Endpoint selection

The primary endpoint was in-hospital mortality. Secondary endpoints were in-hospital neurologic complications, limb complications, bleeding, sepsis and acute kidney failure with or without continuous veno-venous hemofiltration (CVVH). Bridging to VAD and/or HTx was analysed as well. Neurological complications encompassed cerebrovascular events, strokes, transient ischemic attacks and other ischemic and haemorrhagic brain complications. A separate analysis of brain death was also conducted. Long-term survival was assessed at longest “out-of” hospital follow-up available. Outcome definitions were the ones adopted by the investigators of the included studies.

Statistical analysis

Statistical analyses were performed in Comprehensive Meta-Analysis, v. 2 (Biostat, Englewood, NJ). The results are expressed as pooled untransformed proportions (e.g. event rates (%)) and means with their 95% confidence intervals (CI). Heterogeneity across studies was evaluated using the I^2 test. Whenever a single study reported median values and interquartile ranges instead of mean $\pm$ SD, the latter were approximated as described by Wan et al [15]. Where available, we digitised Kaplan-Meier curves using Engauge Digitizer 9.5 (Mark Mitchell, Torrance, CA) and reconstructed time-to-event data using the algorithm specified by Guyot et al [16]. To control for the anticipated heterogeneity among observational studies, absolute values and means were pooled using random effects models. Studies were stratified a priori based on the centre status (non-HTx/VAD vs HTx/VAD performing centre); the interaction coefficient (Q-value) is provided for the comparison non-HTx/VAD vs HTx/VAD along with respective $P_{\text{interaction}}$. Additionally, we investigated if non-HTx/VAD and HTx/VAD status had influence on ECLS duration, weaning rates, bridging to HTx/VAD rates; and further if ECLS duration and weaning rates in these centres correlated with bridging to HTx/VAD by means of meta-regression analyses [17]. For the analysis of long-term survival study-level data were analyzed according to the original report for which outcome data were available. To account for potential differences in study’s duration of follow-up, rate ratios (RRs) with 95%CI derived from an analysis with adjusted models by person-years, a measure incorporating study duration, were used as summary statistics. Sensitivity analyses were performed by excluding from analyses single

studies, one at a time, and repeating the calculations for primary endpoint. Publication bias was assessed 1) by visual approach plotting log event rate against standard error in the funnel plot [18]; and 2) by linear regression approach [egger's regression]

Results

Study characteristics

Initial search process yielded 48,226 records; of these, 761 abstracts were retrieved for scrutiny based on the item's title. Registries were excluded since they incorporated both non-HTx/VAD and HTx/VAD centres. Following detailed assessment, 174 studies (N=13,038) [references to included studies] met inclusion criteria and entered quantitative analyses (Figure 1). Included studies were divided into non-HTx/VAD vs HTx/VAD centres subgroups: 154 studies including 12,022 (92.2%) patients were conducted in HTx whereas 20 studies (1,016 patients [7.8%]) in non-HTx/VAD centres. Prevalence of ECLS ranged from 0.26% [190] to 22.6% [55]. Studies were mostly conducted in the setting of postcardiotomy CS (44.2%) and acute myocardial infarction (20.7%) followed by other indications. Distribution of patients across range of indications for V-A ECLS is detailed in Figure 2.

Figure 2. Distribution of patients across range of indications for veno-arterial extracorporeal membrane oxygenation.

Figure 1. Study selection process according to PRISMA guidelines.

Detailed characteristics of included studies as well as patients' baseline and surgical data are available as Table 1 and Table 2. Publication bias analysis along with reasons for bias risk increase is available as Table 3.

Table 1. Study characteristics.

Study	Prevalence (%)	N. of pts	Age	Male	Etiology of cardiogenic shock (%)				
			(years)	(%)	PCS	AMI	myocarditis	cardiomyopathy	others
HTx/VAD centres									
Acheampong 2016	1.06	24	41 (IQR: 22–75)	58.3	100	0	0	0	0
Akin S 2019	NR	103	49.0 ± 16.0	54	48	24	0	24	4
Ariza-Sole A 2015	NR	29	NR	72	0	48	17	28	7
Arpesella 2008	5.85	11	49.4 ± 13.9	72.7	100	0	0	0	0
Asaumi Y 2005	NR	27	35.6 ± 16.5	70.4	0	0	100	0	0
Aubin H 2016	NR	115	56 ± 15	74	0	39	3	18	40
Avalli 2012	NR	42	58	73.8	19	50	0	7	24
Aziz TA 2010	NR	10	45 ± 18	50	40	10	0	10	40
Bakhtiary 2008	0.78	45	60.1 ± 13.6	77.8	96	0	0	0	4
Barth 2011	NR	242	NR	NR	13	0	0	0	87
Beckmann 2017	NR	8	50.1 ± 15.8	62.5	38	0	0	0	63
Bednarczyk 2014	NR	32	55 ± 11	66	0	75	3	0	22
Beiras-Fernandez 2011	NR	73	49.3 ± 18.0	64.4	74	0	0	0	26
Bermudez 2011	NR	33	55	81	0	100	0	0	0
Bermudez 2011 (2)	NR	9	48	88	0	0	0	100	0
Beurtheret 2013	NR	87	46 ± 15	68	0	46	16	28	10
Biancari 2017	0.6	148	65.4 ± 9.4	78.4	100	0	0	0	0
Boulate D 2013	NR	55	51.2	80	0	44	7	35	15
Cakici 2016	NR	148	56.6 ± 12	66.9	30	14	2	0	54
Carroll 2015	NR	123	47 ± 2	69.1	21	28	12	0	38
Centofanti 2017	NR	24	46.0 ± 14.41	54.2	17	42	25	17	0
Chamogeorgakis 2013	NR	308	57.2 ± 14.9	64	56	18	0	14	12
Chen 2011	NR	102	47 ± 2	60.8	59	4	18	0	20
Chen YS 1999	NR	2	27 ± 2.8	50	0	0	100	0	0
Chen YS 2005	NR	10	35 ± 16.1	NR	0	0	100	0	0
Cho YH 2015	NR	25	41.3 ± 17.2	72	16	0	8	32	44
Choi D-H 2016	NR	10	57.7 ± 6.2	70	NR	NR	NR	NR	NR
Chong SZ 2018	NR	35	40.6 ± 14.8	51.4	0	0	100	0	0
Chung SY 2012	NR	134	51.8 ± 20.5	77.6	23	40	19	4	14
Colafranceschi 2008	NR	11	63.5 ± 12	45.5	18	0	0	0	82
Combes 2008	NR	81	46 ± 16	56.8	32	20	20	22	6
Czobor 2016	NR	25	NR	20	NR	NR	NR	NR	NR
D'Alessandro 2010	22.6	91	47 ± 17	80.2	100	0	0	0	0
de Waha 2017	NR	100	61 (IQR: 50–71)	72	0	60	0	27	13

de Waha S 2016	NR	83	61 (IQR: 50-72)	73.5	0	64	0	23	13
Delmas 2017	NR	82	54 (IQR: 51-57)	64.7	24	35	0	0	40
Demondion 2013	NR	77	56.1 ± 0.7	75.3	0	100	0	0	0
den Uil 2017	NR	132	47 ± 16	55	25	20	5	6	45
Diez-Villanueva P 2014	NR	4	54.5 ± 7.4	75	0	100	0	0	0
Dini CS 2015	NR	14	52.1 ± 13.3	64.3	0	64	7	7	21
Distelmaier 2016/2017	3.35	354	65 (IQR: 55-73)	68.6	100	0	0	0	0
Dobrilovic N 2019	NR	12	56 (39-77)	41.7	0	50	0	0	50
Doll 2003	1.2	95	59.8 ± 13.3	69.5	100	0	0	0	0
Durinka JB 2014	NR	17	45 ± 11.5	70.6	0	29	18	53	0
Elsharkawy 2010	0.58	233	NR	67.4	100	0	0	0	0
Esper 2015	NR	18	60 ± 11.7	72.2	0	100	0	0	0
Fiser 2001	0.91	51	61.0 ± 1.7	56.9	100	0	0	0	0
Flécher 2014	NR	259	54 ± 15	69	42	28	5	7	17
Formica F 2010	NR	42	64.3 ± 11.3	66.7	60	40	0	0	0
Fux 2017	NR	181	58 (IQR: 47-66)	75	58	22	0	0	20
Fux T 2018 PCS	NR	105	62 (IQR: 52-68)	76	100	0	0	0	0
Fux T 2018	NR	76	52 (IQR: 37-60)	74	0	51	13	24	12
Garcia-Gigorro 2017	NR	46	48 ± 15	61	33	22	0	41	4
Guenther 2014	NR	41	52 ± 13	85.4	0	56	0	32	12
Guenther 2015	NR	87	54 ± 13	84	0	60	1	28	11
Guenther SPW 2018	NR	10	36 ± 16	60	20	10	0	50	20
Guihaire 2017	0.7	92	64.5 (18-83)	59	100	0	0	0	0
Hei 2011	NR	68	49.2 ± 13.3	76.5	90	0	0	0	10
Hoefer D 2006	NR	131	48.8 ± 14.7	67	47	0	0	0	53
Hou LS 2013	NR	54	NR	NR	NR	NR	NR	NR	NR
Huang M 2019	NR	127	NR	NR	0	60	27	0	13
Hryniewicz K 2016	NR	37	61 ± 12	76	14	49	0	0	38
Hsu 2009	2.89	51	63.0 ± 15.7	70.6	100	0	0	0	0
Huang S.C. 2006	NR	31	51.3 ± 15.1	74.2	26	45	13	16	0
Idelchik GM 2008	NR	18	47.9 ± 16.5	83.3	0	17	0	83	0
Jaamaa-Holmberg S 2018	NR	133	53 (IQR 18)	69.9	47	19	12	18	5
Jaski 2010	NR	150	57 ± 17	68.7	4	57	1	5	32
Jo 2011	NR	83	58.1±17.3	63.9	0	48	2	0	49
Kanji 2010	NR	50	49.36	72	88	0	0	0	12
Ko 2002	2.61	76	56.8 ± 15.9	63.2	100	0	0	0	0
Koerner MW 2019	NR	184	55 ± 15	71	24	22	3	0	51
Lamarche 2010	NR	32	52.5 ± 21	63	100	0	0	0	0
Lazzara RR 1993	NR	11	63 ± 8	72.7	100	0	0	0	0

Le Guen 2011	NR	51	42 ± 15	90	0	0	0	0	100
Le Pennec-Prigent S 2017	NR	26	52.4 ± 9.2	88.5	0	0	4	73	23
Leprince 2005	11.9	14	36 ± 15	78.6	100	0	0	0	0
Li 2015	0.91	123	56.2 ± 11.8	65.9	100	0	0	0	0
Liao X 2017	NR	33	33 ± 19	48.5	0	0	100	0	0
Liden 2009	NR	52	49.8 ± 15.1	84.6	63	17	4	0	15
Liu 2009	0.58	14	55.7 ± 15.4	50	100	0	0	0	0
Loforte 2014	NR	228	58.3 ± 10	68	68	12	3	0	18
Luo 2009	NR	45	49.0 ± 14.1	75.6	80	0	0	0	20
Maekawa K 2013	NR	24	57 (IQR: 48-63)	79.2	NR	NR	NR	NR	NR
Maggio 2007	NR	19	41.8 ± 13.7	47.4	0	0	0	0	100
Magovern GJ 1994	NR	21	56 ± 2.2	71.4	100	0	0	0	0
Mair P 1996	NR	7	51 ± 11.5	71.4	14	29	0	0	57
Marasco 2010	16.3	39	49.5 ± 12.5	76.9	100	0	0	0	0
Masseti 2005	NR	40	42 ± 15	57.5	10	40	5	10	35
Mateen 2011	NR	87	54	60	84	0	0	0	16
Matsumoto 2018	NR	37	42.4	56.8	0	0	100	0	0
Mazeffi 2016	0.42	23	57 ± 15	60.9	100	0	0	0	0
Meyer 2009	1.23	18	50 ± 15	72.2	100	0	0	0	0
Mohite 2015	NR	68	NR	NR	0	0	0	0	100
Mojoli 2013	NR	23	54 (IQR: 45-61)	78.3	0	65	4	26	4
Moraca 2012	NR	26	54	69.2	0	62	0	0	38
Morshuis M 2019	NR	134	53 ± 13	73	NR	NR	NR	NR	NR
Mozami N 2005	NR	38	NR	NR	NR	NR	NR	NR	NR
Muehrcke 1996	0.38	23	47.3 ± 16.4	73.9	100	0	0	0	0
Muller 2016	NR	138	55 (IQR: 46-63)	79.7	0	100	0	0	0
Musial 2017	NR	27	45 ± 16	70.4	100	0	0	0	0
Nakamura T 2015	NR	22	46.2 ± 14.8	45.5	0	0	100	0	0
Negi 2016	NR	15	57 ± 13	60	0	100	0	0	0
Noon GP 1999	NR	141	61.6	79.4	100	0	0	0	0
Pabst 2018	NR	61	62.2 ± 9.8	77	0	100	0	0	0
Pagani 2000	NR	14	45 ± 9	78.6	0	0	0	0	100
Pages 2009	NR	6	40 ± 4	50	0	0	100	0	0
Papadopoulos 2015	NR	360	62 ± 17	76.1	100	0	0	0	0
Park 2014	NR	152	60.3 ± 16.1	61.2	100	0	0	0	0
Peigh 2015	NR	73	48 ± 14	64.4	21	26	7	3	44
Pineton de Chambrun M 2016	NR	94	50.8 ± 11.5	75.5	0	70	1	9	20
Pokersnik 2012	NR	49	65 ± 13	67.3	100	0	0	0	0
Pontailier 2017	NR	163	75.7 ± 4.7	61.3	78	4	0	0	18

