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TITOLO TESI

EXTRACORPOREAL MEMBRANE OXYGENATION (ECMO) IN REFRACTORY CARDIOGENIC SHOCK: IMPACT OF ACUTE VERSUS CHRONIC ETIOLOGY ON OUTCOME

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Ai miei genitori

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SUMMARY

Refractory cardiogenic shock (CS) is a condition that continues to have a very high mortality despite advances in medical therapy. Conventional treatment typically comprises inotrope infusions, vasopressors and intra-aortic-balloon-pump (IABP). When circulatory instability is refractory to these treatments, mechanical circulatory support represents the only hope for survival, as indicated by current guidelines. As most of these patients present with critical circulatory instability requiring urgent or emergent therapy, the chosen mechanical assistance should be rapidly and easily implanted. For this reason ExtraCorporeal Membrane Oxygenation (ECMO) represents the ideal "bridge-to-life" and increasingly it is used to keep the patient alive while the optimal therapeutic management is determined (bridge-to-decision). Management may then follow one of three courses: "bridge-to-recovery": patient recovery, and weaning from ECMO; "bridge-to-transplant": direct heart transplantation; "bridge-to-bridge": placement of ventricular-assist-device or total artificial longer-term support. There have been several large reports on the use of ECMO as a mechanical support in post-cardiotomy patients but relatively few, mostly small case-series focusing on its role in primary acute cardiogenic shock outside of the post-cardiotomy setting.

We present the results of our centre's experience (Padova) in the treatment of primary acute cardiogenic shock with the PLS-Quadrox ECMO system (Maquet) as a bridge to decision. Furthermore, we evaluated the impact of etiology on patient outcomes by comparing acute primary refractory CS secondary to acute myocardial infarction (AMI), myocarditis, pulmonary embolism (PE) and post-partum cardiomyopathy (PPCM) with acute decompensation of a chronic cardiomyopathy, including dilated cardiomyopathy (DCM), ischemic cardiomyopathy (ICM) and grown-up-congenital-heart-diseases (GUCHD). We also analyzed whether duration and magnitude of support may predict weaning and survival.

Materials and Methods. Between January 2009 and March 2013, we implanted a total of 249 ECMO; in this study we focused on 64 patients where peripheral ECMO was the treatment for primary cardiogenic shock. Thirty-seven cases (58%) were "acute" (Group A-PCS: mostly acute myocardial infarction, 39%), while twenty-seven (42%) had an exacerbation of "chronic" heart failure (Group C-PCS: dilated cardiomyopathy 30%, post-ischemic cardiomyopathy 9%, congenital 3%).

Results. In group C-PCS, 23 patients were bridged to a LVAD (52%) or heart transplantation (33%). In group A-PCS, ECMO was used as bridge-to-transplantation in 3 patients (8%), bridge-to-bridge in 9 (24%), and bridge-to-recovery in 18 patients (49%). One patient in both groups was bridged to conventional surgery. Recovery of cardiac function was achieved only in group A-PCS (18 vs 0 pts, p=0.0001). Mean-flow during support ≤60% of the theoretical flow (BSA*2.4) was a predictor of successful weaning (p=0.02). Average duration of ECMO support was 8.9 ±9 days. Nine patients (14%) died during support; 30-day overall survival was 80% (51/64 pts); 59% of patients were discharged, in whom survival at 48 months was 90%. Better survival was observed in patients supported for 8 days or less (74% vs 36%, p=0.002).

Conclusions. In "chronic" heart-failure ECMO represents a bridge to VAD or heart-transplantation, while in "acute" settings it offers a considerable chance of recovery, often representing the only required therapy.

RIASSUNTO

Lo shock cardiogeno refrattario è una condizione gravata da alta mortalità nonostante i progressi nella terapia medica. Il trattamento convenzionale comprende infusione di inotropi, vasopressori, e contropulsazione aortica (intra-aortic-balloon-pump – IABP). Quando l'instabilità emodinamica è refrattaria a questi trattamenti, il supporto meccanico al circolo rappresenta la sola possibilità di sopravvivenza, come indicato dalle attuali linee guida. Tuttavia, poichè la maggior parte di questi pazienti si presenta con severa instabilità emodinamica che richiede un intervento urgente o emergente, l'assistenza meccanica scelta dovrebbe essere impiantabile in maniera rapida e semplice. Per questa ragione, l'ExtraCorporeal Membrane Oxygenation (ECMO) rappresenta l'ideale "bridge-to-life", che sempre più viene usato per supportare le funzioni vitali in attesa che il programma terapeutico ottimale venga stabilito (bridge-to-decision). L'iter terapeutico può poi seguire tre diversi percorsi: "bridge-to-recovery": il paziente recupera una funzione cardiocircolatoria tale da permettere lo svezzamento dall'ECMO; "bridge-to-transplant": il paziente viene sottoposto a trapianto cardiaco; "bridge-to-bridge": il paziente viene trattato con impianto di un'assistenza ventricolare o di un cuore artificiale totale. Sono state riportate diverse ampie casistiche sull'uso dell' ECMO come supporto meccanico in pazienti con shock dopo intervento cardiochirurgico ("post-cardiotomy"), ma relativamente poche serie, e limitate a pochi casi, focalizzate sul ruolo dell'ECMO nello shock cardiogeno primario (non post-cardiotomico).

In questo studio si presenta l'esperienza del centro di Padova nel trattamento dello shock cardiogeno primario con il sistema ECMO PLS-Quadrox (Maquet) come bridge-to-decision.

In particolare, la ricerca proposta si prefigge di valutare l'impatto della differente eziologia sull'outcome dei pazienti, paragonando gli shock cardiogeni primari "acuti", secondari ad infarto miocardico acuto, miocardite, embolia polmonare e cardiomiopatia post-partum, con scompensi acuti di cardiomiopatie "croniche", includendo cardiomiopatie dilatative primitive, post-ischemiche,

e cardiopatie congenite dell'adulto. Si è infine analizzato se la durata e l'entità del supporto possano predire la chance di sopravvivenza e di svezzamento.

Materiali e metodi. Tra Gennaio 2009 e Marzo 2013, sono stati impiantati con ECMO un totale di 249 pazienti, di questi 64 erano affetti da shock cardiogeno "primario" (52 uomini e 12 donne, di 50±16 anni di età) e sono stati trattati con supporto ECMO periferico. Trentasette casi (58%) sono stati classificati come "acuti" (Gruppo A, Acuti, IMA 39%, miocardite 6%, embolia polmonare 8%, post-partum 2%), mentre i rimanenti 27 (42%) shock erano insorti in un quadro di scompenso cardiaco "cronico" (Gruppo B, Cronici, cardiomiopatia dilatativa primitiva 30%, cardiomiopatia dilatativa post-ischemica 9%, patologie congenite 3%).

Risultati della ricerca. Nel gruppo con scompenso cardiaco cronico (Gruppo B), 23 pazienti sono stati trattati con impianto o di assistenza ventricolare sinistra (52%) o trapianto cardiaco ortotopico (33%). Nel gruppo con scompenso cardiaco acuto (Gruppo A), l' ECMO è stato usato come ponte a trapianto in 3 pazienti (8%), come ponte ad impianto di assistenza ventricolare sinistra in 9 pazienti (24%) e come ponte al recupero della propria funzionalità cardiaca in 18 pazienti (49%).

Un solo paziente in ogni gruppo è stato trattato con chirurgia tradizionale. Il recupero della funzionalità cardiaca si è osservato solo all'interno del Gruppo A (18 vs. 0 pazienti, p=0,0001). E' stato visto che mantenere un flusso medio di supporto ≤60% del flusso teorico (BSA*2,4) costituisce un predittore positivo di svezzamento dal dispositivo (p=0,02). Globalmente, la durata media del supporto ECMO è stata di 8,9±9 giorni. Nove pazienti (14%) sono deceduti durante il supporto ECMO; la sopravvivenza globale a 30 giorni è stata dell' 80% (5/64 pazienti); il 59% dei pazienti è stato dimesso dall' ospedale e, tra questi, la sopravvivenza a 48 mesi è stata del 90%, senza differenze significative nei due gruppi. La sopravvivenza migliore si è osservata in quei pazienti che hanno necessitato di supporto ECMO per un periodo inferiore o uguale ad 8 giorni (74% vs. 36%, P=0,002).

In conclusione nei pazienti con shock cardiogeno refrattario nell'ambito di uno scompenso cardiaco cronico l'ECMO rappresenta un dispositivo-ponte verso l'impianto di assistenza ventricolare sinistra o verso trapianto cardiaco. Nei pazienti con shock refrattario dovuto ad eziologia acuta, invece, tale supporto offre sostanziali chance di *recovery*, costituendo spesso l'unica terapia necessaria.

1. CARDIOGENIC SHOCK (CS)

1.1 INTRODUCTION

Cardiogenic shock (CS) is a common endpoint of multiple disease processes that is characterized by myocardial dysfunction, depressed cardiac output (CO) and end-organ hypoperfusion. CS is associated with significant morbidity and mortality, and conventional medical support such as inotropic agents or intra-aortic balloon counterpulsation is often insufficient to reverse the hemodynamic changes seen in CS [1].

Recent research has suggested that the peripheral vasculature and neurohormonal and cytokine systems play a role in the pathogenesis and persistence of CS.

Advances in management, including early revascularization, have led to a reduction of in-hospital mortality of more than 10% [1-2]. A further reduction may be seen with the advancement of mechanical circulatory support (MCS), which provides a means for patients to recover or transition to long-term therapies for management of their underlying cardiac disease. In particular, the development of percutaneous MCS options has facilitated rapid resuscitation of the cardiogenic shock patient, potentially interrupting the characteristic systemic inflammatory response before it can cause irreversible harm.

1.2 DEFINITION, DIAGNOSIS AND CAUSES OF CARDIOGENIC SHOCK

Cardiogenic shock is a state of end-organ hypoperfusion due to cardiac failure. The definition of CS includes hemodynamic parameters: ***persistent hypotension*** (systolic blood pressure <90 mmHg or mean arterial pressure 30 mmHg lower than baseline) with ***severe reduction in cardiac index*** (<1.8

l/min/m^2 without support or <2.0 to 2.2 l/min/m^2 with support) and ***adequate or elevated filling pressure*** (eg, left ventricular [LV] end-diastolic pressure >18 mmHg or right ventricular [RV] end-diastolic pressure >10 to 15 mm Hg). Hypoperfusion may be manifest clinically by cool extremities, decreased urine output, and/or alteration in mental status. Hemodynamic abnormalities form a spectrum that ranges from mild hypoperfusion to profound shock, and the short-term outcome is directly related to the severity of hemodynamic derangement. In recent studies of cardiogenic shock, eligibility criteria included systolic blood pressure <90 mmHg for >30 min or requirement of catecholamines to maintain systolic pressure >90 mmHg, plus clinical signs of pulmonary congestion and impaired organ perfusion with at least one of the following criteria: (I) altered mental status; (II) cold, clammy skin and extremities; (III) oliguria with urine output <30 mL^{-1}; or (IV) serum lactate >2.0 mmol L^{-1}.

The diagnosis is usually made with the help of pulmonary artery (PA) catheterization; however, Doppler echocardiography may also be used to confirm elevation of LV filling pressures.

Cardiogenic shock often occurs as the result of an acute event that precipitates rapid cardiovascular collapse. Myocardial infarction (MI) with LV failure remains the most common cause of CS. Among patients with an acute ST-elevation myocardial infarction (MI), 8% will develop cardiogenic shock [2] typically within 24 h of the onset of symptoms [3]. In these patients, cardiogenic shock is typically a direct consequence of regional myocardial dysfunction and diminished contractility. Mechanical complications of MI including ventricular septal defect, papillary muscle rupture producing acute mitral regurgitation, and free left ventricular wall rupture can also cause cardiogenic shock. Echocardiography is the technique of choice to rule out these entities and should be performed early unless the diagnosis is extensive anterior MI and the patient is undergoing prompt percutaneous coronary intervention (PCI). In addition, the detection of valvular disease before angiography may alter the revascularization approach.

Hemorrhage, infection, and/or bowel ischemia may contribute to shock in the setting of MI. As with mechanical complications, a high index of suspicion is required to make these diagnoses in MI patients, and survival may depend on timely recognition and treatment.

Any cause of acute, severe left ventricle (LV) or right ventricle (RV) dysfunction may lead to CS. Many non-ischemic disease processes may present acutely or subacutely and result in cardiogenic shock. Acute valvular regurgitation, regardless of cause, can rapidly progress to severe heart failure. Several types of cardiomyopathies can present with a fulminant course, including viral myocarditis, giant-cell myocarditis, peripartum and Takotsubo cardiomyopathy. Extracardiac disease may also result in CS, as with a massive pulmonary embolism or pericardial tamponade. Finally, 3–4% of patients admitted to the hospital for acute decompensation of chronic heart failure will present with shock [4].

1.3 INCIDENCE

After decades of remarkable stability in the incidence of CS, it appears that the incidence is on the decline in parallel with increasing rates of use of primary PCI for acute MI. CS continues to complicate approximately 5% to 8% of STEMI and 2.5% of non-STEMI cases [5]. This translates to 40000 to 50000 cases per year in the United States [6]. The routine use of troponin to define non-STEMI will result in a drop in this percentage as more MIs are detected but will not alter the total number of cases of CS.