Pozzi M 2019 PCS	NR	90	57.5 ± 15.0	62	100	0	0	0	0
Pozzi M 2019 AMI	NR	56	56.7 ± 9.7	89.3	0	100	0	0	0
Ranucci 2011	NR	11	NR	NR	100	0	0	0	0
Rastan 2010	1.28	517	63.5 ± 11.2	71.5	100	0	0	0	0
Reedy JE 1990	NR	38	49.4	78.9	3	32	0	18	47
Rousse 2015	NR	98	42.8	60.2	42	17	5	18	17
Rubino 2017	NR	101	57.1 ± 15.8	63.4	100	0	0	0	0
Russo 2010	NR	14	47.8 ± 16.8	71.4	29	21	7	36	7
Saeed 2014	NR	37	62.6 ± 13.5	56.8	68	0	0	0	32
Salna 2018	NR	355	59 (IQR: 48-68)	68.2	44	30	0	0	26
Saxena 2015†	NR	45	76.8 ± 4.6	68.9	100	0	0	0	0
Scherer 2009	NR	5	47 ± 11	80	0	0	20	80	0
Schmack 2017	NR	48	49.7 ± 19.5	47.9	0	13	19	27	42
Schmidt 2012	NR	220	49 ± 16	66.8	35	19	14	15	16
Schwarz 2003	NR	46	47.8 ± 19.7	76.1	0	24	2	15	59
Sheu JJ 2010	NR	46	NR	NR	0	100	0	0	0
Shibilsky 2017	NR	15	46.1 ± 13	NR	0	33	13	47	7
Shin 2011	NR	85	59.9 ± 15.3	62.4	0	45	0	0	55
Slottosch 2012	NR	77	60 ± 13	76.6	100	0	0	0	0
Slottosch 2017	NR	139	58 ± 15	76.3	72	14	4	9	1
Smedira 2001	NR	202	55 ± 14	71.8	56	16	1	0	25
Tang GHL 2013	NR	21	61 ± 14	66.7	0	100	0	0	0
Tarzia 2015	NR	64	50 ± 16	81.3	0	58	0	0	42
Truby 2015	NR	179	56.9 ± 16.1	67.6	49	26	0	0	26
Tsai 2016	NR	105	57 ± 14	66.7	64	19	9	0	9
Tsai TY 2019	NR	23	57 (IQR 19)	82.6	57	26	4	0	13
Vanzetto G 2009	NR	100	54 ± 17	69	0	46	2	25	27
Villavicencio 2017	NR	28	42 ± 13	82.1	7	0	4	86	4
Wang 2009	0.49	62	51 ± 15	51.6	100	0	0	0	0
Wang 2013	1.79	87	65 ± 7	58.6	100	0	0	0	0
Wang Y 2019	NR	7	43.1 ± 9.3	71.4	100	0	0	0	0
Wester T 2014	NR	8	59	75	50	25	13	0	13
Wu 2010	2.63	110	60 ± 14	70.9	100	0	0	0	0
Wu 2012	NR	60	49	66.7	2	43	27	5	23
Wu MY 2013	NR	35	67	77.1	0	100	0	0	0
Xie 2017	NR	273	NR	NR	100	0	0	0	0
Yeh 2018	NR	99	76.4 ± 6.4	77.8	NR	NR	NR	NR	NR
Yost 2018	NR	107	53.1 ± 14.9	59.8	19	42	1	0	38
Yu K 2011	NR	120	29.3 ± 25	66.9	12	0	0	0	88

Zhang 2006	NR	32	55.4 ± 11.9	56.3	100	0	0	0	0
Zhao 2015	NR	24	59.3 ± 11.9	79.2	100	0	0	0	0
Zhong 2017	0.64	36	50.4 ± 12.2	91.7	100	0	0	0	0
Non-HTx/VAD centres									
Ariyaratnam 2014	NR	14	65.6 ± 10.5	57.1	100	0	0	0	0
Belle L 2012	NR	51	51.1 ± 15.5	74.5	0	33	6	14	47
Deschka 2013	NR	28	66.6 ± 5.3	92.9	100	0	0	0	0
Junqueira N 2015	NR	7	62	85.7	100	0	0	0	0
Khorsandi 2016	NR	15	64.3 ± 14.5	73	100	0	0	0	0
Kim 2018	NR	38	56.7 ± 14.7	68.4	0	0	26	0	74
Kuroki N 2015	NR	217	58.9 ± 15.0	82.9	2	58	5	0	35
Lee HS 2019	NR	135	59.4 ± 16.5	69.9	0	53	0	0	47
Lee SN 2017	NR	95	62.1 ± 8.7	62.1	5	52	8	0	35
Lin 2016	NR	17	NR	NR	0	0	0	0	100
Liu 2011	NR	11	55.9 ± 7.6	81.8	0	100	0	0	0
Mégarbane 2011	NR	66	46 (IQR: 39–55)	77.3	0	39	3	8	50
Mikus 2013	0.26	14	53.1 ± 14.3	64.3	100	0	0	0	0
Raffa 2017	NR	86	65 ± 11.2	65.1	100	0	0	0	0
Rigamonti F 2016	NR	29	NR	86.2	0	100	0	0	0
Sakamoto 2012	NR	98	72 ± 12	66.3	2	98	0	0	0
Smith 2001	NR	17	69	76	94	0	0	6	0
Sun 2018	NR	22	53 (IQR:40-64)	77	0	0	5	0	95
Unosawa 2012	NR	47	64.4 ± 12.5	74.4	100	0	0	0	0
Zhu RQ 2016	NR	10	NR	60	0	40	50	0	10

HTx, heart transplantation; VAD, ventricle assist device; PCS, postcardiotomy shock, AMI, acute myocardial infarction; NR, not reported

Table 2. Procedural characteristics.

Study	IABP (n)	Peripheral cannulation (n)	ECLS at index procedure (n)	ECLS at OR/ICU/other	Distal perfusion (n)	LV venting (n)	Duration	ECLS weaning (%)	Bridge to VAD (n)	Bridge to HTx (n)
HTx/VAD centres										
Acheampong 2016	14	NR	NR	NR	NR	NR	8.4 (0.8–35.4) days	75	5	0
Akin S 2019	NR	103	NR	NR	NR	NR	7 (4-11) days	NR	10	2
Ariza-Sole A 2015	13	NR	NR	NR	NR	NR	NR	52	NR	8
Arpesella 2008	NR	5	6	6/5	NR	NR	9.1 ± 6 days	90.9	0	0
Asaumi Y 2005	7	27	NR	NR	NR	NR	NR	88.9	1	NR
Aubin H 2016	NR	115	NR	NR	NR	NR	4 (2-7) days	53	11	0
Avalli 2012	21	35	NR	3/6/33	8	NR	NR	40.5	NR	NR
Aziz TA 2010	2	10	NR	NR	10	NR	5.8 ± 4 days	60	1	0
Bakhtiary 2008	30	37	NR	30/15	NR	NR	6.4 ± 4.5 days	55.6	5	2
Barth 2011	NR	242	NR	NR	242	NR	NR	43.4	7	8
Beckmann 2017	NR	8	NR	NR	8	NR	12.0 ± 5.9 days	50	1	0
Bednarczyk 2014	19	32	NR	2/12/18	NR	NR	2.9 ± 1.98 days	78.1	2	1
Beiras-Fernandez 2011	36	NR	NR	NR	NR	NR	4.4 ± 4.0 days	74	NR	NR
Bermudez 2011	31	NR	NR	13/7	5	NR	2.88 days	87.9	15	0
Bermudez 2011 (2)	6	NR	NR	1/8	1	NR	2.5 days	77.8	7	0
Beurtheret 2013	27	87	NR	NR	NR	NR	NR	44.8	5	3
Biancari 2017	47	89	76	NR	66	5	6.4 ± 5.6 days	48.6	6	0
Boulate D 2013	NR	46	NR	NR	NR	NR	4 days	100	0	0
Cakici 2016	34	148	NR	NR	NR	6	5 days	51.4	NR	NR
Carroll 2015	13	92	NR	61/31	NR	NR	94 (IQR: 43-172) hours	56.1	29	2
Centofanti 2017	24	24	NR	NR	NR	24	NR	79.2	3	3
Chamogeorgakis 2013	NR	247	NR	NR	NR	NR	NR	NR	8	2
Chen 2011	NR	NR	NR	NR	NR	NR	133 ± 12 hours	54.9	NR	NR
Chen YS 1999	2	2	NR	NR	NR	NR	3.9 ± 0.2 days	100	NR	NR
Chen YS 2005	6	NR	NR	NR	NR	NR	5.7 ± 3.1 days	100	NR	NR
Cho YH 2015	9	NR	NR	NR	NR	NR	8 days	100	NR	25
Choi D-H 2016	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Chong SZ 2018	28	35	NA	NR	8	4	7.8 ± 5.2 days	NR	0	0
Chung SY 2012	NR	NR	NR	NR	NR	NR	5.1 ± 5.7 days	50.7	NR	0
Colafranceschi 2008	NR	NR	NR	NR	NR	NR	3.2 ± 3.1 days	27.3	2	0
Combes 2008	12	60	NR	NR	60	NR	NR	53.1	9	5
Czobor 2016	10	25	NR	NR	25	NR	NR	NR	NR	NR

D'Alessandro 2010	NR	33	NR	NR	33	19	7 ± 4 days	60.4	2	1
de Waha 2017	NR	100	NR	NR	100	NR	5 (IQR: 3–8) days	56	NR	NR
de Waha S 2016	19	83	NR	NR	83	NR	6 (IGR:4-8) days	56.6	1	3
Delmas 2017	12	82	NR	NR	NR	NR	NR	42.7	3	5
Demondion 2013	43	59	NR	20/27/30	NR	NR	9.8 ± 7.1 days	48.1	13	5
den Uil 2017	37	130	NR	NR	127	2	6 (IQR: 3-9)	65.2	11	4
Diez-Villanueva P 2014	4	4	NR	NR	NR	NR	5 ± 2.6 days	100	1	0
Dini CS 2015	13	14	NR	1/5/8	14	NR	5.8 ± 5.5	NR	NR	1
Distelmaier 2016/2017	44	347	NR	NR	NR	NR	4 (IQR: 2–7) days	NR	4	3
Dobrilovic N 2017	1	NR	12	NR	NR	NR	200 (113-379) hours	NR	5	0
Doll 2003	95	26	NR	70/25	NR	NR	2.8 ± 2.1 days	47.4	8	0
Durinka JB 2014	0	17	NR	NR	17	NR	12.1 ± 7.9 days	12.9	17	0
Elsharkawy 2010	22	77	NR	NR	NR	NR	NR	NR	28	25
Esper 2015	3	18	NR	NR	NR	NR	3.2 (IQR: 2-4.75) days	NR	4	NR
Fiser 2001	NR	NR	NR	22/29	NR	NR	67.5 hours	31.4	NR	NR
Flécher 2014	NR	238	NR	150/109	238	20	7 ± 6 days	59.1	7	15
Formica F 2010	29	27	NR	21/10/11	10	NR	7.9 ± 5.3 days	69	NR	NR
Fux 2017	NR	NR	NR	NR	NR	NR	7 (IQR: 3-13) days	54.1	7	11
Fux T 2018 PCS	5	80	NR	51/NR/NR	72	NR	7 (IQR: 3-14) days	51	1	1
Fux T 2018	18	NR	NR	47/18/11	NR	NR	5 (IQR: 2-11) days	37	3	10
Garcia-Gigorro 2017	23	39	NR	NR	NR	NR	17 (8–29) days	67.4	NR	14
Guenther 2014	NR	41	NR	NR	41	NR	5.2 ± 3.7 days	41.5	3	1
Guenther 2015	12	96	NR	NR	96	1	4.7 ± 3.2 days	62.1	9	1
Guenther SPW 2018	5	8	NR	NR	NR	8	753 ± 777 hours	60	3	1
Guihaire 2017	25	78	43	80/12	NR	13	6 days	47.8	2	2
Hei 2011	11	67	NR	29/39	NR	NR	4.8 ± 2.8 days	76.5	NR	8
Hoefer D 2006	0	131	NR	NR	131	NR	2.9 ± 1.9 days	60.3	28	5
Hou LS 2013	NR	NR	NR	NR	NR	NR	1 day	57.4	NR	NR
Huang M 2019	NR	NR	NR	NR	NR	NR	NR	58	9	NR
Hryniewicz K 2016	20	37	NR	8/NR/29	37	NR	4 (IQR: 3-5) days	70.3	4	1
Hsu 2009	51	51	NR	NR	NR	NR	7.5 ± 6.7 days	52.9	0	3
Huang S.C. 2006	27	31	NR	NR	NR	NR	NR	64.5	8	1
Idelchik GM 2008	17	18	NR	NR/NR/18	NR	NR	4.2 ± 2.5 days	77.8	14	NR
Jaamaa-Holmberg S 2018	36	94	NR	NR	NR	NR	6 (IQR 7) days	50	15	17
Jaski 2010	NR	110	NR	NR/76/74	NR	NR	NR	46	7	0
Jo 2011	35	83	NR	NR	83	NR	1.75 days	57.8	NR	7