The only way to prevent CS appears to be very early reperfusion therapy for MI. A randomized trial of early, in-ambulance thrombolysis versus primary PCI found no CS among patients assigned to prehospital thrombolysis [7]. Among PCI-assigned patients, just 0.5% developed CS in the group randomized <2 hours from symptom onset. A major focus of public health campaigns is the very

early recognition and reperfusion of MI, which should reduce CS incidence. Risk factors for development of CS in the context of MI include older age, anterior MI, hypertension, diabetes mellitus, multivessel coronary artery disease, prior MI or angina, prior diagnosis of heart failure, STEMI, and left bundle-branch block [8]. There may be clues to impending shock: heart rate is higher and blood pressure lower on hospital presentation among patients who develop CS after admission.

1.4 PATHOPHYSIOLOGY

Cardiogenic shock is the result of temporary or permanent derangements in the entire circulatory system. LV pump failure is the primary insult in most forms of CS, but other parts of the circulatory system contribute to shock with inadequate compensation or additional defects.

With the exception of acute valvular disease, CS typically occurs in the setting of pronounced myocardial dysfunction and low CO. The reduction in MAP results in poor systemic perfusion and end-organ ischemia. Low coronary perfusion pressure may exacerbate ischemia. Catecholamine release attempts to compensate for the low-output state by increasing inotropy and peripheral vasoconstriction at the cost of increasing myocardial oxygen demand. Up-regulation of pressure but worsening congestion. There are increased cytokine levels and expression of inducible nitric oxide synthase [2], which can exacerbate hypotension and further worsen myocardial function, causing a deterioration of cardiovascular hemodynamics.

The degree of myocardial dysfunction that initiates CS is often, but not always, severe. LV dysfunction in shock reflects new irreversible injury, reversible ischemia, and damage from prior infarction. The unique position of the heart as an organ that benefits from low blood pressure via afterload reduction and also suffers from low blood pressure via compromise of coronary flow

creates a situation in which changes in hemodynamics may be simultaneously beneficial and detrimental.

As depicted in Figure 1, a decrease in coronary perfusion lowers cardiac output (CO), which further decreases perfusion of the heart and other vital organs. Coronary flow may be additionally compromised by atherosclerosis of vessels other than the infarct artery. Metabolic derangements occur in the remote myocardium and in the infarct region [9]. Hypoperfusion causes release of catecholamines, which increase contractility and peripheral blood flow, but catecholamines also increase myocardial oxygen demand and have proarrhythmic and myocardiotoxic effects. Inotropic agents and vasoconstrictors temporarily improve CO and peripheral perfusion but do not interrupt this vicious circle. Rapid intra-aortic balloon pump (IABP) support may temporarily relieve ischemia and support the circulation, but IABP is not definitive therapy. Relief of coronary occlusion, best achieved through PCI or surgery, interrupts the vicious circle and saves lives. RV dysfunction may cause or contribute to CS. Predominant RV shock represents only 5% of cases of CS complicating MI [10]. RV failure may limit LV filling via a decrease in CO, ventricular interdependence, or both. Treatment of patients with RV dysfunction and shock has traditionally focused on ensuring adequate right-sided filling pressures to maintain CO and adequate LV preload; however, patients with CS due to RV dysfunction have very high RV end-diastolic pressure, often >20 mmHg [10]. This elevation of RV end-diastolic pressure may result in shifting of the interventricular septum toward the LV cavity, which raises left atrial pressure but impairs LV filling due to the mechanical effect of the septum bowing into the LV. This alteration in geometry also impairs LV systolic function [11]. Therefore, the common practice of aggressive fluid resuscitation for RV dysfunction in shock may be misguided. Inotropic therapy is

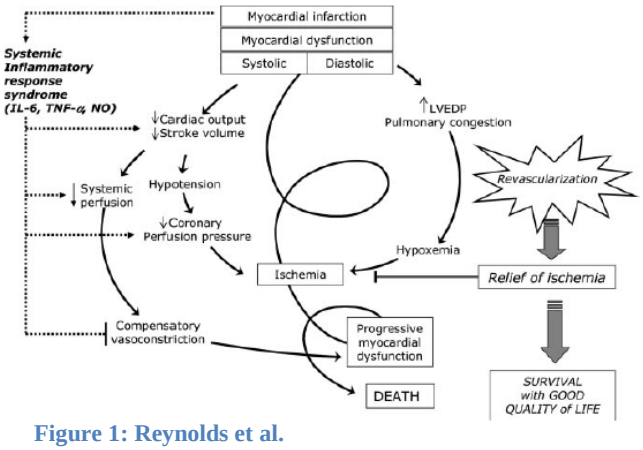

Figure 1: Reynolds et al.

indicated for RV failure when CS persists after RV end-diastolic pressure has been optimized. RV end-diastolic pressure of 10 to 15 mmHg has been associated with higher output than lower or higher pressures [12] but marked variability exists in optimal values. Inhaled nitric oxide (NO) may be useful to lower pulmonary vascular resistance and promote forward flow. Both pericardiectomy and creation of atrial septal defects have been used in extreme cases.

Shock due to isolated RV dysfunction carries nearly as high a mortality risk as LV shock [10]. The benefit of revascularization was similar in the SHOCK registry for patients with primarily RV versus primarily LV dysfunction.

Hypoperfusion of the extremities and vital organs is a hallmark of CS. The decrease in CO caused by MI and sustained by ongoing ischemia triggers release of catecholamines, which constrict peripheral arterioles to maintain perfusion of vital organs. Vasopressin and angiotensin II levels increase in the setting of MI and shock, which leads to improvement in coronary and peripheral perfusion at the cost of increased afterload, which may further impair myocardial function. Activation of the neurohormonal cascade promotes salt and water retention; this may improve perfusion but exacerbates pulmonary edema. The reflex mechanism of increased systemic vascular resistance (SVR) is not fully effective. These findings are consistent with the observation that MI can cause the systemic inflammatory response syndrome (SIRS) and suggest that inappropriate vasodilation as part of SIRS results in impaired perfusion of the intestinal tract, which enables transmigration of bacteria and sepsis. SIRS is more common with increasing duration of shock [13] even though levels of interleukin-6 and tumor necrosis factor-α have been found to be elevated on admission among MI patients who were initially in Killip class I and later developed CS [14]. Cytokine levels rise more dramatically over the 24 to 72 hours after MI. Tumor necrosis factor-α and interleukin-6 have myocardial depressant action. Tumor necrosis factor-α also induces coronary endothelial dysfunction, which may further diminish coronary flow [15]. Other circulating factors (complement, procalcitonin, neopterin, C-reactive protein, and others) have been reported to

contribute to SIRS in CS. Excess NO may also contribute to SIRS. MI is associated with increased expression of inducible NO synthase, which leads to excess NO, which causes vasodilation, myocardial depression, and interference with catecholamine action.

Cardiogenic shock has been divided into four stages to demonstrate severity and progression of disease: preshock, mild shock, profound shock and severe refractory CS [16]. The progression from mild cardiogenic shock to severe refractory cardiogenic shock reflects the severity of hemodynamic compromise and is reflected by the number of vasoactive medications required to maintain reasonable CO and MAP. In mild shock, the cardiovascular system may not require support or can be easily supported with low doses of one inotrope or vasopressor. Patients with profound shock require moderate-to-high doses of a single agent, whereas patients with severe refractory cardiogenic shock remain hemodynamically compromised, despite high doses of multiple vasoactive medications. Mortality increases progressively with each stage, and patients with severe refractory cardiogenic shock generally have a very poor prognosis in the absence of MCS.

However, cardiogenic shock is not a mere decrease in cardiac contractile function, but also a multiorgan dysfunction syndrome (MODS) resulting from peripheral hypoperfusion with microcirculatory dysfunction, often complicated by a systemic inflammatory response syndrome (SIRS) and sepsis [17,18-23].

Once MODS has developed, it is difficult to improve prognosis and reduce mortality by simply increasing cardiac output with a circulatory assist device. Prevention of MODS may depend on three critical factors:

(1) optimal timing (i.e. early initiation) of mechanical circulatory support,

(2) optimal level of mechanical circulatory support with reestablishment of adequate perfusion of critical organs, and

(3) optimal prevention and management of potential device-related complications (i.e. device malfunction, infection).

Intuitively, one would expect that haemodynamic parameters would best discriminate between survivors and non-survivors, and at least for the calculated pressure-flow-product 'cardiac power output/index', this has been demonstrated [24,25]. However, in the IABP-Shock study [20], cardiac index itself was unrelated to patient survival beyond the first 24 h of CSMI. Likewise, biomarkers of heart failure (e.g. BNP) were unrelated to prognosis in the first 96 h of CSMI.

On the other hand ,MODS severity (as indicated by the APACHE II or SAPS II scores) and biomarkers of SIRS (like Interleukin 6 and receptor of advanced glycation end-products, RAGE) can predict mortality more accurately than haemodynamic indices [26].

Although LV contractile failure and low cardiac output are the primary cause of cardiogenic shock, improving cardiac output alone may not reverse or even halt the progression of MODS if initiated too late. Therefore, the haemodynamic improvement of cardiac index may be a measure of technical success of mechanical circulatory support; however, without limiting the progression of SIRS and MODS within the first few days, these haemodynamic improvements may be futile and may not translate into improved survival.

1.5 INITIAL MANAGEMENT OF CARDIOGENIC SHOCK

The initial management goals of cardiogenic shock include cardiovascular resuscitation and identification of the underlying cause. Reversible cardiac causes, including arrhythmias and conduction disturbances, should be identified and treated. If myocardial ischemia or infarction is suspected, patients should rapidly undergo coronary angiography and either percutaneous or surgical revascularization. In the SHOCK (One-year survival following early revascularization for cardiogenic shock) trial, early revascularization in those presenting with cardiogenic shock reduced 1-year mortality from 66 to 53% [27]. Medical therapy of cardiogenic shock is directed at

normalizing hemodynamic parameters, correcting metabolic disarray and minimizing end-organ dysfunction. Vasoactive agents (inotropes, vasopressors) are often required to augment CO but at the expense of worsening myocardial oxygen demand, exacerbation of ischemia and potentiation of arrhythmias. Correction of acidosis may help to prevent damage to end-organs and to promote the effects of vasoactive agents. Those patients with continued worsening or lack of improvement of hemodynamics despite escalation of medical therapy are considered to have severe refractory shock and should immediately be considered for placement of MCS.

1.6 MECHANICAL CIRCULATORY SUPPORT IN THE TREATMENT OF CARDIOGENIC SHOCK

The key concept is to quickly identify patients in need of more support than medical management and/or an IABP can achieve, as early intervention with MCS in the patients at highest risk is most effective when done early. MCS can interrupt the inflammatory cascade initiated by the onset of shock and prevent progression to irreversible end-organ damage and subsequent death; however, there remains a window of opportunity during which rescue is possible. An IABP is typically the first line of mechanical support used due to ease of insertion and minimal risk, but it is often insufficient in providing adequate support in patients with severe cardiogenic shock. Other options for temporary support include the Impella^{TM} percutaneous ventricular assist device (PVAD), TandemHeart^{TM} PVAD, venoarterial extracorporeal membrane oxygenation (V-A ECMO) and the CentriMag^{TM} device, which can be placed surgically or percutaneously. (Figure 2) [28].

Table 1. Characteristics of various devices used in the management of severe refractory cardiogenic shock

Device	IABP	Impella 2.5	Tandem	Impella 5.0	VA ECMO	Centrimag
Maximum support	Add 0.5 l/min	2.5 l/min	4.5 l/m	5.0 l/min	Up to 6 l/min	Up to 10 l/min
Contraindications	AI, aortic aneurysm or dissection, severe PAD (relative), coagulopathy	LV thrombus, mechanical aortic valve severe AS, HOCM, VSD, severe PAD (relative)	Bleeding diathesis, uncontrolled sepsis, severe PAD, LV thrombus	LV thrombus, mechanical aortic valve severe AS, HOCM, VSD, severe PAD (relative)	Irreversible brain injury, contraindication to anticoagulation	Irreversible brain injury, contraindication to anticoagulation
Ease of insertion (1 very easy, 5 most technically challenging)	1	2	4	3	2	5
LV support	+	++	+++	+++	++++	++++
RV support			++ (when placed in a right sided configuration)		++	+++ (when placed in a right sided configuration)
Respiratory support	–	–	–	–	+	–
Hemolysis	–	+++	++	++	+	+
Bleeding	–	–	++	+	+++	++
TCP	+–	+	+?	+	++	+
Duration of use	Up to 90 days	Up to 4 weeks	Days to weeks	Up to 4 weeks	Up to 60 days or more	Months

AI, aortic insufficiency; AS, aortic stenosis; ECMO, extracorporeal membrane oxygenation; HOCM, hypertrophic obstructive cardiomyopathy; IABP, intra-aortic balloon pump; LV, left ventricular; PAD, peripheral artery disease; RV, right ventricular; TCP, thrombocytopenia; VA, venoarterial; VSD, ventricular septal defect.

Figure 2: Sayer et al.

Device selection is based on a number of factors including the degree of hemodynamic support needed, whether right ventricular failure or lung injury is present, individual patient factors (e.g. mechanical valves, peripheral vascular disease) and the availability of interventionalists/cardiac surgeons.

Ouweneel and Henriques [29] defined the *'ideal device for cardiogenic shock'* as follows: *' . . . during an acute critical presentation only those assist devices allowing percutaneous access are suitable due to the invasiveness of surgical devices. The ideal device should enable both haemodynamic support and myocardial protection. Also, a percutaneous approach is preferable to provide for a quick and easy deployment. In addition, the ideal device should be associated with a low complication rate, as complications may sometimes outweigh the potential beneficial effect. Complications associated with any (percutaneous) LV assist device may include limb ischaemia, embolisation of atherosclerotic and/or thrombotic material, stroke, infection and haemolysis'.*

In line with these demands for mechanical circulatory support in CS, different technical strategies have been developed over the past decades to improve cardiac output and unload the critically damaged left ventricle by either afterload or pre-load reduction (i.e. pressure or volume unloading, respectively). Additionally, circulatory support may be provided to the left ventricle alone, the right

ventricle alone, or to both ventricles. Biventricular assist devices may be combined with replacement of pulmonary gas exchange (i.e. extracorporal membrane oxygenation, ECMO) or be administered as pure right and left ventricular haemodynamic support.

Based on the different physiological concepts outlined above, we distinguish among three categories of peripheral/percutaneous circulatory support devices in CS:

(1) mechanical LV support by LV pressure unloading [30]—the IABP;

(2) mechanical LV support by LV volume unloading [30]—the TandemHeart™, the Impella Recover LP® micro-axial rotary pump;

(3) mechanical circulatory support with membrane oxygenation [30]—ECMO;

The possibilities are completed by surgically implanted mechanical support -without simultaneous replacement of pulmonary gas exchange- combining right (RVAD) and/or left (LVAD) paracorporeal ventricular assist device therapy.

1.7 INTRA-AORTIC BALLOON PUMP (IABP)

The IABP (Figure 3) is the most commonly used form of MCS, it's a balloon inserted in the descending aorta that augments coronary blood flow by inflating during diastole, while also assisting myocardial function through reduced afterload by deflating during systole. The ultimate effect is limited to an increase of LV stroke volume and cardiac output by up to 1 l/min (15–30%, respectively). The haemodynamic effects of IABP in CS [31] include:

- an increase in stroke volume and CO,

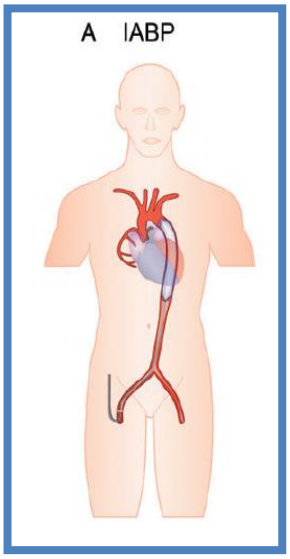

Figure 3: Werdan et al.

- an increase in systemic blood pressure with increased coronary blood flow in open coronary arteries, [32]
- a reduction in LV pre-load, LV end-diastolic pressure, and pulmonary capillary wedge pressure,
- a decrease in LV wall stress and myocardial oxygen demand, and
- improved reperfusion after thrombolysis in STEMI patients.

Outcomes data using the IABP are scarce. In the randomized, prospective, open-label, multicentre IABP SHOCK II Trial [17], a total of 600 patients with CSMI were assigned—after best medical therapy and early revascularization, predominantly with PCI (95.8%)—to additional intra-aortic balloon counterpulsation (IABP group, 301 patients) or no intra-aortic balloon counterpulsation (control group, 299 patients). No difference was found in the primary endpoint—30-day all-cause mortality—with 39.7% mortality in the IABP group and 41.3% mortality in the control group (relative risk with IABP 0.96, 95% confidence interval 0.79–1.17, P=0.69). The authors concluded that the use of IABP did not significantly reduce 30-day mortality in patients with CSMI for whom an early revascularization strategy was planned.

However, despite lingering questions about the efficacy of IABP therapy, it remains the first-line therapy for the treatment of cardiogenic shock at most centers.

Recommendations for the use of intra-aortic balloon pump in patients with cardiogenic shock

There is a large indication list for the adjunctive use of IABP in heart failure and shock states including cardiac surgery [31], with little convincing evidence of proven benefit. On the other hand, those indications with evidence from large RCTs are all negative: (I) CSMI, (II) elective high-risk PCI in patients with LV dysfunction and extensive coronary artery disease [33], and (III) acute anterior STEMI without cardiogenic shock [34].

The American College of Cardiology/American Heart Association STEMI guidelines recommend the use of IABP as a class IIa indication for patients with CSMI [35], whereas the recent European guidelines state that ‘intra-aortic balloon pumping may be considered (IIb/B)’ (Figure 10) [30].

1.8 TANDEMHEART PERCUTANEOUS VENTRICULAR ASSIST DEVICE

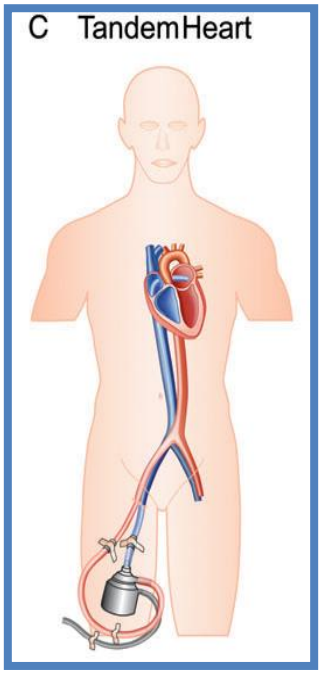

Figure 4: Werdan et al.

The TandemHeart PVAD (Cardiac Assist, Inc., Pittsburgh, Pennsylvania, USA) (Figure 4) is an external centrifugal blood pump with percutaneous cannulae. Oxygenated blood is aspirated from the left atrium and injected into the lower abdominal aorta or iliac arteries via a femoral artery cannula. The inflow cannula is placed in the left atrium via a transseptal puncture. Pump outflow is returned to the body through a 17 French cannula in the femoral artery (Figure 5). It typically augments CO up to 3.0–4.0 l/min. The haemodynamic effects of the TandemHeart are superior to the IABP [35-38] leading to a greater increase in CO and MAP and a decrease PCWP, central venous pressure, and pulmonary artery pressure, resulting in reduced filling pressures in the left and right ventricle, reduced cardiac workload and reduced oxygen demand [35,39], as well as an increase in cardiac power index.

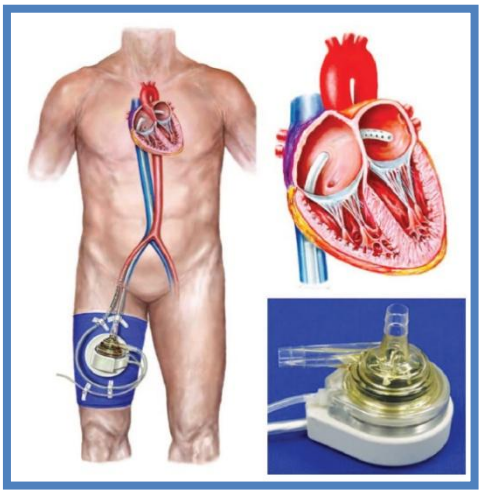

Figure 5: Srihari et al.

Its use is limited by access site complications, limb ischemia and bleeding. Implantation is more time-consuming and requires specialized expertise, due to the need for a transseptal puncture. The presence of a cannula in the left atrium can be a nidus for thrombus formation. One significant advantage of the TandemHeart is that it can be configured to provide right ventricular support with inflow cannula placement into the right atrium and outflow cannula placement into the main pulmonary artery [40]. The TandemHeart is FDA-approved for up to 6h of use, but successful use has been reported for greater than 1 week [41]. In

the largest reported series, 117 patients with refractory cardiogenic shock were implanted with the TandemHeart for an average of 5.8 days [42]. The population was critically ill, with a MAP of 45mmHg, cardiac index of 0.5 l/min/m2 , and lactic acid level of 24.5 mg/dl. TandemHeart support provided rapid reversal of the hemodynamic abnormalities, increasing the MAP to 81mmHg, cardiac index to 3.0 l/min/m2 , and decreasing the lactic acid level to 11.0 mg/dl. Although there was no control group, the 30-day mortality of 40% was considerably better than expected outcomes in this population. The most common complications were bleeding and sepsis.

Recommendations for the use of the TandemHeart in patients with cardiogenic shock

In the European guidelines a class IIB recommendation is given for LV assist devices in CSMI [43] (Figure 6). The 2013 AHA/ACCGuideline for the Management of ST-Elevation Myocardial Infarction assigns a level IIb/C indication for LV assist devices in refractory cardiogenic shock. This includes centrifugal pumpsystems such as the TandemHeart and ECMO [35].

Treatment of cardiogenic shock (Killip class IV)			
Oxygen/mechanical respiratory support is indicated according to blood gasses.	I	C	-
Urgent echocardiography/Doppler must be performed to detect mechanical complications, assess systolic function and loading conditions.	I	C	-
High-risk patients must be transferred early to tertiary centres.	I	C	-
Emergency revascularization with either PCI or CABG in suitable patients must be considered.	I	B	100
Fibrinolysis should be considered if revascularization is unavailable.	IIa	C	-
Intra-aortic balloon pumping may be considered.	IIb	B	1, 98, 305
LV assist devices may be considered for circulatory support in patients in refractory shock.	IIb	C	-
Haemodynamic assessment with balloon floating catheter may be considered.	IIb	B	316
Inotropic/vasopressor agents should be considered: • Dopamine	IIa	C	-
• Dobutamine	IIa	C	-
• Norepinephrine (preferred over dopamine when blood pressure is low).	IIb	B	300, 317

Figure 6: ESC GL for the management of STEMI [43]

1.9 IMPELLA RECOVER PERCUTANEOUS VENTRICULAR ASSIST DEVICE

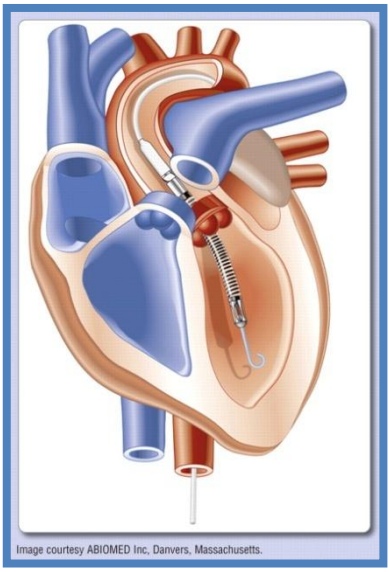

Figure 7.

The Impella Recover PVAD (AbioMed Inc, Danvers, Massachusetts, USA) is a micro-axial rotary pump positioned across the aortic valve to provide active support by transvalvular LV assistance, expelling aspirated blood from the left ventricle into the ascending aorta (Figure 7).

Two versions are currently available: the Impella Recover LP® 2.5 can provide up to 2.5 L min^{-1} and can be inserted percutaneously. The Impella Recover LP® 5.0 can deliver up to 5.0 L min^{-1} but requires surgical cutdown of the femoral or axillary artery.

The Impella 2.5 is an axial flow motor that pumps blood from the left ventricle into the ascending aorta. The catheter is placed percutaneously through a tapered 13 or 14 French sheath and is connected to an external power source. Flow is less robust than the Tandem-Heart, averaging less than 2.5 l/min. However, implantation is quicker and there are fewer access site complications due to the smaller sheath size. A comparison of the Impella 2.5 with IABP showed better initial hemodynamic support with the Impella PVAD, but no difference in mortality or support after 6h [44]. The primary complication of the Impella 2.5 is hemolysis, which can be severe and often limits the duration of use. Another common issue is pump migration from its intended position, which may lead to poor support or contribute to hemolysis.

The Impella 5.0 is a larger device, providing flows up to 5.0 l/min. Due to its size, it must be implanted surgically, either directly into the ascending aorta or through a vascular graft to the femoral or axillary artery. Due to the larger size of the inflow, hemolysis is a less frequent complication.

Several studies have demonstrated that the Impella device is safe and haemodynamically effective in STEMI and high-risk PCI patients [29]. The unloading of the left ventricle is associated with reduced end-diastolic wall stress and an immediate decrease in PCWP [29]. Coronary perfusion pressure and coronary flow are reported to be increased and myocardial oxygen consumption reduced [29].

With respect to the role of the Impella pump in cardiogenic shock and especially in CSMI, the multicentre Impella EUROSHOCK-Registry [45] included 120 patients with CSMI receiving temporary circulatory support with the Impella- 2.5-pLVAD. Thirty-day mortality was 64.2%. After Impella-2.5- pLVAD-implantation, lactate levels significantly decreased from 5.8±5.0 to 2.5±2.6 mmol L^{-1} ($p = 0.023$) at 48 h.