Kanji 2010	36	22	NR	NR	NR	NR	2.5 (IQR: 1.0-4.8) days	NR	0	23
Ko 2002	54	61	39	23/30	20	NR	NR	28.9	2	2
Koerner MW 2019	NR	NR	NR	NR	NR	NR	7.8 ± 7.9 days	51.6	12	NR
Lamarche 2010	NR	15	NR	24/8	NR	NR	46.25 ± 61 hours	78.1	6	3
Lazzara RR 1993	11	1	NR	6/5	NR	NR	2 days	72.7	NR	NR
Le Guen 2011	NR	51	NR	NR	51	NR	NR	NR	NR	NR
Le Pennec-Prigent S 2017	NR	26	NR	NR	26	NR	7.1 ± 6.3 days	50	1	1
Leprince 2005	NR	13	6	6/8	13	NR	5 ± 2.5 days	78.6	1	1
Li 2015	73	123	61	NR	123	NR	4.3 days	56.1	NR	NR
Liao X 2017	5	NR	NR	NR	NR	NR	3 days	NR	NR	NR
Liden 2009	18	NR	NR	NR	NR	NR	7.7 ± 11.4 days	50	2	2
Liu 2009	10	14	9	NR	NR	NR	71 ± 52 hours	64.3	NR	1
Loforte 2014	228	126	NR	202/26	83	NR	10.9 ± 9.7 days	63.2	6	31
Luo 2009	11	40	NR	15/30	40	0	5.3 ± 4.3 days	60	NR	5
Maekawa K 2013	9	NR	NR	NR	NR	NR	49 (IQR: 43-66) min	NR	NR	NR
Maggio 2007	NR	NR	NR	NR	2	NR	4.6 ± 4.3 days	NR	NR	NR
Magovern GJ 1994	19	5	12	NR	NR	NR	41.8 ± 7.4 min	76.2	NR	NR
Mair P 1996	1	7	0	0/6/1	NR	NR	NR	57.1	NR	1
Marasco 2010	9	16	NR	NR	16	NR	6.78 ± 2.64 days	87.2	3	NR
Masseti 2005	2	40	NR	16/11/13	NR	NR	105 ± 44 min	15	9	2
Mateen 2011	NR	NR	NR	NR	NR	NR	3.8 days	NR	NR	NR
Matsumoto 2018	28	37	NR	NR	3	NR	NR	83.8	9	0
Mazeffi 2016	3	9	3	NR	NR	0	3 (IQR: 1-8) days	60.9	2	NR
Meyer 2009	NR	18	NR	NR	18	NR	4 ± 4 days	66.7	NR	NR
Mohite 2015	NR	NR	NR	NR	NR	NR	NR	60.3	NR	NR
Mojoli 2013	13	23	NR	NR	NR	NR	3 (IQR: 2-14) days	43.5	NR	6
Moraca 2012	21	26	NR	NR	NR	NR	3 days	84.6	9	1
Morshuis M 2019	NR	NR	NR	NR	NR	NR	NR	44	29	0
Mozami N 2005	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Muehrcke 1996	17	17	NR	15/8	0	NR	58.4 + 35.1 h	56.5	4	0
Muller 2016	96	NR	NR	NR	NR	NR	7 (IQR: 4-10) days	35.5	18	13
Musial 2017	NR	27	27	NR	NR	NR	8.89 days	NR	NR	NR
Nakamura T 2015	21	22	NR	NR	22	NR	7.5 ± 1.1 days	NR	1	0
Negi 2016	9	15	NR	NR	NR	NR	1.9 days	53.3	1	NR
Noon GP 1999	NR	97	114	114/27	NR	NR	3.8 days	31.2	NR	NR
Pabst 2018	38	61	6	NR	61	NR	6.6 days	60.7	8	2
Pagani 2000	9	14	NR	NR	1	NR	6 ± 5 days	57.1	7	0

Pages 2009	1	6	NR	4/2	6	NR	13 ± 4 days	100	1	0
Papadopoulos 2015	NR	324	NR	NR	NR	NR	7 ± 1 days	58.1	6	0
Park 2014	NR	152	41	11/76/65	152	NR	67.3 ± 107.4 hours	44.1	NR	3
Peigh 2015	NR	NR	NR	NR	NR	NR	9.2 ± 6.1 days	64.4	NR	NR
Pineton de Chambrun M 2016	47	94	NR	NR	94	NR	4 (IQR: 2-6) days	35.1	4	2
Pokersnik 2012	29	32	NR	NR	32	NR	3.8 ± 3.4 days	55.1	2	NR
Pontailier 2017	55	136	NR	NR	136	NR	5.6 ± 4.3 days	41.1	NR	NR
Pozzi M 2019PCS	9	54	63	63/27/0	NR	NR	6.4 ± 6.3 days	50	0	0
Pozzi M 2019AMI	46	54	NR	NR	NR	NR	8.1 ± 14.3 days	50	5	4
Ranucci 2011	NR	0	NR	NR	NR	NR	122.1 ± 80.5 hours	63.6	NR	NR
Rastan 2010	383	203	NR	NR	121	NR	3.28 ± 2.85 days	63.4	15	5
Reedy JE 1990	25	NR	NR	NR	NR	NR	1.2 days	0	0	0
Rousse 2015	13	78	NR	NR	78	NR	4.5 days	50	7	13
Rubino 2017	NR	NR	63	NR	NR	NR	5 (IQR: 3-8) days	57.4	3	3
Russo 2010	12	8	NR	NR/5/NR	8	1	11.5 ± 8.2 days	78.6	2	2
Saeed 2014	NR	25	NR	NR	25	NR	5.9 ± 4.2	NR	4	NR
Salna 2018	NR	305	NR	NR	NR	NR	4 (IQR: 1-6) days	72.4	NR	NR
Saxena 2015†	NR	15	NR	NR	NR	NR	103.8 ± 74.3 hours	53.3	NR	NR
Scherer 2009	1	5	NR	NR	5	NR	8 ± 4 days	100	5	0
Schmack 2017	17	10	NR	NR	NR	20	6.10 ± 3.81 days	NR	14	5
Schmidt 2012	NR	NR	NR	106/65/49	NR	NR	13.4 days	NR	NR	NR
Schwarz 2003	NR	46	0	NR	NR	NR	1.7 ± 1.5 days	60.9	NR	6
Sheu JJ 2010	46	46	NR	NR	3	NR	NR	78.3	NR	1
Shibilsky 2017	NR	15	NR	NR	15	NR	7.5 ± 2.6 days	100	15	0
Shin 2011	NR	85	NR	NR	NR	NR	42.1 ± 25.7 min	NR	NR	2
Slottosch 2012	72	77	34	34/43	77	NR	79 ± 57 hours	62.3	NR	NR
Slottosch 2017	104	110	NR	NR/59/NR	110	NR	113 ± 74 hours	63.3	15	NR
Smedira 2001	115	153	NR	NR	NR	NR	NR	58.9	42	6
Tang GHL 2013	NR	21	NR	14/NR/7	NR	NR	9.0 ± 7.5 days	76.2	2	0
Tarzia 2015	25	63	NR	33/31	NR	NR	7 days	85.9	23	12
Truby 2015	57	134	NR	71/108	9	NR	3.58 (IQR: 1.6 –5.9) days	NR	52	NR
Tsai 2016	NR	NR	NR	NR	NR	NR	7 ± 5 days	70.5	NR	NR
Tsai TY 2019	18	NR	NR	0/23/0	NR	NR	5 (IQR 5) days	NR	NR	NR
Vanzetto G 2009	30	93	NR	NR	NR	NR	2.38 ± 2.8 days	33	NR	NR
Villavicencio 2017	8	0	NR	28/0	NR	NR	40 days	71.4	NR	18
Wang 2009	19	NR	NR	36/26	NR	0	61 ± 37 hours	64.5	NR	NR
Wang 2013	41	NR	37	37/50	37	NR	61 ± 37 hours	58.6	NR	NR

Wang Y 2019	NR	NR	6	6/1/0	NR	NR	244.5 ± 57.8 hours	100	0	0
Wester T 2014	6	7	NR	NR	NR	NR	5.1 ± 2.8 days	62.5	NR	NR
Wu 2010	NR	NR	NR	98/12	NR	NR	143 ± 112 hours	60.9	2	0
Wu 2012	44	NR	NR	1/25/34	NR	NR	NR	63.3	NR	NR
Wu MY 2013	NR	NR	NR	NR	NR	NR	3 days	62.9	NR	16
Xie 2017***	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Yeh 2018	NR	99	NR	NR	99	NR	5.2 ± 5.2 days	28.3	NR	NR
Yost 2018	NR	NR	5	NR	NR	NR	14 days	NR	NR	NR
Yu K 2011	12	78	NR	NR	NR	NR	5.7 ± 4.8 days	NR	NR	NR
Zhang 2006	10	19	NR	NR	NR	NR	2.7 ± 1.7 days	43.8	NR	NR
Zhao 2015	16	23	9	NR	NR	NR	115.2 ± 70.2 hours	66.7	1	NR
Zhong 2017	9	29	24	24/12	NR	NR	77.5 ± 34.5 hours	66.7	NR	NR
Non-HTx/VAD centres										
Ariyaratnam 2014	NR	0	NR	NR	NR	NR	5.6 ± 3.4 days	50	NR	NR
Belle L 2012	5	51	NR	0/8/43	4	NR	NR	33.3	1	0
Deschka 2013	25	0	NR	NR	NR	NR	8.7 ± 3.9 days	42.9	NR	NR
Junqueira N 2015	6	7	5	5/2/0	NR	NR	5.4 days	57.1	NR	NR
Khorsandi 2016	NR	5	NR	NR	NR	NR	5.5 ± 8.9 days	40	NR	NR
Kim 2018	NR	NR	NR	NR	NR	NR	9.0 ± 7.6 days	55.3	NR	NR
Kuroki N 2015	146	217	NR	NR	NR	NR	3.2 ± 3.3 days	39.2	NR	NR
Lee HS 2019	22	NR	NR	NR	NR	NR	99.6 ± 103.2 hours	39.3	NR	NR
Lee SN 2017	NR	NR	NR	NR	NR	NR	7.6 ± 6.9 days	42.1	NR	NR
Lin 2016	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Liu 2011	11	11	NR	0/2/9	NR	NR	80.2 ± 62.7 hours	63.6	NR	NR
Mégarbane 2011	NR	66	NR	0/66	66	NR	8 (IQR: 3–26) hours	1.5	NR	1
Mikus 2013	13	6	12	NR	14	14	5 days	50	NR	0
Raffa 2017	23	30	48	48/38	NR	NR	5 days	48.8	NR	NR
Rigamonti F 2016	NR	NR	NR	NR	20	NR	NR	NR	NR	NR
Sakamoto 2012	94	98	NR	NR/NR/98	NR	NR	2.9 ± 2.6 days	55.1	0	0
Smith 2001	14	11	NR	NR	NR	0	3.6 days	64.7	NR	NR
Sun 2018	9	22	NR	7/2/13	5	NR	2.2 (IQR: 1.78-4.55) days	81.8	6	0
Unosawa 2012	39	32	33	33/14	NR	NR	63.5 ± 61.5 hours	61.7	0	0
Zhu RQ 2016	3	NR	NR	NR	NR	NR	NR	90	NR	NR

HTx, heart transplantation; VAD, ventricle assist device; ECLS, extracorporeal life support; LV, left ventricle

Table 3. ROBINS-I tool bias assessment.

Study	Bias due to confounding	Bias in selection of participants into the study	Bias in measurement of interventions	Bias due to departures from intended interventions	Bias due to missing data*	Bias in measurement of outcomes*	Bias in selection of reported result*	Overall bias	Cohen's Kappa
Acheampong 2016	Critical	Critical	Serious	NA	Serious	Moderate	Low	Critical	0.57
Akin S 2019	Critical	Low	Low	NA	Low	Serious	Moderate	Moderate	0.86
Ariza-Sole 2015	Critical	Low	Critical	NA	Serious	Critical	Critical	Critical	0.86
Arpesella 2008	Critical	Serious	Serious	NA	Moderate	Serious	Serious	Serious	0.86
Asaumi 2005	Critical	Serious	Critical	NA	Moderate	Serious	Serious	Serious	0.71
Aubin 2016	Critical	Moderate	Moderate	NA	Low	Low	Low	Low	0.86
Avalli 2012	Critical	Moderate	Low	NA	Moderate	Serious	Serious	Serious	0.71
Aziz 2010	Critical	Low	Low	NA	Low	Low	Low	Low	0.86
Bakhtiary 2008	Critical	Low	Serious	NA	Moderate	Low	Low	Low	0.71
Barth 2011	Critical	Low	Critical	NA	Critical	Serious	Serious	Critical	0.86
Beckmann 2017	Critical	Critical	Serious	NA	Low	Moderate	Low	Critical	0.71
Bednarczyk 2014	Critical	Moderate	Low	NA	Low	Low	Low	Low	0.86
Beiras-Fernandez 2011	Critical	Low	Low	NA	Serious	Critical	Critical	Critical	0.71
Bermudez 2011	Critical	Serious	Low	NA	Serious	Low	Low	Low	0.86
Bermudez 2011 (2)	Critical	Serious	Low	NA	Serious	Low	Low	Low	0.86
Beurtheret 2013	Critical	Low	Serious	NA	Low	Low	Low	Low	0.86
Biancari 2017	Critical	Serious	Serious	NA	Low	Low	Low	Low	0.86

Boulate 2013	Critical	Critical	Critical	NA	Moderate	Serious	Serious	Critical	0.71
Cakici 2016	Critical	Low	Low	NA	Moderate	Low	Low	Low	0.86
Carroll 2015	Critical	Low	Moderate	NA	Low	Critical	Moderate	Critical	0.57
Centofanti 2017	Critical	Moderate	Serious	NA	Moderate	Moderate	Moderate	Moderate	0.86
Chamogeorgakis 2013	Critical	Low	Critical	NA	Moderate	Moderate	Moderate	Moderate	0.86
Chen 2011	Critical	Critical	Critical	NA	Serious	Critical	Critical	Critical	0.86
Chen 1999	Critical	Serious	Critical	NA	Low	Serious	Serious	Serious	0.86
Chen 2005	Critical	Serious	Low	NA	Critical	Serious	Serious	Serious	0.86
Cho 2015	Critical	Moderate	Critical	NA	Moderate	Serious	Serious	Critical	0.86
Choi 2016	Critical	Moderate	Low	NA	Moderate	Critical	Critical	Critical	0.86
Chong SZ 2018	Critical	Low	Low	NA	Low	Serious	Moderate	Moderate	0.71
Chung 2012	Critical	Low	Low	NA	Moderate	Moderate	Moderate	Moderate	0.86
Colafranceshi 2008	Critical	Low	Serious	NA	Moderate	Moderate	Moderate	Moderate	0.86
Combes 2008	Critical	Low	Low	NA	Low	Critical	Moderate	Low	0.86
Czobor 2016	Critical	Low	Low	NA	Critical	Serious	Serious	Critical	0.86
D'Alessandro 2010	Critical	Serious	Serious	NA	Moderate	Serious	Serious	Serious	0.71
de Waha 2017	Critical	Serious	Low	NA	Moderate	Serious	Serious	Serious	0.86
de Waha S 2016	Critical	Low	Low	NA	Low	Low	Low	Low	0.86
Delmas 2017	Critical	Low	Low	NA	Moderate	Low	Low	Low	0.86
Demondion 2013	Critical	Serious	Serious	NA	Moderate	Moderate	Moderate	Moderate	0.71
den Uil 2017	Critical	Low	Low	NA	Moderate	Moderate	Moderate	Moderate	0.86

Diez-Villanueva 2014	Critical	Serious	Critical	NA	Low	Moderate	Moderate	Critical	0.86
Dini 2015	Critical	Low	Low	NA	Low	Moderate	Moderate	Low	0.86
Distelmaier 2016/2017	Critical	Low	Low	NA	Moderate	Critical	Serious	Critical	0.86
Dobrilovic N 2017	Critical	Low	Low	NA	Low	Serious	Moderate	Moderate	0.86
Doll 2003	Critical	Serious	Low	NA	Moderate	Low	Low	Low	0.71
Durinka 2014	Critical	Critical	Serious	NA	Moderate	Moderate	Moderate	Moderate	0.71
Elsharkawy 2010	Critical	Serious	Low	NA	Critical	Moderate	Moderate	Critical	0.71
Esper 2015	Critical	Serious	Critical	NA	Moderate	Moderate	Moderate	Moderate	0.86
Fiser 2001	Critical	Low	Critical	NA	Serious	Moderate	Moderate	Critical	0.86
Flécher 2014	Critical	Low	Low	NA	Moderate	Serious	Serious	Serious	0.71
Formica 2010	Critical	Moderate	Serious	NA	Moderate	Moderate	Moderate	Moderate	0.86
Fux 2017	Critical	Low	Serious	NA	Serious	Serious	Serious	Serious	0.86
Fux T 2018 PCS	Critical	Low	Low	NA	Low	Serious	Low	Moderate	0.86
Fux T 2018	Critical	Low	Low	NA	Low	Serious	Low	Moderate	0.71
Garcia-Gigorro 2017	Critical	Low	Low	NA	Low	Moderate	Moderate	Low	0.86
Guenther 2014	Critical	Low	Serious	NA	Low	Low	Low	Low	0.86
Guenther 2015	Critical	Moderate	Serious	NA	Moderate	Low	Low	Moderate	0.86
Guenther SPW 2018	Critical	Low	Low	NA	Low	Serious	Low	Moderate	0.71
Guihaire 2017	Critical	Serious	Low	NA	Low	Moderate	Low	Low	0.86
Hei 2011	Critical	Low	Low	NA	Low	Low	Low	Low	0.86

Hoefler 2006	Critical	Low	Critical	NA	Moderate	Moderate	Moderate	Moderate	0.86
Hou 2013	Critical	Moderate	Low	NA	Critical	Serious	Serious	Critical	0.57
Huang M 2019	Critical	Low	Low	NA	Low	Serious	Serious	Moderate	0.86
Hryniewicz 2016	Critical	Low	Critical	NA	Moderate	Moderate	Moderate	Moderate	0.86
Hsu 2009	Critical	Low	Low	NA	Moderate	Moderate	Low	Low	0.86
Huang 2006	Critical	Moderate	Low	NA	Low	Serious	Serious	Serious	0.86
Idelchik 2008	Critical	Critical	Low	NA	Moderate	Serious	Serious	Critical	0.71
Jaamaa-Holmberg S 2018	Critical	Low	Low	NA	Low	Serious	Moderate	Moderate	0.86
Jaski 2010	Critical	Low	Critical	NA	Moderate	Serious	Serious	Critical	0.86
Jo 2011	Critical	Moderate	Serious	NA	Low	Moderate	Moderate	Moderate	0.86
Kanji 2010	Critical	Low	Serious	NA	Moderate	Moderate	Low	Moderate	1
Ko 2002	Critical	Low	Critical	NA	Low	Moderate	Moderate	Critical	0.86
Koerner MM 2019	Critical	Low	Low	NA	Low	Serious	Serious	Moderate	0.86
Lamarche 2010	Critical	Serious	Moderate	NA	Moderate	Moderate	Low	Moderate	0.71
Lazzara 1993	Critical	Serious	Moderate	NA	Moderate	Moderate	Moderate	Moderate	0.86
Le Guen 2011	Critical	Moderate	Moderate	NA	Moderate	Serious	Serious	Moderate	0.86
Le Pennec-Prigent 2017	Critical	Moderate	Low	NA	Low	Moderate	Moderate	Moderate	0.86
Leprince 2005	Critical	Serious	Moderate	NA	Moderate	Serious	Serious	Serious	0.57
Li 2015	Critical	Low	Low	NA	Low	Moderate	Low	Low	0.86
Liao 2017	Critical	Serious	Low	NA	Serious	Moderate	Moderate	Serious	0.86
Liden 2009	Critical	Moderate	Critical	NA	Serious	Moderate	Low	Critical	0.57

Liu 2009	Critical	Critical	Moderate	NA	Low	Moderate	Low	Critical	0.71
Loforte 2014	Critical	Low	Critical	NA	Low	Moderate	Low	Low	0.71
Luo 2009	Critical	Low	Low	NA	Low	Moderate	Low	Low	1
Maekawa 2013	Critical	Moderate	Critical	NA	Serious	Critical	Critical	Critical	0.71
Maggio 2007	Critical	Serious	Low	NA	Serious	Critical	Critical	Critical	0.86
Magovern 1994	Critical	Serious	Serious	NA	Moderate	Serious	Serious	Serious	0.86
Mair 1996	Critical	Low	Moderate	NA	Low	Moderate	Moderate	Moderate	0.86
Marasco 2010	Critical	Serious	Low	NA	Moderate	Low	Low	Low	0.86
Massetti 2005	Critical	Low	Serious	NA	Moderate	Low	Low	Low	0.71
Mateen 2011	Critical	Serious	Critical	NA	Serious	Serious	Serious	Serious	0.86
Matsumoto 2018	Critical	Serious	Serious	NA	Low	Moderate	Moderate	Serious	0.86
Mazeffi 2016	Critical	Low	Moderate	NA	Moderate	Moderate	Moderate	Moderate	1
Meyer 2009	Critical	Low	Low	NA	Moderate	Moderate	Moderate	Moderate	0.71
Mohite 2015	Critical	Low	Critical	NA	Critical	Critical	Critical	Critical	1
Mojoli 2013	Critical	Low	Low	NA	Low	Low	Low	Low	0.86
Moraca 2012	Critical	Low	Low	NA	Moderate	Moderate	Moderate	Moderate	0.86
Morshuis M 2019	Critical	Low	Low	NA	Low	Serious	Serious	Moderate	0.86
Mozami 2005	Critical	Moderate	Moderate	NA	Serious	Serious	Serious	Serious	0.86
Muehrcke 1996	Critical	Serious	Critical	NA	Low	Low	Low	Low	0.86
Muller 2016	Critical	Serious	Low	NA	Serious	Moderate	Moderate	Serious	0.86
Musial 2017	Critical	Low	Critical	NA	Low	Serious	Moderate	Critical	0.71
Nakamura 2015	Critical	Serious	Serious	NA	Low	Moderate	Moderate	Serious	0.57

Negi 2016	Critical	Serious	Low	NA	Low	Low	Low	Low	0.86
Noon 1999	Critical	Serious	Serious	NA	Moderate	Moderate	Moderate	Moderate	0.86
Pabst 2018	Critical	Serious	Critical	NA	Moderate	Moderate	Moderate	Moderate	0.71
Pagani 2000	Critical	Critical	Low	NA	Moderate	Serious	Serious	Critical	0.86
Pages 2009	Critical	Serious	Critical	NA	Moderate	Serious	Serious	Serious	0.86
Papadopoulos 2015	Critical	Low	Low	NA	Moderate	Moderate	Low	Low	0.86
Park 2014	Critical	Moderate	Low	NA	Low	Moderate	Moderate	Moderate	0.86
Peigh 2015	Critical	Low	Critical	NA	Serious	Critical	Serious	Critical	0.57
Pineton de Chambrun M 2016	Critical	Low	Low	NA	Low	Moderate	Moderate	Low	0.86
Pokersnik 2012	Critical	Serious	Critical	NA	Low	Moderate	Moderate	Critical	0.71
Pontailier 2017	Critical	Low	Serious	NA	Low	Critical	Serious	Critical	0.86
Pozzi M 2019 PCS	Critical	Low	Low	NA	Low	Serious	Low	Moderate	0.86
Pozzi M 2019 AMI	Critical	Low	Low	NA	Low	Serious	Moderate	Moderate	0.71
Ranucci 2011	Critical	Critical	Critical	NA	Critical	Critical	Critical	Critical	0.86
Rastan 2010	Critical	Low	Low	NA	Low	Moderate	Low	Low	0.71
Reedy 1990	Critical	Moderate	Moderate	NA	Serious	Serious	Serious	Serious	0.86
Rousse 2015	Critical	Low	Serious	NA	Moderate	Critical	Moderate	Critical	0.71
Rubino 2017	Critical	Low	Critical	NA	Serious	Moderate	Low	Critical	0.71
Russo 2010	Critical	Low	Low	NA	Low	Critical	Serious	Low	0.71
Saeed 2014	Critical	Critical	Critical	NA	Moderate	Moderate	Moderate	Critical	0.86
Salna 2018	Critical	Moderate	Low	NA	Moderate	Critical	Critical	Critical	0.86