The ISAR-SHOCK randomized trial compared the Impella 2.5 with the IABP in cardiogenic shock patients [46] As showed in this study, CI and MAP increased more in the Impella group; furthermore, serum lactate levels were lower in the Impella group than in the IABP group. No differences in mortality, major bleeding, distal limb ischaemia, arrhythmias, and infections were found.

It has been suggested that, in severe cardiogenic shock, the Impella 5.0 device may provide superior haemodynamic support [29,47]. A lower mortality rate has been reported for Impella 5.0 in patients with post-cardiotomy low-output syndrome with a residual CO of 1 L min^{-1} vs. IABP [48,49]

1.10 CENTRIMAG VENTRICULAR ASSIST DEVICE

The Thoratec CentriMag VAD (Thoratec Corporation, Pleasanton, California, USA) (Figure 8) is a centrifugal pump with a magnetically levitated rotor that can provide up to 10 l/min of blood flow. The CentriMag can be connected to many different types of circuits, including ECMO, but is designed as an extracorporeal, surgically implanted VAD for short-term or intermediate-term support. For left ventricular support, an inlet cannula is placed in the left ventricular apex (the left atrium is not recommended due to the potential for thromboembolic complications) with the outlet cannula delivering blood to the aorta. The CentriMag can also provide right ventricular support with inflow from the right atrium and outflow into the pulmonary artery. Two CentriMags can also be configured to provide biventricular support.

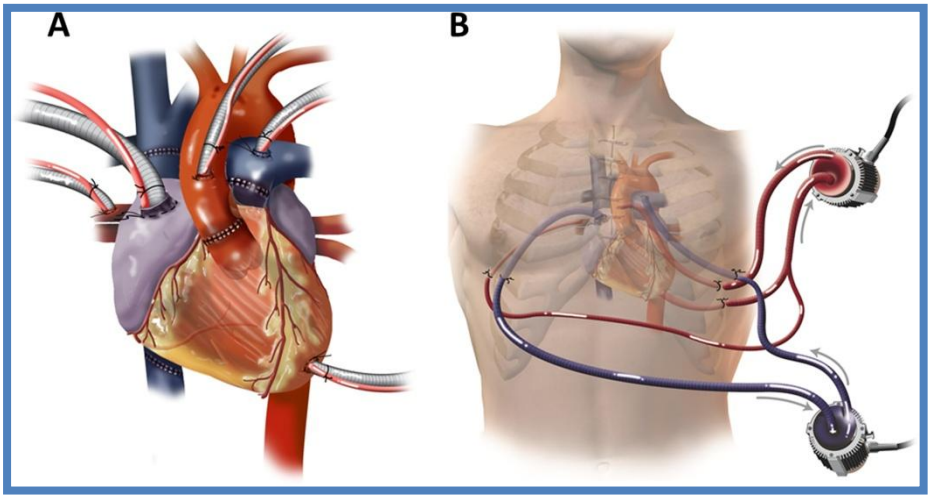

Figure 8. Kaczorowski et al.

The primary advantage of the CentriMag system is its ability to deliver high-flow rates and to completely unload the LV. The system is relatively easy to use and has a low rate of thromboembolism when high-flow rates are maintained The CentriMag is more durable than PVADs and can provide effective support for weeks to months [50]. A multicenter investigation of

the CentriMag in 38 patients demonstrated a 47% 30-day survival. The major complications included infection and neurological dysfunction [51]. The CentriMag can be configured to support the right ventricle percutaneously with an inflow cannula placed in the right atrium via the femoral vein and the outflow cannula placed in the pulmonary artery via the internal jugular vein [52].

1.11 EXTRACORPOREAL MEMBRANE OXYGENATION (ECMO)

The complete ECMO system (Figure 9)—a modified heart–lung machine—generally consists of a centrifugal pump, a heat exchanger, and a membrane oxygenator. Venous desaturated blood is aspirated from the right atrium into a centrifugal pump through canulla inserted into the right atrium. The pump outflow is directed into a membrane oxygenator and is guided via an outflow cannula into the aorta or femoral/axillary artery.

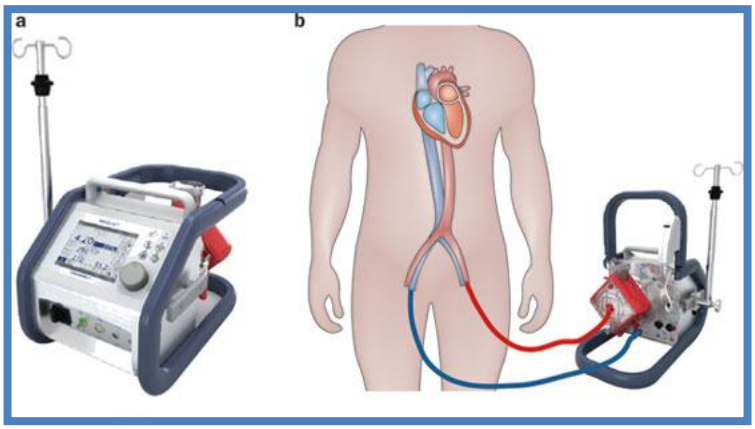

Figure 9. Westaby et al.

Veno-Arterial (V-A) ECMO can provide support for patients with lung injury as well as either univentricular or biventricular failure. It's has been applied in STEMI [53], myocarditis [54], post-cardiotomy [55], interhospital transfer [56,57] and also in the cardiac catheterization laboratory in patients who developed cardio-respiratory arrest during PCI and TAVI [58].

In the most commonly used percutaneous configuration, the inflow cannula is inserted into the right atrium through either the femoral or jugular vein and the outflow cannula is placed in the lower descending aorta via the femoral artery. Due to the large size of the arterial cannula (18 French), an antegrade catheter is often placed in the ipsilateral femoral artery to provide adequate perfusion to the leg. A percutaneous circuit can be established in less than 30 min, and it is feasible to put patients on ECMO at the bedside during an emergency. When percutaneous access is not possible, the ECMO circuit can be placed centrally, with direct cannulation of the right atrium and aorta.

Of the percutaneous MCS options, ECMO provides the most cardiac support, with the ability, based on cannula size and position, to achieve flow of greater than 6.0 l/min. However, ECMO is resource intensive, requiring continuous monitoring by nursing and trained perfusion staff. Complications include limb ischemia, bleeding, stroke, and infection. Adequate levels of anticoagulation must be maintained to prevent thromboembolic complications. In patients with pulsatility during support, care must be taken to ensure that blood leaving the heart is adequately oxygenated, as perfusing the coronary arteries and brain with deoxygenated blood may result in catastrophic anoxic injury. Alternatively, with severe ventricular dysfunction, the left ventricle (LV) may not be adequately decompressed due to return of blood to the left atrium through the bronchial circulation. Left ventricular distension can lead to excess wall stress and may impede ventricular recovery. Several methods of decompressing the LV have been described, including a transseptal catheter [59], a pulmonary artery cannula [60], and minimally invasive placement of an apical vent [61]. Several recent reports have described successful use of an Impella Recover 2.5 as a vent for the LV [62-64]. Following institution of ECMO, there is often a rapid reversal of hemodynamics with a decrease in inotrope/vasopressor requirement, improvement in gas exchange, and reduction in markers of endorgan failure. With meticulous care, ECMO support can be maintained for weeks.

Recommendations for the use of ECMO in patients with cardiogenic shock

There is a class IIb/C recommendation in the European STEMI guidelines [43] to consider an LV assist device for circulatory support in patients with refractory cardiogenic shock (Figure 10). The European guidelines on myocardial revascularization recommend considering— without a definite recommendation—ECMO implantation for temporary support in CSMI patients who continue to deteriorate due to inadequate circulatory support of the IABP. This recommendation is based on expert consensus.

Table 4 Guideline recommendations of percutaneous assist devices in cardiogenic shock complicating myocardial infarction

Indication	Assist device	European Guidelines	American Guidelines	German–Austrian Guidelines
Cardiogenic shock	IABP	IIb/B Intraaortic balloon pumping may be considered in patients with cardiogenic shock (Killip class IV)	IIa/B Haemodynamic support for patients with cardiogenic shock after STEMI who do not quickly stabilize with pharmacological therapy	⇑ In patients undergoing fibrinolysis ⇔ In patients undergoing PCI ⇑ In patients with mechanical complications
	Left ventricular assist devices	IIb/C LV assist devices may be considered for circulatory support in refractory shock in patients with cardiogenic shock (Killip class IV)	IIb/C Alternative left ventricular (LV) assist devices for circulatory support may be considered in patients with refractory cardiogenic shock.	Routine use not recommended

European Guidelines[27]; American Guidelines[38]; German-Austrian Guidelines[28].
Recommendation grades of the German-Austrian Guidelines[28] ⇑⇑ strongly recommended ('shall'); ⇑ recommended ('should'); ⇔ no recommendation ('may'; no confirmed study results exist that demonstrate either a beneficial or harmful effect); ⇓ rejected ('should not'); ⇓⇓ strongly rejected ('shall not').
LVAD, left ventricular assist device; BiVAD, biventricular assist device.

Figure 10: Werdan et al.

1.12 CONCLUSIONS

Despite optimal up-to-date therapy of CS, mortality continues to remain unacceptably high. Limited data may support the use of levosimendan [65] but innovations in pharmacological therapy are not forthcoming. Mild therapeutic hypothermia is promising as a potential therapeutic strategy for CSMI [66]. It has multiple potentially beneficial effects, including the potential to improve post-ischaemic cardiac function and haemodynamics, decrease myocardial damage, and reduce end-organ injury from prolonged hypoperfusion. The neutral results of the IABP-SHOCK II Trial remind us that immediate haemodynamic improvement may not automatically translate into

improved survival. In view of the dissociation between improvements in haemodynamic parameters and clinical outcomes, including mortality, device therapy may be the best therapy for the future.

In fact mechanical circulatory support not only improves haemodynamics, but prevent or reduce MODS and ultimately, mortality.

However clinical success of device therapy in CS does not depend on the mechanical qualities of the device alone. The ease and safety of device implantation—especially under emergency conditions and during cardiopulmonary resuscitation—will also greatly influence patient outcome. Additionally, the rates of device-related complications such as limb ischaemia, access site bleeding, haemolysis, and infection are still too high, and the contact of blood with these devices may cause/worsen SIRS and MODS. Patients with CS have minimal reserve to tolerate operator error or device complications.

Data from morbidity studies with a focus on the time course of SIRS and MODS development indicate that haemodynamic support has limited ability to change outcome if initiated when overt MODS has already developed. Mechanical circulatory support should not be considered the treatment of last resort for CS, but should probably be initiated early in the disease course to minimize the negative effects of high-dose catecholamine therapy on microcirculation and before end-organ dysfunction with MODS.

Finally among the other mechanical circulatory support devices for CS, we believe that ECMO is likely to have the greatest potential for wider clinical use.

Its major advantages are:

- quick and easy percutaneous insertion of inflow and outflow cannulas,
- full circulatory support with up to 4.0 L min^{-1},
- ECMO rapidly improves tissue oxygenation in situations of cardiogenic shock combined with severe pulmonary oedema.

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2.EXTRACORPOREAL MEMBRANE OXYGENATION (ECMO)

2.1 INTRODUCTION

Since the first successful application of the heart–lung machine in 1953 by John Gibbon [1], great efforts havebeen made to modify the bypass techniques and devices in order to allow prolonged extracorporealcirculation in the intensive care unit (ICU), commonly referred to as extracorporeal membrane oxygenation(ECMO). It is instituted for the management of life threatening pulmonary or cardiac failure (or both), when no other form of treatment has been or is likely to be successful. ECMO uses classic cardiopulmonary bypass technology to support circulation. It provides continuous, non-pulsatile cardiac output and extracorporeal oxygenation [2] and it is used as temporary support, usually awaiting recovery of organs.

At the time, Gibbon's invention was revolutionary and propelled the field of cardiac surgery. Although Gibbon's creation allowed for the care of the cardiac patient in the operating room, its applicability outside the operating theater was largely unimaginable at the time. Eventually, the need to provide mechanical circulatory support (MCS) expanded outside the operating room, resulting in the development of extracorporeal membrane oxygenator (ECMO) technology. However, innovations in the MCS field progressed, leading to the development of smaller implantable pumps compact enough to be inserted through a peripheralvessel but powerful enough to maintain end-organ perfusion.

2.2 HISTORY AND DEVELOPMENT OF OXYGENATORS

Extracorporeal oxygenators are artificial devices that substitute for anatomical lungs by delivering oxygen to, and extracting carbon dioxide from, blood. They were first conceptualised by the English scientist and philosopher Robert Hooke (1635–1703) who demonstrated experimentally in 1667 that inflation and deflation of the lungs of an animal was not mandatory for the oxygenation of the blood flowing through them. He also speculated as to 'whether suffering the blood to circulate through a vessel, so that it may be openly exposed to the fresh air [might] not suffice for the life of an animal' without using the lungs for oxygenation [3,4].The artificial oxygenation and perfusion of individual organs was an objective of early 19th century physiologists. Julien-Jean Cesar le Gallois failed in his attempts to perfuse isolated decapitated rabbits by the injection of arterial blood in 1812 because of coagulation [5] but, following the description of the method of defibrinating blood by Prevost and Dumas in 1821 [6], Lobell [7] successfully perfused an isolated kidney by injecting arterial blood in 1849. In 1858, Brown-Sequard perfused the head of a dog with moderate success by injection, and showed that 5 min of ischaemia of the brain resulted in death of the organ [8,9].