Saxena 2015	Critical	Serious	Low	NA	Low	Moderate	Low	Low	0.86
Scherer 2009	Critical	Critical	Critical	NA	Moderate	Moderate	Moderate	Critical	0.86
Schmack 2017	Critical	Low	Low	NA	Moderate	Serious	Serious	Serious	0.71
Schmidt 2012	Critical	Critical	Low	NA	Serious	Critical	Critical	Critical	0.86
Schwarz 2003	Critical	Moderate	Serious	NA	Moderate	Moderate	Moderate	Moderate	0.86
Sheu 2010	Critical	Serious	Low	NA	Critical	Moderate	Moderate	Critical	0.86
Shibilsky 2017	Critical	Critical	Critical	NA	Low	Serious	Serious	Critical	0.71
Shin 2011	Critical	Moderate	Low	NA	Moderate	Serious	Serious	Serious	0.71
Slottosch 2012	Critical	Low	Low	NA	Low	Low	Low	Low	0.86
Slottosch 2017	Critical	Low	Low	NA	Low	Moderate	Low	Low	0.86
Smedira 2001	Critical	Low	Critical	NA	Moderate	Low	Low	Low	0.71
Tang 2013	Critical	Serious	Serious	NA	Moderate	Low	Low	Serious	0.57
Tarzia 2015	Critical	Serious	Low	NA	Moderate	Low	Low	Low	0.86
Truby 2015	Critical	Low	Serious	NA	Low	Critical	Moderate	Critical	0.86
Tsai 2016	Critical	Critical	Critical	NA	Serious	Critical	Critical	Critical	0.57
Tsai TY 2019	Critical	Low	Low	NA	Low	Serious	Serious	Moderate	0.71
Vanzetto 2009	Critical	Low	Moderate	NA	Moderate	Serious	Serious	Serious	0.86
Villavicencio 2017	Critical	Serious	Low	NA	Moderate	Low	Low	Low	0.86
Wang 2009	Critical	Low	Low	NA	Serious	Low	Low	Low	0.71
Wang 2013	Critical	Critical	Low	NA	Serious	Low	Low	Low	0.86
Wang Y 2019	Critical	Low	Low	NA	Low	Serious	Serious	Moderate	0.71
Wester 2014	Critical	Serious	Critical	NA	Moderate	Serious	Serious	Serious	0.71

Wu 2010	Critical	Low	Critical	NA	Serious	Low	Low	Low	1
Wu 2012	Critical	Serious	Low	NA	Serious	Moderate	Moderate	Serious	0.86
Wu MY 2013	Critical	Serious	Low	NA	Serious	Moderate	Moderate	Serious	0.86
Xie 2017	Critical	Serious	Critical	NA	Critical	Critical	Critical	Critical	0.86
Yeh 2018	Critical	Critical	Serious	NA	Low	Critical	Critical	Critical	0.86
Yost 2018	Critical	Low	Critical	NA	Serious	Critical	Critical	Critical	0.71
Yu 2011	Critical	Low	Critical	NA	Moderate	Low	Low	Low	0.71
Zhang 2006	Critical	Serious	Critical	NA	Low	Serious	Moderate	Critical	0.86
Zhao 2015	Critical	Critical	Critical	NA	Low	Moderate	Moderate	Critical	0.71
Zhong 2017	Critical	Critical	Low	NA	Low	Serious	Moderate	Critical	0.57
Ariyaratnam 2014	Critical	Serious	Critical	NA	Low	Critical	Critical	Critical	1
Belle 2012	Critical	Low	Low	NA	Moderate	Low	Low	Low	0.86
Deschka 2013	Critical	Serious	Serious	NA	Moderate	Low	Low	Serious	0.86
Junqueira 2015	Critical	Serious	Serious	NA	Moderate	Moderate	Moderate	Moderate	0.71
Khorsandi 2016	Critical	Serious	Serious	NA	Low	Low	Low	Low	0.86
Kim 2018	Critical	Serious	Critical	NA	Serious	Critical	Critical	Critical	0.86
Kuroki 2015	Critical	Moderate	Serious	NA	Moderate	Serious	Serious	Serious	0.86
Lee HS 2019	Critical	Low	Low	NA	Low	Serious	Moderate	Moderate	0.86
Lee 2017	Critical	Low	Low	NA	Serious	Serious	Serious	Serious	0.71
Lin 2016	Critical	Serious	Critical	NA	Critical	Critical	Critical	Critical	0.86
Liu 2011	Critical	Serious	Serious	NA	Moderate	Moderate	Moderate	Moderate	0.86
Mégarbane 2011	Critical	Moderate	Serious	NA	Moderate	Moderate	Moderate	Moderate	0.86

Mikus 2013	Critical	Serious	Low	NA	Low	Moderate	Low	Low	0.71
Raffa 2017	Critical	Serious	Serious	NA	Low	Low	Low	Low	0.71
Rigamonti 2016	Critical	Serious	Low	NA	Critical	Critical	Critical	Critical	0.86
Sakamoto 2012	Critical	Serious	Low	NA	Low	Moderate	Moderate	Moderate	0.86
Smith 2001	Critical	Low	Low	NA	Low	Moderate	Moderate	Low	0.71
Sun 2018	Critical	Serious	Serious	NA	Moderate	Low	Low	Serious	0.86
Unosawa 2012	Critical	Serious	Low	NA	Low	Moderate	Low	Low	0.86
Zhu 2016	Critical	Low	Moderate	NA	Low	Serious	Serious	Serious	0.71

*When multiple outcomes were reported for a study, the highest level of bias at the outcome level is reported in the table. Bias reported for comparison of peripheral vs central extracorporeal circulation and not for a study in general.

Studies were judged to be moderate to severe risk of bias as none previously compared directly non-HTx/VAD vs HTx/VAD centres performance; no signs of small/big study effect was seen on visual inspection of funnel plot for primary endpoint (Figure 3).

FIGURE 3. Funnel-plot of primary endpoint.

ECLS strategy

ECLS was initiated in the operating room in 43.0% of patients (36.5-49.8%), followed by intensive care unit, cardiac catheterization laboratory, telemetry floor and emergency department without statistical differences between HTx/VAD - as compared to non-HTx/VAD centres: 43.6% (36.8-50.7%) and 37.3% (19.2-59.8%), respectively ($p=0.589$). Median ECLS duration in the entire series was 6.11 days again without apparent differences between HTx/VAD (mean weighted average = 5.95 days) vs non-HTx/VAD (4.77 days) centres ($p=0.204$). Successful weaning from ECLS was most often defined as decannulation after >48 hours. Overall, estimated 57.5% (55.2-59.9%) patients were weaned from ECLS with the weaning rates ranging from 0 to 100% in the entire series. These rates were significantly higher in HTx/VAD vs non-HTx/VAD centres 58.7% (56.2-61.1%) vs 48.9% (42.0-55.9%): $p=0.010$.

Survival and complications following ECLS institution

Analysis of in-hospital mortality, complications, rate of bridge to VAD/HTx and remote survival following V-A ECLS institution in non-HTx/VAD vs HTx/VAD centres are shown in Figure 4.

Figure 4. Analysis of in-hospital mortality, complications, bridge to VAD/HTx and remote survival following V-A ECLS institution in non-HTx/VAD vs HTx/VAD centres. Squares represent point estimates of pooled studies; horizontal lines are respective 95% confidence intervals. HTx, heart transplantation; VAD, ventricle assist device.

21.2% [17.6-25.3%]; $p=0.819$); and 3) acute kidney injury (36.4% [25.9-48.4%] vs 42.8% [39.1-46.5%]; $p=0.312$).

Detailed analyses of individual studies are available as Figures 7-12.

FIGURE 6. Estimated long-term survival in non-HTx/VAD as compared to HTx/VAD centres.

FIGURE 7. Limb complications incidence in non-HTx/VAD as compared to HTx/VAD centres.

FIGURE 8. Neurologic complications incidence in non-HTx/VAD as compared to HTx/VAD centres.

Limb complications incidence was reported in 102 studies (8,157 pts). Overall, 1,075 patients (12.4% [11.0-14.0%]) had limb complications; in the analysis stratified by centre status there was no difference between

FIGURE 9. Brain death incidence in non-HTx/VAD as compared to HTx/VAD centres.

FIGURE 10. Major bleeding requiring intervention incidence in non-HTx/VAD as compared to HTx/VAD centres.

FIGURE 11. Sepsis incidence in non-HTx/VAD as compared to HTx/VAD centres.

FIGURE 12. Acute kidney injury incidence in non-HTx/VAD as compared to HTx/VAD centres.

ECLS as bridging therapy

Data regarding ECLS bridge to HTx was available from 97 studies that included 7,857 patients; in an overall analysis, 474 patients underwent HTx which translated to an estimated rate of 6.3% (5.0-7.9%); there was numerical, yet not statistically significant difference between non-HTx/VAD (2.7% [0.8-8.3%]) as compared to

HTx/VAD (6.6% [5.2-8.3%]) favoring the latter ($p=0.131$); Figure 3. Similarly, there were no marked differences between non-HTx/VAD centres as compared to HTx/VAD centres with respect to ECLS bridge to VAD: across 94 studies (7,873 patients), 754 underwent bridging to VAD: 10.4% (8.4-12.9%); again, only numerical difference was observed between non-HTx/VAD (3.0% [0.3-24.2%]) and HTx/VAD (10.5% [8.5-13.1%]); $p=0.266$; Figure 4.

Additional analyses

In several conducted meta-regressions counter-opposing logER of in-hospital mortality and percentage of patients undergoing ECLS therapy for different indications, there was higher mortality with increasing (%) postcardiotomy ECLSs; 0.4214 (0.1843-0.6587); $p<0.001$, which was maintained in the subgroup of only HTx/VAD centres (0.4652 [0.2108-0.7197]; $p<0.001$. Figure 13.

FIGURE 13. Meta-regression analysis: in-hospital mortality vs postcardiotomy shock (%).

Conversely, lower rates of mortality were observed with increasing (%) of ECLSs for 1) acute myocardial infarction (-0.3765 [-0.7324-{-0.0206}]; $p=0.0381$); Figure 14; 2) graft failure (-0.8846 [-1.5415-{-0.2277}]; $p=0.0083$) Figure 15; 3) acute decompensated heart failure (-1.7919 [-3.2789-{-0.3049}]; $p=0.0181$); Figure 16;

4) myocarditis (-1.5322 [-2.0919-{-0.9726}]; $p<0.001$); Figure 17; and 5) cardiomyopathy (-1.1074 [-1.7685-{-0.4462}]; $p=0.0010$); Figure 18; without differences between between non-HTx- as compared to HTx/VAD centres.

FIGURE 14. Meta-regression analysis: in-hospital mortality vs acute myocardial infarction (%).

FIGURE 15. Meta-regression analysis: in-hospital mortality vs graft failure (%).

FIGURE 16. Meta-regression analysis: in-hospital mortality vs acute decompensated heart failure (%).

FIGURE 17. Meta-regression analysis: in-hospital mortality vs myocarditis (%).

FIGURE 18. Meta-regression analysis: in-hospital mortality vs cardiomyopathy (%).

In sensitivity analysis for mortality performed deleting single studies, one at a time, and repeating the calculations, no single study effect was seen changing neither direction nor the magnitude of the estimates. Additionally we repeated the calculations for the comparison non-HTx/VAD vs HTx/VAD centres after excluding studies 1) judged to be at critical risk of bias; 65.8% (59.8-71.1%) vs 56.2 (53.7-58.6%); $p=0.001$; and those enrolling 2) <50 patients: 70.9% (64.8-76.3%) vs 58.9 (55.9-61.8%); $p=0.001$; 3) <100 patients: 72.4% (67.5-76.8%) vs 58.0% (54.0-62.0%); $p<0.001$; only to prove maintenance of the effect.

Discussion

The current meta-analysis represents the first attempt to compare, although in indirect fashion not only in-hospital but also remote outcomes of patients supported with V-A ECLS for refractory cardiogenic shock between HTx/VAD and non-HTx/VAD performing centres. The main findings are as follows: 1) in an overall analysis, in-hospital mortality regardless of the underlying cause of cardiogenic shock remained high and was estimated at: 57.2% (54.9-59.4%); 2) in-hospital mortality rates were significantly higher in non-HTx/VAD (65.5% [59.8-70.8%]) as compared to HTx/VAD centres (55.8% [53.3-58.2%]); $P<0.001$; 3) in the overall analysis,

estimated late survival was 61.8% (55.7-67.9%) without significant differences between non-HTx/VAD as compared to HTx/VAD centres; 4) no differences were found between centres with respect to ECLS complications; 5) numerically, more patients were bridged to HTx and VADs in the centres that perform these procedures but the differences were not statistically significant; 6) postcardiotomy cardiogenic shock yielded higher in-hospital mortality irrespective of centre status; increasing percentage of patients treated with V-A ECLS for CS of other etiology correlated with lower mortality rates.

In the lack of randomised controlled trials in the area of V-A ECLS best evidence comes from meta-analyses of observational studies which questioned factors associated with survival including unloading of left ventricle [19], peripheral cannulation [20] or baseline surgical status in postcardiotomy setting [21]. Prolonging of V-A ECLS duration after 7 days was associated with a disproportionate increase in mortality [22,63]. Consequently, this led to hypothesis of the present meta-analysis that potentially shorter bridging times in HTx/VAD units due to readability of well-experienced ECLS teams experienced in dealing with both acute, chronic and end-stage heart failure also with prompt resources availability (medium- and long-term mechanical circulatory support and heart transplantation) might prevent life-threatening complications and contribute to better results.

The majority of reports came from HTx/VAD centres. 154 out of 174 studies included were conducted in HTx/VAD units and as a result 92.2% of reported patients were treated there. This is similar to findings from analysis focused exclusively on postcardiotomy patients [23]. Overrepresentation of reports on V-A ECLS from HTx/VAD centres seem to apply to different etiologies of CS. Hypotheses explaining this notion might include higher disease burden and subsequent risk of patients treated in HTx/VAD centres, higher preference for ECLS use in the treatment of refractory CS in this centres, or unexplained underreporting from non-HTx centres.

The main finding of present analysis is that 30 day/in-hospital weaning and survival rates were significantly lower in non-HTx/VAD as compared to HTx/VAD centres. This is in contrast to results of analysis focusing exclusively on postcardiotomy patients where no differences were observed [23]. Different risk profiles of postcardiotomy and non-postcardiotomy patients must be taken to account. V-A ECLS after adult cardiac surgery had been associated with higher risk of in-hospital mortality compared with other indications [42,159]. Its exponential

increase in use in this setting has not been paralleled by improved results [4]. The current meta-analysis demonstrates that postcardiotomy yielded higher in-hospital mortality irrespective of centre status. Indeed, in the mixed etiology population overall 30-day survival was 42.8% (40.6-45.1%) and in the postcardiotomy setting it was estimated at 35.3% (32.5-38.2%) [23]. Negative prognostic effect of postcardiotomy on survival may be explained by the impact of the underlying cardiac disease with its accompanying risk factors as well as the extent of the surgical procedure and its potential complications. In acute settings such as postcardiotomy shock V-A ECLS is mainly instituted as a temporizing measure and a bridge to recovery rather than bridge to ventricular assist device or heart transplantation which are, indeed, more frequent therapeutic options in chronic heart failure patients [3,4,158]. In fact, in the overall analysis, estimated rates of HTx and bridging to VAD were 6.3% (5.0-7.9%) and 10.4% (8.4-12.9%), respectively. On the other hand, in the postcardiotomy setting respective estimated rates were 3.5% [1.8–6.6%] and 4.3% [2.8–6.5%] [23].

Despite difference in short-term outcomes, estimated late survival (5,824 person years) was similar. In the study of Smedira et al. survival after being bridged from ECLS to a VAD/HTx versus after being weaned from ECLS without a bridge was 67% versus 52% at 30 days and 5-year survival was similar (44% and 40%, respectively) [156]. The profit from potentially shorter bridging times in HTx/VAD units might be more apparent in the early period of intensive treatment characterised by high risk of mortality. Failure to wean from V-A ECLS support or chronic heart disease and thus need for bridging to more durable VAD or HTx might be associated with patient's high disease burden and thus effect of such procedure in the long-term might be less evident.

What could be responsible for observed differences in mortality remain inconclusive. There was no statistically significant difference in rates of HTx and bridging to VAD between non-HTx/VAD as compared to HTx/VAD centres, however numerically higher in the latter. Also, there was no statistical difference between HTx/VAD (mean weighted average = 5.95 days) vs non-HTx centres (4.77 days) in the median ECLS duration. Unexpected, yet complex finding, we could not demonstrate any difference in complication rates between HTx/VAD and non-HTx/VAD centres, in contrast to previous meta-analysis focusing on postcardiotomy CS alone, which found neurological complications occurred less frequently in HTx centres. On one hand, distinct

shock protocols, designated, well-trained response teams, daily monitoring, neurovascular assessment, end-organ perfusion and hemodynamics assessment, daily evaluation for weaning vs escalation of support could be responsible at least in part for the overall low number of complications and, in particular, in HTx/VAD centres. On the other, significantly shorter time needed and spent on ECLS in non-HTx/VAD centres is a proxy for overall lower risk profiles in these patients, thus lower baseline risk for complications.

Limitations

Current meta-analysis is based on observational, one-arm comparisons and because of that is more prone to confounding as compared to head-to-head comparisons. On the other hand, no randomized controlled trial exist regarding analyzed topic and presumably will not be organized due to ethical issues. One limitation of the study may be underrepresentation of patients treated in non-HTx/VAD institutions. Random effect meta-analysis and inverse variance analysis was used to account for that fact. These methods appoint random weights also in a subgroup analysis which could overcome discrepancies between population sizes. There was no standard definition for secondary endpoints or risk of bias of the included studies. Conducting detailed subgroup analyses was precluded by not sufficient data on timing and location of implantation, exact device type, cannulation strategies, LV unloading techniques if any, status and duration of surgical procedure in case of postcardiotomy shock and likewise other baseline characteristic.

Conclusions

There was an apparent difference in weaning rates and survival after V-A ECLS implantation for refractory cardiogenic shock between centres which perform heart transplantations and/or implant ventricular assist device and those which do not in favor of transplant centres. Potentially different risk profiles of patients in these facilities must be taken account for before definite conclusions are drawn.

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CHAPTER 8

GENERAL DISCUSSION

ECMO-related technology has witnessed a remarkable progress in the last 20 years. More advanced, user friendly, miniaturized technology has made a wider application of such a temporary support possible with promising results. In particular interest lie several instances once viewed as absolute contraindications. Indeed, patients at prohibitive risk, who were often denied heart surgery in the first place, or those who suffered severe post-AMI cardiogenic shock are of greatest concern, since in those very patients the safety and efficacy of MCSs may sway the balance towards survival or mortality. In the context of recent exponential increase in the use of MCS in general, it is reasonable to question in which patients it is truly beneficial, giving patients time to recover rather than simply prolonging the time to death.

With all recent advancements in technology and skillsets, overall survival for patients undergoing ECMO for post-cardiotomy cardiogenic shock is not improving which is looming large in minds of ECMO enthusiasts. While the trends in mortality have been rather stable in the past 20 years, the patient characteristics undergoing cardiac surgery have changed. Indeed, salvage of patients who otherwise would never have survived e.g. feared post bypass myocardial dysfunction is now not surprising any longer. Reoperations, advanced age, surgical urgency and poor cardiac reserve are increasingly present in candidates for cardiac surgery, which may contribute to higher risk for cardiopulmonary insufficiency after CPB weaning. Nevertheless, due to improvements in surgical techniques higher risk patients and more complex procedures can be safely performed. ECMO institution is relatively easy and can be done in both ICU and peripheral fashion; unloading techniques have evolved, all contributing to balanced life/death ratio.

Adding to the balance is the subsequent pressure on the caregiving team to institute ECMO as soon as possible to avoid intra-operative fatal outcome. As a consequence, intraoperative death is nowadays a rare event. These phenomena and new circumstances increase over-utilization of ECMO in an effort to avoid intraoperative mortality often moving the mortality events from OR to ICU. In addition, mortality after weaning from ECMO accounts for 40-50% of 30-day deaths suggesting too early ECMO withdrawal or still high burden of complications occurring after termination of ECMO therapy. ECMO over-utilization needs to be recognized and

managed, to maximize survival, minimizing its futile use. Obvious targets to accomplish this include, improvements in technological aspects of the circuitry, e.g the pump, oxygenator, and tubing design, more reliable anticoagulation, rational vasoactive/inotropic support, a better understanding of the most effective ways to achieve temporary cardiopulmonary support, more effective monitoring, and improving care-giver education and training.

Patient selection for ECMO poses a true challenge; what once was viewed as a last-resort therapy can now be used as prophylaxis. With ECMO in one's armamentarium complex surgical procedures may be performed in high risk patients. Among high risk patients, the elderly is a separate group of interest because these individuals have higher risk profile due to cardiovascular co-morbidity combined with frailty and polypharmacy. Despite increasing use and expertise, V-A ECMO represents an aggressive treatment in complex patients, thereby associated with high complication and mortality rates. The search for predictors for unfavorable patient outcome is, therefore, critical in an attempt to improve results, resource utilization, and decision-making in challenging conditions. While decision on whether to institute ECMO in such patients should be based on individual risk factors, elderly patients are rarely candidates for such therapy given their small chance for recovery and resistance to bridging to more durable/permanent support. Indeed, as demonstrated in chapter 2, the most frequent condition for ECMO implant in the elderly patients was non-postcardiotomy cardiogenic shock which is in line with other reports suggesting post-cardiotomy indication for V-A ECMO placement is indeed less common in older patients as compared to younger subjects. This aspect may indicate that clinicians are less inclined to consider and accept the use of temporary support due to RCS in the elderly patients than in non-surgical environment. However, we were able to identify subgroups of elderly patients reaching up to 50% survival which is comparable to their younger counterparts; lower mortality was observed in heart transplantation recipients, post-TAVR and in pulmonary embolism. On the other hand, sepsis had almost always an ominous prognosis in the elderly; higher mortality rates were also observed on ECMO following coronary artery bypass graft (CABG) combined with valve surgery. (Chapter 2)

In chapter 3 we discussed that counterintuitively, the type of surgery, rather than urgency and patients baseline status, contributes to mortality on-ECMO. Indeed, ECMO implantation in an otherwise elective case yet complicated by cardiogenic shock dramatically increases the mortality risk well beyond the mortality threshold for ECMO salvage cases. (Chapter 3)

Complication rates on the other hand, were only associated with patients baseline status. (Chapter 3) Indeed, in this analysis, more neurologic and limb complications as well as more bleeding were seen in the emergency/salvage scenarios. Excess of bleeding complications can easily be explained by different coagulation profiles of emergency/salvage coronary patients that indeed constituted more than 40% of the entire analysis population (e.g. failed PCI, prior GP IIB/IIIA administration, high thrombotic burden requiring additional heparin for ECMO run etc.). However, increased rates of neurologic complications is presumably a multifactorial entity with pre-ECMO illness severity and treatments, ECMO management, and post-ECMO events all potentially contributing to cerebral injury. Loss of cerebral autoregulation during severe arterial hypertension or hypotension, thromboembolic events, haemorrhage related to anticoagulation use, cerebral vasospasm, and secondary brain injury from reactive tissue oedema around an area of focal cerebral insult may all contribute to brain injury in V-A ECMO patients.

The application of V-A ECMO in patients with refractory isolated cardiac or cardiopulmonary failure is a matter of debate in adult patients; the choice between “central” access, with the direct cannulation of the right atrium and ascending aorta, and “peripheral” access, most commonly using the femoral vein and artery, is dependent on patients’ characteristics and not rarely, physicians preference. (Chapter 4) This is also true for the choice between LV unloading techniques. Despite observational evidence suggesting improved outcomes with peripheral cannulation and LV unloading, employing these two approaches have not been assessed in a randomized fashion. In our analyses LV unloading was effective and safe in both PCS and non-PCS patients regardless of device.(Chapter 4) This is of particular importance given worse clinical conditions usually pertained by post-cardiotomy situation because of pre-ECMO comorbidities, impact of pre-operative cardiac illnesses and complicated surgical procedures, as well as type of complications more frequently observed in such a setting

such as bleeding. Other etiologies might have better results. In fact, AMI patients more often have undergone prior escalation to a balloon pump or Impella®, with eventual escalation to ECMO as compared to post-cardiotomy setting. Escalation may occur due to failure of MCS, vascular complications or progression of shock with development of renal failure and rising lactate which can often result in patients lingering in shock for prolonged periods of time.

Decision to implant or continue a temporary MCS as ECMO, is often difficult and several clinicians may avoid or limit the indications for such intensive therapy to reduce resource consumption in limitedly successful procedures. From a clinical perspective, the majority of centers look at physical and neurologic status prior to the event necessitating ECMO, the severity of insult, duration/degree of shock, presence of prior arrest, and associated medical comorbidities when selecting potential candidates for ECMO therapy. The availability, therefore, of indicators for more favorable outcome might be precious and guiding clinical management, either prior or during ECMO support.