The first 'direct contact' artificial oxygenation of blood in an extracorporeal circulation was achieved in 1869 byLudwig and Schmidt [10] by shaking together defibrinated blood with air in a balloon. Further development of'direct-contact', 'three-dimensional' extracorporeal oxygenation of blood was the perfusion of an isolated kidney in 1882 by Schroder of Strasburg, using the first simple'bubble oxygenator' [4,8,11,12] and, from the same laboratory in 1882, Frey and Gruber described the first'two-dimensional', direct-contact extracorporeal oxygenator that exposed a thin film of blood to air in an inclined cylinder which was rotated at a frequency of 30 min^{-1} by an electric motor [4,8,12,13].

Several bubble and surface type oxygenators were developed in the first two decades of the 20th century [12]. For example, Hooker described in 1910 a bubble oxygenator [12,14] and in 1915 a film oxygenator in which blood flowed over a single rotating disc to be oxygenated [12,13]. Richards and Drinker described anoxygenator in 1915 that incorporated a perforated silk screen through which the blood flowed [12,16].

The problem of reliably preventing coagulation in perfusion was solved by the 1916 discovery of heparin by Jay Maclean. Maclean, a medical student working in the laboratory of W. H. Howell at the John Hopkins University at Baltimore, demonstrated that a phosphatide (cuorin) extracted from canine heart muscle prevented coagulation of the blood [4,8,17]. Subsequently, it was discovered that the active substance could also be extracted from dog liver in reasonable quantities and it was given the name ‘heparin’ [8,18]. The discovery of the anticoagulant property of heparin paved the way to the development of whole body perfusion in animals and, subsequently, extracorporeal oxygenators for use in human cardiac surgery [4,8].

The first whole body extracorporeal perfusion with isolation of the heart was, in fact, demonstrated in a canine model by the Russian scientists Brukhonenko and Tchetchuline in 1929 [4,19–21]. They used the quiescent isolated lung as an oxygenator in a remarkable series of perfusion experiments, first with the isolated head and then using the whole body of the animal. Many workers described ingenious oxygenating systems for isolated organs between 1920 and 1950. Von Schroder of Strasburg, for instance, built the first bubble oxygenator in 1882 [11], in which air was introduced into a venous reservoir and the subsequent increase in pressure in the reservoir forced oxygenated blood into an arterial reservoir, which then perfused an isolated organ. VonEuler and Heymans [22] in 1932 developed the opposite and novel approach of introducing ‘atomised’ blood into an air/oxygen environment. However, there were three important devices that were to be ultimately developed into apparatus for clinical open heart surgery in man:the film oxygenator developed by

Gibbon between 1937 and 1953 [4,12,23–27]; the rotating disc oxygenator described in 1948 by Bjork [4,12,28]; and the improved all-glass bubble oxygenator described in 1952 by Clarke, Gollan and Gupta [4,29].

2.3 THE USE OF OXYGENATORS DURING THE EARLY YEARS OF OPEN-HEART SURGERY

2.3.1 The Mayo-Gibbon pump-oxygenator

The painstaking work of Gibbon in designing experimental film oxygenators that had extended over two decades [23–27] was crowned with success when he carried out the first successful human intracardiac operation under direct vision using a mechanical extracorporeal pump-oxygenator on 18th May 1953 [4,12,24,27].Gibbon's original objective was to develop an apparatus capable of suspending the natural circulation during Trendelenburg's emergency operation for pulmonary artery embolectomy [23,24]. However, the first human operation was in fact closure of an atrial septal defect [27]. Gibbon's early experimental oxygenator filmed blood over the inner surface of a rotating cylinder in an oxygen atmosphere [4,23–25]. However, this could not be enlarged to perfuse animals larger than a cat [30]. Thus, in Gibbon's later animal experiments and the first human operation, he used a stationary screen oxygenator that he had developed [26,27]. This consisted of a series of six to eight wire mesh screens arranged vertically and in parallel in a plastic container down which the blood flowed, forming a stable film that was exposed to a flow of oxygen [12]. Each of the screens was 60 cm high and had a width of 10 cm. Kirklin et al. [31,32], at the Mayo Clinic in Rochester Minnesota, further developed the Gibbon-type stationary screen oxygenator into the Mayo-Gibbon pump-oxygenator apparatus after careful animal experimentation. This was a sophisticated commercially available unit [8]. Kirklin et al. began their

pioneering series of human intracardiac operations in March 1955 using the Mayo-Gibbon pump-oxygenator and were very successful [33]. A number of cardiac surgery units worldwide obtained and used this apparatus [4,33,35]. The results were satisfactory but the apparatus was bulky and cumbersome, quite complicated to sterilise and operate, prone to the problem of blood streaming (resulting in diminishing blood surface area for gas exchange), and also required a large blood and saline priming volume [35].

2.3.2 The Kay-Cross disc oxygenator

The Bjork rotating disc film oxygenator (1948) [4,28] employed in animal studies was modified for clinical use by Melrose in 1953, by Kay and Cross and their colleagues in 1956 [36,37], by Osborn, Bramson and Gerbode in 1960 [38] and by other workers. The Melrose model described in 1953 after comprehensive animal studies was used clinically very successfully for open heart surgery for human patients at the Royal Postgraduate Hospital in London and other cardiac units [4,39]. It was an ingenious drum and disc oxygenator. It gave good service in the early days of clinical cardiopulmonary perfusion, but it was cumbersome and required considerable time and expertise to service and assemble. Later, simpler versions with Teflon®-coated stainless steel discs in a silicone-coated Pyrex®chamber were preferred [8,12,24,36–38]. Some disc oxygenators with presterilised disposable plastic discs became available later [8].The need for blood conservation required the filming discs to be placed close to their disc enclosure. This led to risks of foaming and haemolysis when the discs spun, which limited their clinical applicability [24,35]. Nevertheless, rotating disk oxygenators continued to be favoured by many clinicians in the 1960s and 1970s despite the dominance of the practical disposable single use disposable bubble oxygenators until single-use membrane oxygenators became generally available. This was in part due to their perception that the Kay-Cross oxygenator caused less blood damage than the bubble oxygenator in longer surgical cases [12,40].

2.3.3 The DeWall bubble oxygenator

Studies of the function of the version of the bubble oxygenator devised by Clarke, Gollan and Gupta were important for the subsequent design of the DeWall bubble oxygenator [41] that was used by Lillehei and his team in their continuing pioneer work in intracardiac surgery [4,8,41–43]. Clarke, Gollan and Gupta [29] reported in 1950 that although small bubbles with their large surface area to volume ratio favoured oxygen uptake, they were less buoyant. This means that smaller bubbles are less likely to rise spontaneously to the surface and are more likely to remain in suspension – airembolism is therefore more likely. An optimum balance has therefore to be obtained. This optimum is believed to exist if the bubbles are between 2 mm and 7 mm in diameter [44]. Alternatively, a mixture of small and big bubbles may be used [43]. Furthermore, since carbon dioxide removal occurs by diffusion, the partial pressure of the gas vented from the oxygenator cannot exceed its partial pressure in blood, which is normally 4.5 kPa, in contrast to the 13.3 kPa of oxygen [35]; increasing the gas exchange area is of limited benefit. Carbon dioxide removal is therefore limited by the rate of fresh gas flow necessary to maintain an optimum carbon dioxide partial pressure differential.The commercially available DeWall oxygenator [12] had a vertical oxygenating column through which oxygen bubbled upwards at a high gas flow rate. The resulting foamy blood subsequently entered a defoaming chamber, in which silicone-coated surfaces decreased the surface tension of the bubbles, causing the smaller bubbles to coalesce into larger bubbles. These larger bubbles were then eliminated in a helical tubular reservoir in which the bubbles floated upwards while the blood was pumped downwards. In March 1954, after careful animal research, Lillehei and his team of the University of Minneapolis, Minnesota,began to conduct an interesting and relatively successful series of intracardiac operations for the closure of atrioventricular defects in children using the arterialblood of an adult in a controlled cross-circulation technique [45]. Lillehei et al. then began to use the DeWall bubble oxygenator clinically

in May 1955 [42,46]. DeWall type bubble oxygenators gained widespread acceptance, being used in an estimated 90% of open heart operations worldwide in 1976 [46]. This was because of their many advantages: they were highly efficient because of the large cumulative surface area of the oxygen bubbles; they had a simple design without moving parts other than the mechanical pumps that drove the circulation; the components of the circuit were easily sterilized and they were disposable [4,8,40,47]. Their popularity was cemented with the advent of single-use, relatively inexpensive, presterilised and prepacked plastic versions[4,47–50]. A further advantage was that the priming volume required for these disposable devices was so small that a saline prime would often suffice without the addition of donor blood. Some bubble oxygenators were fitted with integral heat exchangers and had plastic venous reservoirs that allowed direct observation of the changes of blood volume in the circuit [35]. The DeWall oxygenator is a 'sequential bubble oxygenator', i.e. the components (bubbler, defoamer, reservoir and pump) are arranged linearly in series. Other variants have been designed that are 'concentric bubble oxygenators', in which for the sake of compactness the components are arranged concentrically,and also 'foam oxygenators', in which gas exchange is achieved when blood films down a column in a counter-current system [51]. Foam oxygenators consequently share some functional properties with both filmand bubble oxygenators.

2.3.4 Limitations Of The Performance Of Direct Contact Extracorporeal Oxygenators

The length of time for which either bubble or film direct contact extracorporeal oxygenators could be used without causing serious complications did not extend muchbeyond 4 h [8,47]. The principal limiting factor was damage to blood constituents due to the direct contact of blood with air surfaces and to contact with the plastic and metal constituents of the pump oxygenator circuit. Blood trauma included damage and destruction of red blood cells and platelets, coagulation disorders and protein denaturation. Prolonged extracorporeal perfusion could also result in vascular problems, including diffuse capillary leakage, poor peripheral perfusion, acidosis and progressive organ failure [52].

These disadvantages of direct contact extracorporeal oxygenators could be accepted and usually counteracted for the relatively short duration of intracardiac surgery.Many cardiac surgery units used profound hypothermia, cooling the body with the aid of a heat exchanger to a nasopharyngeal, i.e. brain, temperature of 10–12 °C. This allowed the perfusion to be turned off completely for up to 1 h while prolonged intracardiac surgery was performed [8,47]. Some units adopted the Drew method of profound hypothermia [53,54]. This technique eliminated the use of an extracorporeal oxygenator completely. The patient's own lungs were employed as oxygenators during cooling by bypassing both the left and right sides of the heart with separate simultaneous perfusions [8,47,53,54]. The Mayo-Gibbon type screen oxygenators, the disposable versions of the DeWall-type bubble oxygenator, and the Kay-Cross disc oxygenator and its modifications remained in use throughout the 1960s and 1970s. The disposable bubble oxygenators became very popular because of their convenience in use and low prime volume but there was a general view that the rotating disc oxygenators were somewhat better for longer cases [4,12,40,47]. There are very few papers attempting to make direct comparisons of the clinical performance of the various forms of direct contact extracorporeal oxygenators. However, in 1961 Gerbode et al. gave their reasonsfor marginally preferring a rotating disc over a bubble oxygenator [55]. Engell et al., writing in the same year, also gave their reasons for marginally preferring the disposable bubble oxygenator over a stationary screen oxygenator [56].The limit on the length of time that direct-contact extracorporeal oxygenators could be used made them unsuitable for use in the longer term for the therapeutic support of adults and infants suffering from respiratory distress syndrome (RDS). One thing was certain: clinicians concerned with cardiopulmonary perfusion in the 1950s, 1960s and 1970s followed the lengthy gestation of membrane oxygenators very closely, and looked forward with keen anticipation to the advent of a practical, disposable version.

2.3.5 Introduction of the membrane oxygenator

The idea of a protective membrane between blood and air to decrease the problem of blood trauma inherent in direct-contact extracorporeal oxygenators began with observations by Kolff and Berk in 1944 [57]. They noted that blood in their haemodialysis machine, which contained 20 000 cm^2 of cellophane tubing, became oxygenated when exposed to aerated dialysates; the gas contents of the blood equilibrated with that of the dialysate through the process of passive diffusion. Although the potential advantage of the membrane oxygenator in decreasing the degree of blood trauma associated with direct-contact oxygenators was immediately evident, the problems were also quickly appreciated, namely:

- *a dearth of suitable membrane biomaterials, which were judged on their gas permeabilities, mechanical strength, how thinly they can be made without pinhole defects and blood–artificial surface interactions;*
- *the membrane constituted an additional barrier to gas exchange;*
- *the problem of optimal distribution of blood and gas flows so that there is efficient gas exchange.*

The emphasis in early membrane oxygenator development concentrated on finding suitable biomaterials [58], as early biomaterials had low gas exchange performance and poor mechanical properties, limiting the developmentof membrane oxygenators. Of the earliest available materials, ethylcellulose and polyethylene were the most permeable to oxygen and carbon dioxide [59]. Polyethylene offered good mechanical strength and was rolled into a coil for the first experimental membrane oxygenator [60,61]. Clowes, Hopkins and Neville in 1958 used25 m^2 of the more permeable ethylcellulose [62] (soon replaced by the mechanically stronger polytetrafluoroethylene or Teflon® [63]) in multiple sandwiched layers in their device that constituted the first clinical membrane oxygenator. Membrane support with grooved plates was later added, making an arrangement akin to a manifold of straight capillaries in parallel. This was to stop blood collecting

unpredictably in thick rivulets, a problem similar to that of blood streaming in film oxygenators. One disadvantage of hydrophilic membrane oxygenators is their tendency to leak plasma in a manner akin to tents leaking water when wetted on the inside. This severely shortened the duration of the use of the membrane lung. To prevent this, membranes made of hydrophobic polymers [58] were used. These materials were initially derived from packaging materials used inthe capacitor industry, such as polytetrafluoroethylene (Teflon®). With hydrophobic membranes, Melrose [64] realised in 1958 that it is carbon dioxide removal that was the limitation, as carbon dioxide solubility inhydrophobic solids is much less than its solubility inhydrophilic solids. To emphasise the importance of carbon dioxide transfer, the term 'membrane lung' was coined. This problem was partly solved by the use of silicone as the hydrophobic material in membrane lungs. Although silicone had been discovered in 1947 and had played an important role as a defoaming agent in direct contact devices, its excellent gas exchange properties [65] were not discovered until 1957. Silicone had a permeability (the product of diffusivity and solubility) for oxygen from four to five times higher than this for carbon dioxide, these figures being some 40 times higher than those for Teflon®. Early silicone membranes had a number of problems. They had low mechanical strength and were not free of pinholes when made into a thin film. Solutions were found to these problems. In 1959, Thomas designed the first silicone membrane lung using a thin continuous silicone membrane on a fabric support, which was made by dip-coating a nylon mesh, and the pairing of two sheets of ultrathin membranes together so as to decrease the risk of leakages through random pinhole defects. The definitive solution belonged to Burns [66] who, in1959, developed a new process at Hammersmith Hospital in London for the low-cost production of thin films of silicone membranes that were virtually free of pinholes and had greatly increased strength. Modern versions of the silicone membrane oxygenators are still in use and are marketed as long-term extracorporeal oxygenators [67].

2.3.6 Improving the gas exchange efficiency of membrane oxygenators

With sufficiently thin membranes, the gas exchange bottleneck was now recognised as having shifted from the membrane to gas diffusion through blood. This was a result of the thickness of the blood layer. Marx et al. [68] determined that oxygen transfer into a blood film is proportional to the square of the thickness of the blood film and the diffusion resistance of the boundary layer. This latter factor requires elaboration. In alveolar capillaries, the blood channels are one cell thick, resulting in efficient gas exchange. In artificial oxygenators, the blood channels are much thicker. With laminar flow, blood flows in orderly layers through these channels. The boundary layer, i.e. the layer that is adjacent to the gas exchange surface, quickly equilibrates with the venting gas. However, this equilibration is slow to spread through the other layers because of the low diffusivity of gas through blood, with consequent deterioration of gas exchange efficiency. Subsequent development therefore concentrated on minimising these two bottlenecks. The first silicone capillary oxygenator, comprising capillaries that were 100–500 μm in diameter, was designed by Bodell et al.[69] in 1963. The small diameter of the hollow fibres decreases the distance of the blood layers from the gas exchange surface in two dimensions. Capillary oxygenators also have the additional advantage of being better able to control the volumes of both gas and blood compartments. Configurations with blood inside the fibres and oxygen outside and the reverse configuration of blood outside the fibres and oxygen inside were tried. Wilsonet al. [70] showed that the preferred configuration used blood flowing inside the fibres. However, the opposite is the case with current microporous hollow-fibreoxygenators, as is described later. The second problem, i.e. the diffusion resistance of the boundary layer, was addressed by the induction of secondary flows in blood. Secondary flows are fluid flows that are additional to the mainstream. They may be used to disrupt laminar flow and impart convective mass transfer to the mass of the fluid. Mixing and therefore gas exchange performance are thus increased. Passive internal secondary flows are

induced by forcing blood to ‘eddy’ around passive obstacles, e.g. forcing blood to move in curved paths around a helically wound tube [71] or by the insertion of surface elements into blood passages [72]. Active secondary flows are induced by using energetic mechanisms to disrupt laminar flow more effectively, resulting in greater gas exchange efficiency. Mechanisms devisedfor this include:

- periodic deformation of the membrane through cyclical oxygen pressure to produce microscopic foci of mixing [73];
- a rocking membrane envelope [74];
- pneumatic pulsation of the membrane [74];
- arotating membrane-bound disk [74];
- moving rod massage [75];
- the toroidal membrane oxygenator [76,77];
- the annular membrane oxygenator by Gaylor et al. [78];
- vortex-shedding designs [79,80].

The measures employed were very successful in enhancing gas mass transfer. Kolobow’s device [73] infact exceeded 200 ml oxygen.min^{-1}.m^2, the limit for the thickness of the silicone membrane used. This was because the membrane inverted and stretched into the gas side, increasing the surface area when hypobaric pressure was applied. Kolobow’s device was mass-manufactured and marketed by SciMed, then AveCor and now MedTronic, becoming the only solid silicone membrane device consistently available for long-term life support during the past few decades [81].

2.4 ECMO MODALITIES

ECMO is an invasive technique where blood is drained from the venous system, pumped through an oxygenator, and then re-infused to the patient [82]. There are two basic types of ECMO support: venovenous (VV) ECMO provides only respiratory support, whilst venoarterial (VA) ECMO bypasses both the heart and lungs and is thus the appropriate type of ECMO for patients with circulatory failure.

2.4.1 VV ECMO

VV ECMO is the preferred route to provide either complete or partial support of the lungs in the management of severe respiratory failure when cardiac output is sufficient [83]. However, cardiac function is often improved with VV ECMO because mechanicalventilation is concurrently reduced and oxygen supply to the heart is ameliorated. With VV ECMO, both drainage and return cannula are placed in systemic venous system. The cannulation site depends on patient size [84]. In older children and adults, the drainage of the oxygen-poor blood is from femoral vessels, and the reinfusion of oxygen-rich blood is through the right internal jugular vein [85] (Figure 1).

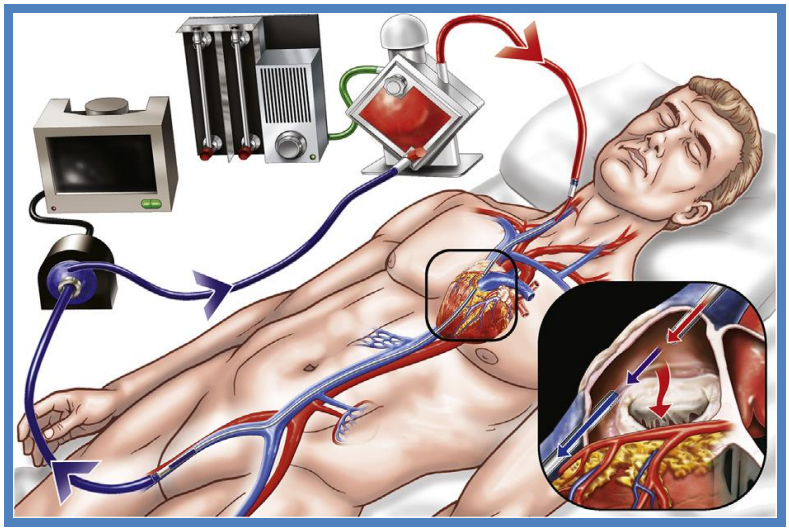


Figure 1: Abrams et al.

VV ECMO can also be delivered using a single double-lumen cannula inserted through the internal jugular vein into the right atrium, although cannula size constraints have previously restricted this technique to infants [86] (Figure 2).

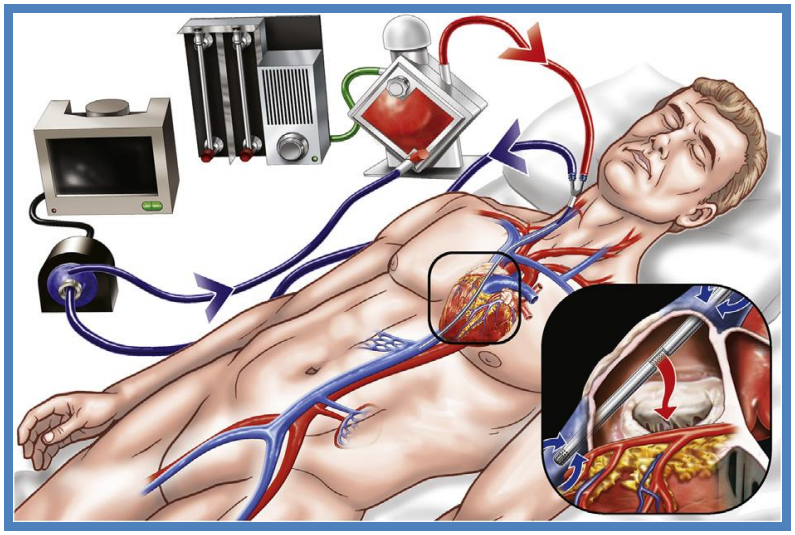


Figure 2: Abrams et al.

One hundred percent oxygenated blood from the ECMO return cannula mixes with systemic venous blood, which than traverses the pulmonary system. Theoretically, only oxygen-depleted systemic venous blood enters the ECMO drainage cannula. However, depending on the positions of the inserted cannula, a variable proportion of oxygenated blood from the return cannula enters the drainage cannula, known as recirculation. Mixed venous oxygen saturation (SvO2) is determined by the relative contributions of the ECMO return cannula (oxygenated blood) to pulmonary blood flow and the systemic venous return (deoxygenated blood). Recirculation reduces the delivery of oxygenated blood to the pulmonary artery, and thus reduces the SvO2. SaO2 is determined by ECMO flow, patient's systemic venous return, the degree of recirculation, the SvO2 venous blood

and pulmonary function. Of these parameters, ECMO circuit flow is the most important and easily manipulated determinant of SaO2 in the absence of significant recirculation [87].

2.4.2 ECMO for Respiratory Failure

Acute respiratory distress syndrome. The most extensively studied respiratory indication for ECMO is acute respiratory distress syndrome (ARDS) [88]. In circumstances in which invasive mechanical ventilation is necessary to support gas exchange, positive-pressure ventilation may potentiate lung injury [89]. The only ventilation strategy proved to reduce mortality in ARDS is a volume and pressure-limited ventilation strategy [90]. ECMO has he potential to improve outcomes in patients with ARDS by providing adequate oxygenation while facilitating lung protective ventilation by correcting unsustainable levels of hypercapnia and respiratory acidosis that may accompany low–tidal volume ventilation [91]. Potential indications for ECMO in the setting of ARDS have been proposed [88].

Early randomized trials were unsuccessful in demonstrating a survival benefit from ECMO in patients with severe forms of ARDS. More recently, the impact of modern extracorporeal support on survival in patients with severe ARDS was evaluated in the Conventional Ventilation or ECMO for Severe Adult Respiratory Failure trial, in which 180 subjects with severe, potentially reversible respiratory failure were randomized to conventional mechanical ventilation or referral to a specialized center for consideration of ECMO (92). Compared with the conventionally managed group, those referred for consideration of ECMO had a significantly lower rate of death or severe disability at 6 months (37% vs. 53%; relative risk: 0.69; $p = 0.03$).

Other nonrandomized observational studies, particularly during the influenza A (H1N1) pandemic in 2009, have shown conflicting results of the impact of ECMO on survival in severe ARDS [93].

Hypercapnic respiratory failure. With an improved risk benefit ratio, there is great potential to use $ECCO_2R$ to manage hypercapnic respiratory failure, thereby minimizing or even eliminating the need for a ventilator. In chronic obstructive pulmonary disease, invasive mechanical ventilation is associated with multiple complications, including dynamic hyperinflation and elevations in intrinsic positive end-expiratory pressure, ventilator-associated pneumonia, and impaired delivery of aerosolized medications [94,95]. Several small case series have demonstrated the feasibility of avoidance of or rapid weaning from invasive mechanical ventilation, with $ECCO_2R$ used to manage gas exchange [96–98]. With correction of hypercapnia and respiratory acidosis, dyspnea and work of breathing rapidly improve, facilitating early mobilization [98]. Although early mobilization has been described with invasive mechanical ventilation [99], it is more likely to be successful with the substitution of $ECCO_2R$ for mechanical ventilation because of the significant improvement in dyspnea that is seen with $ECCO_2R$ compared with mechanical ventilation in the hypercapnic population [98]. The risks of $ECCO_2R$ must be weighed against the benefit of minimizing invasive mechanical ventilation, and additional studies are required to define the ideal patient population and the economic impact of such a strategy before it can be recommended for clinical use. Similarly, $ECCO_2R$ may be considered in other forms of hypercapnic respiratory failure, including refractory status asthmaticus, in which the ability to avoid invasive mechanical ventilation altogether is potentially advantageous (100,101).