From the current studies, that include most of published evidence on the topic, it is apparent that there are differences in outcome between centres with heart failure programs and centres without such programs. Indeed, centres dealing with ECMO patients on a daily basis produce better results. In addition, they usually enroll patients at higher baseline risk, often denied cardiac surgery in other centre or transferred to a referral hub after developing complications. These observations led to the hypothesis of our meta-analyses that potentially shorter bridging times in HTx/VAD units due to readability of well-experienced ECLS teams experienced in dealing with both acute, chronic and end-stage heart failure also with prompt resources availability (medium- and long-term mechanical circulatory support and heart transplantation) might prevent life threatening complications and contribute to better results. (Chapter 5) Indeed, there seems to be a strong association between volume and outcome as well, with lower mortality and complications burden in higher volume centres. (Chapter 5)

The application of ECMO as a rescue therapy/support, in the presence of perioperative shock like in HTx or general cardiac surgery, has shown the potential benefits, but also the high rate of complications, somehow

apparently strictly related to the extent of maladaptive body reaction, secondary to the interaction between the body and a prolonged extracorporeal circulation, but also to intrinsic potential shortcomings related to the invasiveness of the technique. The use of ECMO as a transient circulatory or respiratory, or concomitant assistance of both impaired systems, has been shown to represent an invaluable opportunity, although characterized by several drawbacks. Therefore, additional efforts aimed at minimizing the above is mandatory, such that, hopefully, in the near future, the rationale for its use will be understood and justifiable in all cases.

Valorization

This thesis highlights the incidence, results, complications and innovative management of patients submitted to ECMO because of cardiogenic shock from various etiologies. The main findings of the performed research for this thesis can be summarized as follows; careful and vigilant patient selection together with aggressive management of patient himself and ECMO circuit can lead to promising results in the most complex and difficult clinical scenarios. The thesis provides relevant insights about the efficacy of ECMO in several settings, including cardiac surgery and related interventions. Indeed, the favorable results obtained in complex settings, like post-cardiotomy cardiogenic shock after general cardiac surgery, confirms the efficacy of such a temporary support in case of refractory and life-threatening postcardiotomy conditions.

The focus of the analyses was not limited to postcardiotomy cardiogenic shock though; indeed, cardiogenic shock resulting from acute coronary syndromes, myocarditis, cardiomyopathies and other causes can also be managed with ECMO with encouraging outcomes.

We were able to demonstrate by means of registry big data analyses and also in meta-analytical approach, that addressing and tackling certain mortality predictors could improve the ultimate outcomes. Similarly, minimizing the invasiveness of the approach as with peripheral cannulation, employing different techniques to unload the LV and referral of patients in cardiogenic shock to experienced high volume centres, are important features of successful ECMO therapy.

Patient selection

The performed research demonstrated that proper selection of patient for the most intensive management modality can lead to better outcomes. In fact, prompt initiation of ECMO in selected patient and timely (before severe end-organ dysfunction appears) offers “appealing” survival rates. More importantly, we could show that advanced age, often considered as contraindication for ECMO or, in fact, for any MCS, should not be viewed as prohibitive or as an absolute contraindication. Factors other than age, like general condition, postcardiotomy or non-postcardiotomy shock and reversibility of the condition play more important role and should be considered first. The above information is calling, from one side, for a more focused patient selection whatever the indication; from another, an algorithm or a guideline is to be introduced, not denying MCS to the elderly subjects, as this

may be at least as effective treatment modality in this very particular group of patients. Indeed, we have provided, for a first time, a list of variables contributing to reduced survival to be considered rather than age.

Another important finding, of the conducted research is that baseline surgical status in post-cardiotomy patients, whether elective or salvage, albeit impacts the propensity for complications, does not affect mortality rates when ECMO is initiated. This, in turn, suggests that initiation of ECMO in the postcardiotomy setting has the survival predictive function outweighing every single EuroSCORE risk stratification components and should be taken account for. What needs to be addressed in the future research is, undeniably, a risk stratification tool and a scoring system for both postcardiotomy and non-postcardiotomy setting which would combine the predictive abilities of yet available scoring systems (REMEMBER, SAFE) but validated on a broader group of patients and not limited to single indications.

Advancements in ECMO management

As already shown, the performed research confirmed that ECMO configurations do affect the outcomes of patients in cardiogenic shock. In particular, it has been shown that the access to implement such a support may also influence the patient outcome with regards to the complication types and rate with the peripheral approach. With the biggest dataset of post-cardiotomy patient series ever analyzed, peripheral cannulation was shown to be associated with improved in-hospital survival and lower complication rates which is in line also with a recent meta-analysis by our group. Additionally, several LV unloading techniques were investigated; when applied to ECMO circuit, IABP and Impella have potential to reduce mortality in both post-cardiotomy and non-postcardiotomy shock, thereby representing an important insight for the clinical and ECMO communities. Importantly the benefit is seen also with percutaneous implantation of these devices; allowing cardiologists and intensivists for a prompt and successful application with ultrasound guidance rather than with surgical approach.

ECMO experience

Ultimately, we have also performed a set of meta-analyses based on a presumption that centres which perform VAD implantations and heart transplantations may have better outcomes in patients on MCS due to their experience in dealing with end-stage heart failure; in fact, centres in which VADs and HTXs are performed had better results in terms of complication rates in patients undergoing ECMO for postcardiotomy shock. When both

postcardiotomy and medical applications were considered, survival was as well affected with higher in-hospital survival in more experienced centres.

Central figure. Proposed algorithm of patient management: V-A ECMO in cardiogenic shock with respect to potential referral to HTx/VAD centre. V-A ECMO, veno-arterial extracorporeal membrane oxygenation; LV/RV, left/right ventricle; CVVH, continuous veno-venous hemofiltration; CK-MB, creatin kinase muscle-brain isoenzyme; HTx, heart transplantation; VAD, ventricle assist device

This means that experienced and well established ECLS program may indeed make a difference in patient outcome. With this finding, a call for appropriate personnel training and the creation of dedicated team, also in centres not performing transplant/VAD procedure, is highlighted and suggested. What is also important from clinical standpoint, is management of ECMO as a bridging therapy. It was shown that patients managed in experienced centres are more likely to be bridged to destination therapy (HTx or VAD); we have, again for a first time, proposed an algorithm taking into account ECMO duration and clinical variables in order to find a best time frame for transferring a patient from non-HTx/VAD unit to destination centre as well as to determine a best time for bridging to more advanced or longer MCS.

What needs to be addressed in the future?

The information available for ECMO has been always rather poor and limited to single-centre experiences. A tendency not to present poor outcomes is not to be missed; a thorough review, with the provision on detailed information about prevalence, in relation to the overall cardiac surgery procedural number, medical conditions, patient profiles, support modalities, complications and outcome at short or long-term are certainly precious for investigators and people involved in dealing with cardiogenic shock in such settings.

SUMMARY

Chapter 2. In this chapter, we analyzed the multicenter ELSO registry. 2,644 patients ≥ 70 years (1,395 [52.8%] 70-74 years of age, 858 [32.5%] 75-79 years, and 391 [14.8%] ≥ 80 y.o.) were managed with V-A ECMO, for refractory cardiogenic shock due to various etiologies. Overall in-hospital mortality was estimated at 68.3% (1,807/2,644 pts.) with highest crude mortality rates observed in 75-79 y.o. subgroup (70.1%). Complications were mostly cardiovascular and bleeding, without apparent differences between subgroups. Airway pressures, 24-hours pH after ECMO start, ECMO duration, and renal replacement therapy were associated with higher mortality. This study confirmed the remarkable increase of V-A ECMO use in the elderly affected by RCS. Despite in-hospital mortality remained high, we declared that V-A ECMO should still be considered in such a setting even in very elderly patients, since age itself was not linked to increased mortality, whereas several predictors may guide indication and management.

Chapter 3 is a systematic review and meta-analysis on left ventricle unloading with veno-arterial extracorporeal membrane oxygenation for cardiogenic shock. Included adult patients from studies published between January 2000 and March 2019. The search was conducted through numerous databases. Overall, from 62 papers, 7581 patients were included, among whom 3337 (44.0%) received LV unloading concomitant to VA-ECMO. Overall, in-hospital mortality was 58.9% (4466/7581). A concomitant strategy of LV unloading as compared to ECMO alone was associated with 12% lower mortality risk (RR 0.88; 95% CI 0.82–0.93; $p < 0.0001$; $I^2 = 40\%$) and 35% higher probability of weaning from ECMO (RR 1.35; 95% CI 1.21–1.51; $p < 0.00001$; $I^2 = 38\%$). In an analysis stratified by setting, the highest mortality risk benefit was observed in case of acute myocardial infarction: RR 0.75; 95%CI 0.68–0.83; $p < 0.0001$; $I^2 = 0\%$. There were no apparent differences between two techniques in terms of complications. In heterogeneous populations of critically ill adults in CS and supported with VA-ECMO, the adjunct of LV unloading is associated with lower early mortality and higher rate of weaning.

Chapter 4 is an attempt to address certain mortality differences between patients undergoing ECMO for PCS; in a meta-analysis we stratified patients based on baseline surgical status (elective/ urgent/ emergency/ salvage) and assessed its impact on short-term mortality. Twenty-two studies enrolling N=2,235 post-cardiotomy ECMO patients were found. Patients were mostly of non-emergency status (65.2%). Overall in-hospital/30-day mortality

was 66.7%. Yet, there were no differences in in-hospital/30-day mortality with respect to baseline surgical status in the subgroup analysis. Similarly, no differences between mortality in studies enrolling <50 vs ≥50% of emergency/salvage cases was found. There was a significant positive association between increasing percentage of emergency/salvage cases and rates of: neurological complications ($p<0.001$), limb complications ($p<0.001$) and bleeding ($p=0.051$). Incidence of brain death ($p=0.099$) and sepsis ($p=0.134$) was increased as well. We concluded that other factors than baseline surgical status may, to a higher degree, influence the mortality in patients treated with ECMO for post-cardiotomy cardiogenic shock. Baseline status, however, strongly influences the complication occurrence while on ECMO.

In **Chapter 5**, we again analysed data from the Extracorporeal Life Support Organization (ELSO) registry regarding outcomes of V-A ECMO for PCS in adult patients. The analyses examined trends in use, patient profiles, and in-hospital outcomes including complications. Predictors of in-hospital mortality were assessed by multivariate logistic regression. During the study period, 8,053 patients submitted to V-A ECMO for PCS were found in the ELSO Registry. There was a significant trend toward more ECMO use in recent years. Mean age was 56.3 ± 14.9 years and significantly increased over time. Most commonly, V-A ECMO was instituted after coronary artery bypass surgery and valvular surgery followed by heart transplantation. Overall, successful ECMO weaning occurred in 4,520 cases (56.1%), and survival to hospital discharge was achieved in 41.4% of cases. In-hospital mortality rates remained constant over time. Kidney injury, surgical site bleeding, cardiac arrhythmias, sepsis, metabolic disorders, and neurologic complications were the most common adverse events. Higher mortality was observed after CABG, combined CABG with valve and vascular aortic procedures than other indications. Better survival rates were observed in heart transplantation recipients. Age, central cannulation and occurrence of complications while on ECMO were independently associated with poorer prognosis. In conclusion, with the largest dataset ever analyzed we showed mortality rates to remained relatively constant over time despite a decrease in complications, in the setting of supporting older, higher risk patients.

Chapter 6 is a systematic review and meta-analysis of studies reporting in-hospital outcomes of V-A ECMO for PCS together with transplant status of the centre. While reported mortality rates on ECMO vary from center

to center, aim of the current report was to assess if the outcomes differ between centres according to volume and heart transplantation status. Fifty-four studies enrolling N=4,421 ECMO patients were included. Of those, 6 series were performed in non-HTx centres. Overall 30-day survival was 35.3% and did not statistically differ between non-HTx: 33.3% and HTx centres: 35.7%. No statistical differences were seen between HTx and non-HTx with respect to ECMO duration, limb complications, reoperations for bleeding, kidney injury and sepsis. There were however significantly less neurological complications in the HTx as compared to non-HTx centres: 11.9% vs 19.5% respectively. An inverse relationship was seen for neurologic complications in centres performing more ECMOs annually. Weaning rates and bridging to HTx and/or VADs were higher in HTx facilities. We concluded that there was no apparent difference in survival after ECMO implantation for refractory PCS according to centre's ECMO volume and transplantation status; yet, potentially different risk profiles of patients in these centres must be taken account for.