Bridge to lung transplantation and post-transplantation primary graft dysfunction. Although ECMO has traditionally been considered a relative contraindication to lung transplantation because of poor perioperative outcomes [102], more recent studies have reported excellent post transplantation survival, especially at centers with more extensive experience [103,104]. With the potential for ECMO to provide sufficient gas exchange to supplant the ventilator, a nonintubated ECMO strategy may be considered for some transplantation candidates who would otherwise be

ventilator dependent, a population with poor outcomes related to ventilator-associated complications [105]. Outcomes may be further optimized when such a strategy is combined with active physical therapy and should be considered in patients who would otherwise be inactivated from the transplantation list because of deconditioning. This is particularly true for those patients in whom ECMO or $ECCO_2R$ alleviates dyspnea sufficiently to permit rehabilitation [104,106,107]. A major limitation to the use of ECMO for end-stage respiratory failure is the lack of a destination device therapy, with ECMO remaining an intervention for which an intensive care unit is required. In severe cases of primary graft dysfunction, a form of acute lung injury that is the leading cause of early death after lung transplantation [108], ECMO may be used to support gas exchange while the allograft recovers. Studies have described similar survival in cases of ECMO-supported severe primary graft dysfunction compared with those with less severe primary graft dysfunction without ECMO support, particularly when instituted early [109]. However, ECMO has not been shown to affect long-term allograft function.

2.4.3 VA ECMO

VA ECMO is essentially a modification of the cardiopulmonary bypass circuit which is used routinely in cardiac surgery. In VA ECMO, oxygen-depleted blood drains into the circuit from venous system and oxygenated blood is pumped back into the systemic side, which both augments gas exchange and supports cardiac function. Cannulation for VA ECMO can be established centrally or peripherally. With ***central cannulation*** (Figure 3), blood is drained directly from the right atrium and return to the proximal of ascending aorta.

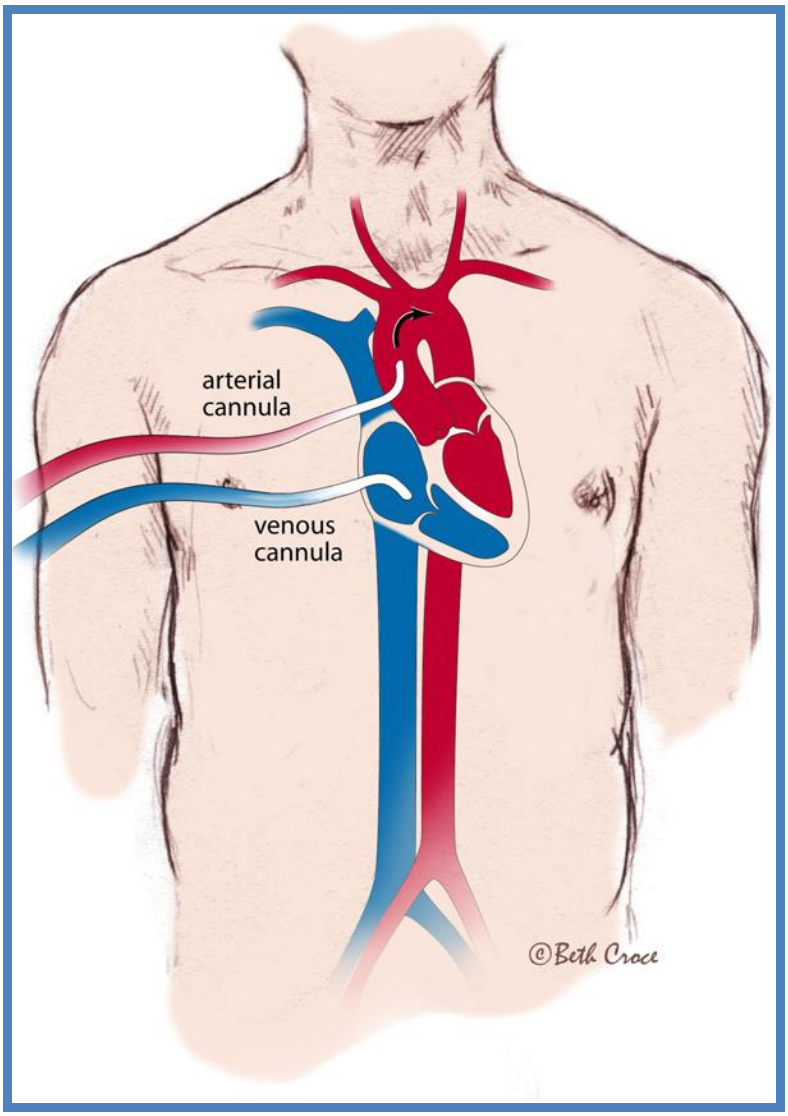


Figure 3: Marasco et al.

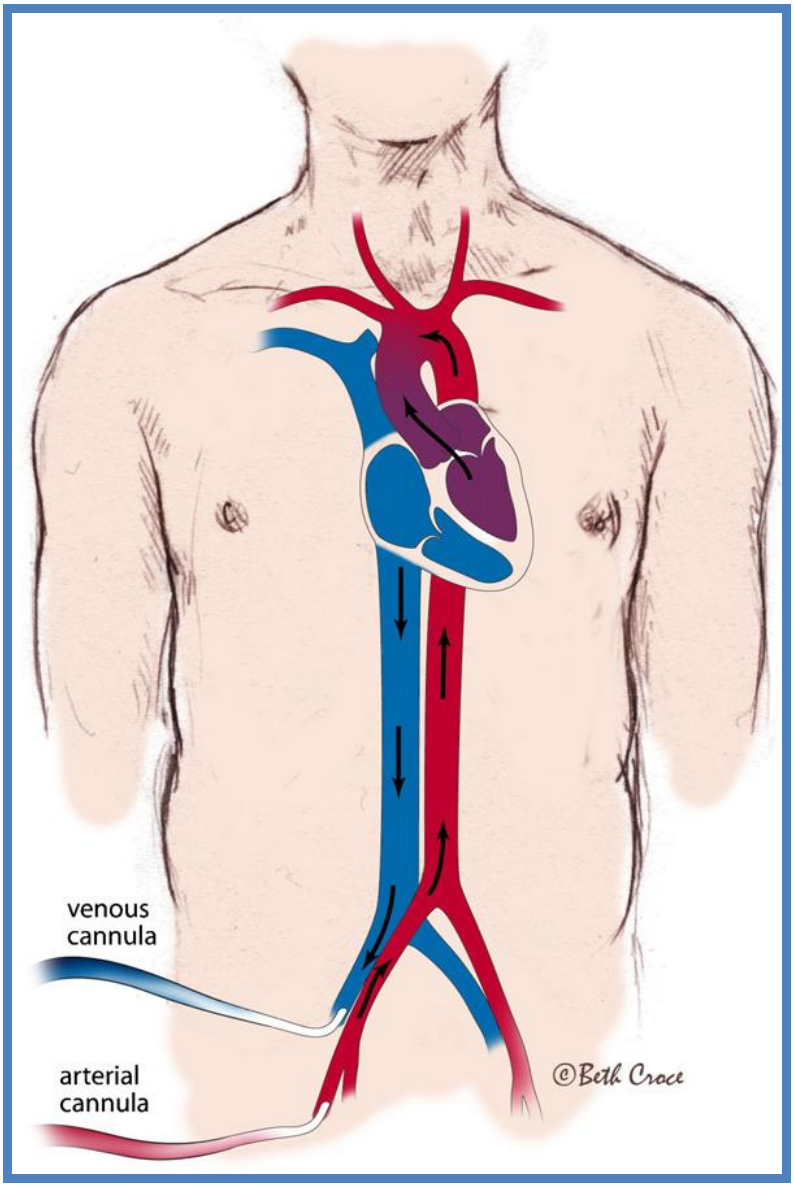


Figure 4: Marasco et al.

With ***peripheral cannulation*** (Figure 4)**,** blood is drained from the proximal great veins (via a femoralor jugular vein) using a surgically cut-down or modified Seldinger technique, and returned to the aorta via cannulation of a carotid, axillary or femoral artery (Figure 5).

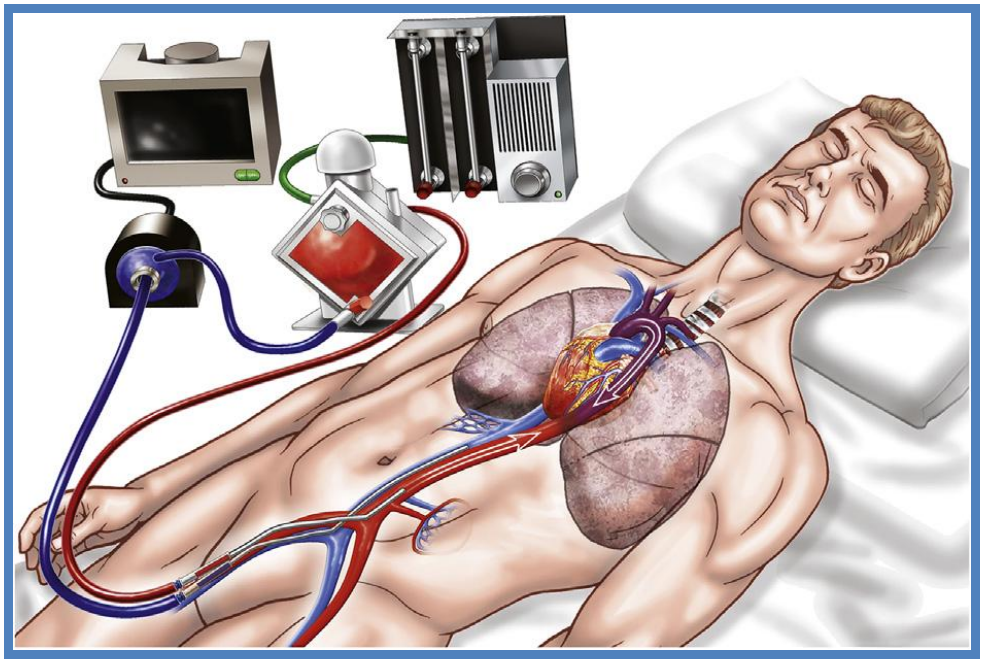


Figure 5: Abrams et al.

Systemic arterial blood flow is the total of the ECMO circuit flow and any ejection from the left ventricle. Systemic blood pressure is determined by total arterial blood flow and the vascular tone. When left ventricle (LV) cannot contribute to the systemic arterial blood flow, the patient's systemic arterial oxygen saturation (SaO2) is determined entirely by the oxygen saturation of blood in the ECMO return cannula, which is 100%. However, if there is a contribution from the LV, SaO_2 depends on the relative flow and oxygen saturation of blood from both the ECMO circuit and blood ejected by LV. This detail becomes important if you place the ECMO return cannula via femoral artery in a patient suffering from a severely compromised lung function. In this condition, coronary arteries, cerebral blood vessels and upper limbs are under threat of hypoxaemia because proximal branches of the aorta receive predominantly deoxygenated blood ejected from the left heart. Even though there is a presence of sufficient LV function, this situation persists as long as pulmonary function is good or the return cannula is placed centrally [87].

ECMO remains a short-term support device, essentially the circuit is smaller than a standard cardiopulmonary bypass circuit, transportable and closed to the atmosphere. The cannulae are also specifically designed for ECMO. The duration of support with ECMO has greatly increased with improving oxygenators and medical management,and whereas support was previously in the order of days, patients can now be maintained on ECMO for weeks. In most patients the duration of support required is approximately1 week. Most commonly, it is instituted in an emergency or urgent situation after failure of other treatment modalities.

2.4.4 ECMO for Cardiac Failure

In terms of cardiac failure, the most common indications for ECMO are ***post-cardiotomy*** (that is unable to get the patient off cardiopulmonary bypass following cardiac surgery) [110], ***post-heart transplant*** (usually due to primary graft failure) [111] and ***severe cardiac failure*** due to almost any other cause (e.g. ***decompensated cardiomyopathy, myocarditis, acute coronary syndrome with cardiogenic shock, profound cardiac depression due to drug overdose or sepsis***).

In making the decision to institute ECMO, several considerations must be weighed. Most importantly, one must consider the likelihood of organ recovery. If the organ failure is thought to be reversible with therapy and rest on ECMO, then institution of this mechanical support is appropriate. If recovery is thought not to be a possibility in that particular patient, then other factors must be taken into account. With regards to cardiac failure, if recovery is not expected, what other options are there available for this patient? Consideration must be given to the patient's eligibility for transplantation, other mechanical assist devices to bridge the patient to transplant or whether it is appropriate for a definitive mechanical assist device to be inserted as destination therapy. Obviously implantation of ECMO in an 80 year old with no hope of native organ recovery is a futile exercise as there is no endpoint for this patient's treatment. Such implementation of ECMO could be seen as

unethical in that it puts a patient (and their family) through a futile exercise, falsely raises their hopes, utilizes resources better used on someone with achance of survival and blocks an intensive care bed. Other contraindications to the institution of ECMO include disseminated malignancy, advanced age, graft vs.host disease, known severe brain injury, unwitnessed cardiac arrest or cardiac arrest of prolonged duration. There may be other technical contraindications to consider such as aortic dissection or aortic incompetence (discussed below).