Chapter 7 is a natural continuity and expanding the findings of previous analysis to non-PCS field and thus cardiogenic shock in general. The aim of the current meta-analysis was to assess the outcomes between units performing heart transplantation and/or implanting ventricular assist device (HTx/VAD) versus non-HTx/VAD units in patients undergoing V-A ECLS for cardiogenic shock. Of 174 studies enrolling N = 13,308 patients, 20 series were performed in non-HTx/VAD centres. Majority of patients underwent V-A ECLS for postcardiotomy shock (44.2%) and acute myocardial infarction (20.7%). Estimated overall in-hospital mortality was 57.2% but mortality rates were higher in non-HTx/VAD: 65.5% as compared to HTx/VAD centres: 55.8%; $P < 0.001$. No differences were seen with respect to ECLS duration, limb complications, reoperations for bleeding, kidney injury and sepsis. Weaning rates were 10% higher in HTx/VAD vs non-HTx/VAD centres. Estimated rate of bridge to heart transplant was 6.6% with numerical, yet not statistically significant difference between non-HTx/VAD as compared to HTx/VAD units.

SAMENVATTING

Hoofdstuk 2. In dit hoofdstuk hebben we het multicenter ELSO-register geanalyseerd. 2.644 patiënten ≥ 70 jaar (1.395 [52,8%] 70-74 jaar, 858 [32,5%] 75-79 jaar en 391 [14,8%] ≥ 80 jaar) werden behandeld met VA ECMO, voor refractaire cardiogene shock als gevolg van verschillende etiologieën. De totale mortaliteit in het ziekenhuis werd geschat op 68,3% (1.807 / 2.644 pt.) Met de hoogste ruwe sterftecijfers waargenomen in 75-79 jaar. subgroep (70,1%). Complicaties waren meestal cardiovasculair en bloeden, zonder duidelijke verschillen tussen subgroepen. Luchtwegdruk, 24 uur pH na ECMO-start, ECMO-duur en niervervangende therapie waren geassocieerd met hogere mortaliteit. Deze studie bevestigde de opmerkelijke toename van het gebruik van V-A ECMO bij ouderen met RCS. Ondanks dat de mortaliteit in het ziekenhuis hoog bleef, verklaarden we dat V-A ECMO in een dergelijke setting nog steeds overwogen zou moeten worden, zelfs bij zeer oudere patiënten, aangezien leeftijd zelf niet gekoppeld was aan verhoogde mortaliteit, terwijl verschillende voorspellers indicatie en management kunnen sturen.

Hoofdstuk 3 is een systematische review en meta-analyse van het ontladen van de linker ventrikel met veno-arteriële extracorporale membraanoxygenatie voor cardiogene shock. Ik heb volwassen patiënten opgenomen uit onderzoeken die tussen januari 2000 en maart 2019 zijn gepubliceerd. De zoekopdracht werd uitgevoerd via talrijke databases. In totaal werden van 62 papers 7581 patiënten geïncludeerd, van wie 3337 (44,0%) LV-lossing gelijktijdig met VA-ECMO kregen. De totale mortaliteit in het ziekenhuis was 58,9% (4466/7581). Een gelijktijdige strategie van LV-lossing in vergelijking met alleen ECMO was geassocieerd met 12% lager sterfterisico (RR 0,88; 95% BI 0,82-0,93; $p < 0,0001$; $I^2 = 40\%$) en 35% hogere kans op spenen van ECMO (RR 1,35; 95% -BI 1,21-1,51; $p < 0,00001$; $I^2 = 38\%$). In een analyse gestratificeerd naar setting, werd het hoogste risico op mortaliteit waargenomen in geval van een acuut myocardinfarct: RR 0,75; 95% BI 0,68-0,83; $p < 0,0001$; $I^2 = 0\%$. Er waren geen duidelijke verschillen tussen twee technieken in termen van complicaties. In heterogene populaties van ernstig zieke volwassenen in CS en ondersteund met VA-ECMO, wordt de toevoeging van LV-lossing geassocieerd met een lagere vroege mortaliteit en een hogere mate van spenen.

Hoofdstuk 4 is een poging om bepaalde sterfteverschillen aan te pakken tussen patiënten die ECMO voor PCS ondergaan; in een meta-analyse hebben we patiënten gestratificeerd op basis van de chirurgische status van de baseline (electieve / dringende / nood / berging) en de impact ervan op de mortaliteit op korte termijn beoordeeld. Er werden 22 studies gevonden met N = 2.235 ECMO-patiënten na een cardiectomie. Patiënten hadden meestal een niet-noodstatus (65,2%). De totale mortaliteit in het ziekenhuis / 30 dagen was 66,7%. Toch waren er geen verschillen in sterfte in het ziekenhuis / 30-dagen met betrekking tot de chirurgische status bij aanvang in de subgroepanalyse. Evenzo werden geen verschillen gevonden tussen mortaliteit in onderzoeken met <50 versus ≥50% van de nood- / reddingsgevallen. Er was een significant positief verband tussen toenemend percentage nood- / reddingsgevallen en het percentage van: neurologische complicaties ($p < 0,001$), complicaties van de ledematen ($p < 0,001$) en bloeding ($p = 0,051$). De incidentie van hersendood ($p = 0,099$) en sepsis ($p = 0,134$) was ook verhoogd. We concludeerden dat andere factoren dan de baseline chirurgische status, in hogere mate, de mortaliteit kunnen beïnvloeden bij patiënten die met ECMO werden behandeld voor cardiogene shock na een cardiectomie. De baselinestatus heeft echter een sterke invloed op het optreden van complicaties tijdens ECMO.

In Hoofdstuk 5 hebben we opnieuw gegevens geanalyseerd uit het register van de Extracorporeal Life Support Organization (ELSO) met betrekking tot de uitkomsten van V-A ECMO voor PCS bij volwassen patiënten. Bij de analyses werd gekeken naar trends in gebruik, patiëntprofielen en uitkomsten in het ziekenhuis, inclusief complicaties. Voorspellers van mortaliteit in het ziekenhuis werden beoordeeld door middel van multivariate logistische regressie. Tijdens de onderzoeksperiode werden 8.053 patiënten die bij V-A ECMO voor PCS waren ingediend, aangetroffen in de ELSO-registratie. Er was de afgelopen jaren een significante trend naar meer ECMO-gebruik. De gemiddelde leeftijd was 56,3 - 14,9 jaar en nam in de loop van de tijd significant toe. Meestal werd V-A ECMO ingesteld na een bypassoperatie van de kransslagader en een hartklepoperatie gevolgd door een harttransplantatie. In totaal trad succesvolle ECMO-ontwenning op in 4.520 gevallen (56,1%), en overleving tot ontslag uit het ziekenhuis werd bereikt in 41,4% van de gevallen. Het sterftcijfer in het ziekenhuis bleef in de loop van de tijd constant. Nierletsel, bloeding op de operatieplaats, hartritmestoornissen, sepsis, stofwisselingsstoornissen en neurologische complicaties waren de meest voorkomende bijwerkingen. Een

hogere mortaliteit werd waargenomen na CABG, gecombineerd CABG met klep- en vasculaire aorta-ingrepen dan bij andere indicaties. Er werden betere overlevingspercentages waargenomen bij ontvangers van harttransplantaties. Leeftijd, centrale canulatie en het optreden van complicaties tijdens ECMO waren onafhankelijk geassocieerd met een slechtere prognose. Concluderend, met de grootste dataset die ooit is geanalyseerd, toonden we aan dat het sterftcijfer relatief constant bleef in de tijd ondanks een afname van complicaties, in de setting van het ondersteunen van oudere patiënten met een hoger risico.

Hoofdstuk 6 is een systematische review en meta-analyse van studies die de uitkomsten van V-A ECMO voor PCS in het ziekenhuis rapporteren, samen met de transplantatiestatus van het centrum. Hoewel de gerapporteerde sterftcijfers op ECMO variëren van centrum tot centrum, was het doel van het huidige rapport om te beoordelen of de uitkomsten verschillen tussen centra op basis van volume en harttransplantatiestatus. Vierenvijftig onderzoeken met N = 4.421 ECMO-patiënten werden geïnccludeerd. Daarvan werden 6 series uitgevoerd in niet-HTx-centra. De totale overleving na 30 dagen was 35,3% en verschilde statistisch niet tussen niet-HTx: 33,3% en HTx-centra: 35,7%. Er werden geen statistische verschillen gezien tussen HTx en niet-HTx met betrekking tot ECMO-duur, ledemaatcomplicaties, heroperaties voor bloeding, nierletsel en sepsis. Er waren echter significant minder neurologische complicaties in de HTx in vergelijking met niet-HTx-centra: respectievelijk 11,9% versus 19,5%. Een omgekeerd verband werd gezien voor neurologische complicaties in centra die jaarlijks meer ECMO's uitvoeren. Speencijfers en overbrugging naar HTx en / of VAD's waren hoger in HTx-faciliteiten. We concludeerden dat er geen duidelijk verschil was in overleving na ECMO-implantatie voor refractaire PCS volgens het ECMO-volume en de transplantatiestatus van het centrum; toch moet rekening worden gehouden met mogelijk verschillende risicoprofielen van patiënten in deze centra.

Hoofdstuk 7 is een natuurlijke continuïteit en uitbreiding van de bevindingen van eerdere analyses naar niet-PCS-veld en dus cardiogene shock in het algemeen. Het doel van de huidige meta-analyse was om de resultaten te beoordelen tussen eenheden die een harttransplantatie uitvoeren en / of een ventriculair hulpmiddel (HTx / VAD) implanteren versus niet-HTx / VAD-eenheden bij patiënten die V-A ECLS voor cardiogene shock ondergaan. Van de 174 onderzoeken met N = 13.308 patiënten, werden 20 series uitgevoerd in niet-HTx / VAD-

centra. De meerderheid van de patiënten onderging V-A ECLS voor postkaartiotomieschok (44,2%) en acuut myocardinfarct (20,7%). De geschatte totale mortaliteit in het ziekenhuis was 57,2%, maar het sterftcijfer was hoger in niet-HTx / VAD-centra: 65,5% in vergelijking met HTx / VAD-centra: 55,8%; $P < 0,001$. Er werden geen verschillen gezien met betrekking tot ECLS-duur, complicaties van de ledematen, heroperaties wegens bloeding, nierletsel en sepsis. De speencijfers waren 10% hoger in HTx / VAD-centra versus niet-HTx / VAD-centra. Het geschatte aantal brug-naar-harttransplantaties was 6,6% met een numeriek, maar niet statistisch significant verschil tussen niet-HTx / VAD-eenheden in vergelijking met HTx / VAD-eenheden.

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ABOUT THE AUTHOR

The author of this thesis, Mariusz Kowalewski, was born on 3 Oct 1988 in Łódź, Poland. He graduated high school in Bydgoszcz and the same year was admitted to Collegium Medicum of Nicolaus Copernicus University in Toruń at the Medical Faculty. During 3rd year he became chair of students' cardiac surgery research society involved in students' conference and workshops organization. As an exchange student he spent 1 year in Milan, Italy (mainly in Cardiac Surgery Department, Humanitas, Milano-Rozzano under Dr Giuseppe Tarelli). This is where he met PG Malvindi and GM Raffa his future collaborators and friends beyond the surgical scope. He started residency program in cardiac surgery in Bydgoszcz University Hospital shortly after returning from Milan in 2014. He defended his PhD thesis on "Effectiveness of Gentamycin Collagen Sponge in Preventing post-CABG sternal wound infections" in April 2016. Several later publications will focus on preventing other post-CABG complications including stroke and bleeding. With collaboration with Drs Szwed and Słomka, he investigated the impact of different surgical techniques of off-pump CABG on the incidence of neurological events both clinically evident and silent as with biomarkers for neuronal damage. He took part in conception and design of Carbon Dioxide Surgical Field Flooding and Aortic No-touch Off-pump Coronary Artery Bypass Grafting to Reduce Neurological Injuries After Surgical Coronary Revascularization (CANON) trial. After moving to Warsaw and began collaboration with Prof Dr Piotr Suwalski, president of International Society of Minimally Invasive Cardiothoracic Surgery his particular interest switched to minimally invasive techniques in cardiac surgery and atrial fibrillation. In parallel, however, he was extending his research network to European and American centres. With a few of his friends and research partners he founded Thoracic Research Centre, a platform designed to promote research and evidence-based medicine approach in Cardiothoracic Surgery. Among a number of invited congress prelections, at one in Rome (SICCH), he met Prof Dr Roberto Lorusso who invited him to extend the area of interest to extracorporeal life support. After completion of several projects he begun the PhD in Maastricht University with the purpose of identifying factors determining high on-ECMO mortality in high risk individuals and complex clinical scenarios. He is married to Magdalena Kowalkowska, a gynecologist and esthetic medicine consultant, and has a son Vincent (12 months now). Surgical interests include minimally invasive aortic root and arch surgery, high risk cardiac surgery w/wo prophylactic ECMO,

minimizing neurological complications in CABG. Research interests are epidemiological studies on efficacy and safety of heart surgery in patients with underlying atrial fibrillation. Interest not related to work include speed alpine skiing, high altitude mountaineering, ice climbing and moto racing. He is a wine and food lover.

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