If ECMO has been instituted for cardiac support, thereare several other end points to their recovery pathway. ECMO can either be weaned if the heart has recovered, a more permanent mechanical device can be inserted orthe patient may receive a heart transplant. The more permanent mechanical devices which can be implanted allow the patient to ambulate, rehabilitate, and be discharged home with the device. The aim then is to either wait for further cardiac recovery to allow explant of the device or to list the patient for transplantation. Patients can be supported by a VAD (Ventricular Assist Device) at home for months or even a year prior to receiving a heart transplant. More recently, fully implantable mechanical assist devices are being used as destination therapy. Destination therapy is considered in patients who have end stage heart failure which has not responded to any other form of treatment, and who are not suitable for transplantation. This is usually due to advanced age (>65) or other comorbidities. Several technical considerations need to be taken into account also before instituting ECMO. Aortic incompetence is a relative contraindication, particularly if severe. In such situations consideration of aortic valve replacement would need to be made. Lesser degrees of aortic incompetence may be managed with a left ventricular vent. Failure to insert a vent leads to ventricular distension, compromised subendocardial blood flow and would impact on recovery and the ability to wean ECMO.

Post-operative cardiogenic shock and post-transplant primary graft failure. Post-cardiotomy cardiogenic shock is an uncommon but highly lethal complication of cardiac surgery. ECMO may

be considered as temporary support post-operatively, particularly when unable to wean from cardiopulmonary bypass in the operating room [112]. Mortality in patients requiring this level of support remains high [113]. Primary graft failure (PGF) is a well-recognized complication of heart transplantation associated with a high mortality, for which ECMO has been used as temporary support [114,115]. As expected, overall survival for patients with PGF requiring ECMO is worse than in those who do not develop PGF. However, patients with ECMO-supported PGF who survive beyond the early post-transplantation period have comparable long-term survival with non-PGF transplant recipients [115,116].

Cardiogenic shock complicating acute myocardial infarction. There are no randomized controlled trials comparing ECMO with other mechanical support systems in myocardial infarction–associated cardiogenic shock, but several nonrandomized studies suggest a survival advantage from the early use of ECMO in such circumstances (117,118). In an observational study of patients with ST-segment elevation myocardial infarction–related cardiogenic shock undergoing percutaneous coronary intervention (PCI) with and without ECMO support, those receiving ECMO had significantly lower 30-day mortality (39.1% vs. 72%;p = 0.008) (54). Interpretation of these data is limited by the fact that cohorts were enrolled over different time frames (1993 to 2002 for the non-ECMO cohort vs. 2002 to 2009 for the ECMO cohort), potentially leading to discrepancies in treatment between groups, especially given that coronary stents were unavailable at the study center before 1998. Higher rates of Thrombolysis In Myocardial Infarction flowgrade 3 achieved in the ECMO group may reflect improved hemodynamic stability in the catheterization laboratory or, alternatively, may be a consequence of improved PCI technique over time. Ultimately, randomized controlled trials are needed to determine the true benefit, if any, of ECMO in myocardial infarction–associated cardiogenic shock.

Fulminant myocarditis. ECMO use has been investigated as a modality to support non ischemic cardiogenic shock, including fulminant myocarditis [119-122]. Patients with fulminant myocarditis who are successfully bridged with ECMO to recovery may have long-term prognoses comparable with those of hemodynamically stable patients with acute myocarditis [119]. In 1 cohort of patients who received either a biventricular assist device (n = 6) or ECMO (n = 35) for fulminant myocarditis with refractory cardiogenic shock, overall intensive care unit survival was 68%, with higher severity of illness and elevated cardiac biomarkers serving as independent predictors of mortality and an inability to wean from ECMO (121). ECMO may be as efficacious as a ventricular assist device (VAD) while having the advantage of being less invasive. In a study comparing ECMO with biventricular assist devices for fulminant myocarditis, those receiving ECMO had comparable rates of weaning from device therapy and survival to hospital discharge without the need for transplantation (83% vs. 80%) and more rapid improvement in renal and hepatic laboratory profiles, despite having a higher severity of illness and worse left ventricular function before device implantation [122].

Sepsis-associated cardiomyopathy. Myocardial depression is a well-recognized consequence of severe septic shock [123]. There are emerging data suggesting that ECMO may have a role in supporting patients who develop refractory cardiac failure in this setting [124,125]. Larger studies are needed to determine whether the benefit of ECMO outweighs the risk, especially in cases in which septic shock is complicated by marked disturbances in coagulation.

Pulmonary hypertension. ECMO is an emerging management option in patients with decompensated pulmonary hypertension with concomitant right ventricular failure, particularly when there is an acutely reversible process, medical management has not been optimized, or lung transplantation is a consideration [126]. ECMO for this indication typically requires a femoral venoarterial configuration to bypass the high resistance of the pulmonary vasculature and

decompress the right ventricle. However, 3 configurations have been used to avoid femoral cannulation. Internal jugular venous drainage may be combined with subclavian arterial reinfusion. In patients with pre-existing intra-atrial defects, a dual-lumen cannula maybe oriented with the reinfusion jet directed across the defect (rather than across the tricuspid valve), effectively providing an oxygenated right-to-left shunt while decompressing the right ventricle [127,128]. Additionally, arteriovenous ECMO can be inserted between the main pulmonary artery and the left atrium, though this typically requires a sternotomy [129]. When ECMO is initiated as a bridge to recovery, pulmonary vasodilators may be optimized while the underlying acute process is treated [126]. When the goal of ECMO is to bridge to transplantation, pulmonary vasodilators may be down-titrated to preferentially shunt blood through the extracorporeal circuit and away from the high-resistance pulmonary vasculature, thereby optimizing systemic oxygenation [130]. Reducing the dosage of intravenous pulmonary vasodilators will also minimize the degree of systemic vasodilation that may occur as the medications pass through the ECMO circuit and into the arterial circulation.

Pulmonary embolism. Massive pulmonary embolism may likewise benefit from ECMO. A retrospective single-center review of ECMO for massive pulmonary embolism, including patients in active cardiac arrest, demonstrated 62% overall survival when combined with anticoagulation or surgical embolectomy [131]. The combination of ECMO, thrombolysis, and catheter-directed thrombectomy or embolus fragmentation has also been reported, with 30-day survival of 70% [132].

Extracorporeal cardiopulmonary resuscitation. "Extracorporeal cardiopulmonary resuscitation" (ECPR) is the term used to describe the institution of extracorporeal support to restore circulation during cardiac arrest. Although there are no randomized controlled trials investigating the efficacy of ECPR for cardiac arrest, its use has been steadily increasing [133–136). In a prospective,

observational study of witnessed in-hospital cardiac arrests, propensity analysis matching 46 subjects who received conventional cardiopulmonary resuscitation (CPR) with 46 subjects who received ECPR demonstrated significantly higher survival at discharge in the ECPR group (32.6% vs. 17.4%; $p < 0.0001$) and at 1 year (hazard ratio: 0.53; $p = 0.006$) (69), with a trend toward improved neurological outcomes. In multivariate analysis, an initial rhythm of ventricular fibrillation or ventricular tachycardia and use of ECPR were positively associated with survival to discharge. A more recent propensity analysis of patients who experienced in-hospital cardiac arrest demonstrated significantly higher 2-year survival with minimal neurological impairment in those treated with ECPR compared with conventional CPR (20% vs. 5% $p = 0.002$). Independent predictors associated with minimal neurological impairment included age <65 years, CPR duration <35 min, and subsequent cardiovascular intervention [135]. Regarding out-of-hospital cardiac arrests, a recent matched propensity analysis demonstrated significantly higher neurologically intact survival at 3 months in those who received ECPR compared with conventional CPR (29.2% vs. 8.3%; $p = 0.018$) (72).With the ability of ECMO to both maintain systemic circulation during cardiac arrest and increase coronary perfusion pressure, the combination of ECPR and intra-arrest PCI may greatly improve the likelihood of successful defibrillation and recovery in cardiac arrest due to an acute coronary syndrome. A multicenter nonrandomized study demonstrated the feasibility of combining ECMO and emergency coronary angiography in 81 subjects, 61 of whom received intra-arrest PCI [137]. Compared with those who received ECMO and coronary angiography without PCI, those receiving PCI achieved higher rates of resumption of spontaneous beating (100% vs. 60%; $p < 0.001$), weaning from ECMO (59% vs. 28%; $p = 0.009$), 30-day survival (36% vs. 12%; $p = 0.03$), and favorable neurological outcomes(33% vs. 4%; $p = 0.005$). In-hospital (vs. out-of-hospital) cardiac arrest and shorter duration from collapse to initiation of ECMO were correlated with 30-day survival. Although observational trials suggest a possible survival advantage of ECPR over conventional CPR, overall survival remains relatively low. More research

is needed to define the patient population that would derive the greatest benefit from extracorporeal resuscitation, with an emphasis on survival with minimal neurological impairment. The 2010 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care do not recommend the routine use of ECPR for cardiac arrest. However, ECPR may be considered when the time without spontaneous circulation is short, resuscitation attempts are adequate, and the cause of cardiac arrest is potentially reversible [138]. The guidelines emphasize that ECPR use should be restricted to centers at which it is readily available and that its initiation and management require highly trained personnel and specialized equipment.

Bridge to VAD implantation or heart transplantation. VADs may be used as a bridging therapy to heart transplantationin appropriately selected patients with severe cardiac dysfunction [139], with the advantage of being able to function as destination devices if transplantation is not feasible. ECMO has also been reported as a bridging therapy to heart transplantation or VAD implantation or as a bridge to decision when prognosis is uncertain [140–142]. However,the duration of support that can be provided is shorter than for VADs, making transplantation or transition to VAD of greater urgency, and patients receiving ECMO support must remain within an intensive care unit [142]. Success of ECMO bridging varies greatly and depends in large part on pre-ECMO patient characteristics and organ availability in the cases in which transplantation is the goal. In a retrospective review of 70 patients in whom ECMO was used as a bridgeto heart transplantation, 31 (44%) were bridged to either heart transplantation (n = 15) or VAD implantation (n = 16), though only 11 (73%) and 8 (50%) of the heart transplantand VAD recipients, respectively, survived to hospital discharge, highlighting the limitations of bridging therapy in this highly morbid patient population [140]. Age > 50 years, CPR before ECMO initiation, and high sequential organ failure assessment score were independent predictors of unsuccessful bridging. Pre-implantation CPR as a predictor of poor outcomes was corroborated in a more recent single-center study of 90 patients

who received mechanical circulatory support (VAD or ECMO) for refractory cardiogenic shock [143]. Forty-nine percent received short-term VAD support as a bridge to decision, and 51% received ECMO when neurological status was uncertain or there was complete hemodynamic collapse or severe coagulopathy. Overall survival was 49%, with 26% of patients transitioned to implantable VADs, 18% recovering sufficient native cardiac function, and 11% bridged to transplantation. CPR at the time of implantation was an independent predictor of in-hospital mortality (odds ratio: 5.79; $p = 0.022$). These studies highlight the need for careful consideration of relative and absolute contraindications to mechanical circulatory support. In particular, ECMO for cardiogenic shock superimposed on chronic cardiomyopathymay be associated with particularly poor outcomes [144].

ECMO to prevent acute right ventricular failure after LVAD implantation. Both femoral venoarterial ECMO and percutaneous venous-to-pulmonary arterial ECMO have been successfully used to provide right ventricular support in patients with biventricular dysfunction undergoing LVAD implantation [145,146]. In this setting, ECMO can allow time for the already compromised right ventricle to get accustomed to the increasing preload,thereby avoiding distension and right ventricular failure leading to poor filling of the LVAD.

2.5 ECMO CIRCUITS AND EQUIPMENT

Basically, an ECMO circuit consists of the drainage and return cannulae, tubing, a driving force (pump) and a gas/heat exchanger. Apart from differences in the cannulae, similar circuits are used for VV and VA ECMO.

2.5.1 Pump

Most ECMO circuits use two-types of pumps: roller and centrifugal. The literature is inconsistent with regard to biocompatibility and complication rates comparing these two pump principles, with a slight tendency in favour of the roller pump [146–148]. Centrifugal pumps consist of a vaned impeller or nested, smooth plastic cones, which when rotated rapidly up to 3000 revolutions/min, propel blood by centrifugal force [149]. Centrifugal blood pumps generate up to 900 mmHg of forward pressure, but only 400–500 mmHg of negative pressure, and therefore less cavitation and fewer gaseous microemboli. Blood flow is preload and afterload dependent. Thus, there is no fixed relationship between pump speed and blood flow, necessitating the presence of a flowmeter within the circuit. They can pump small amounts of air, but become "deprimed" if more than 30–50 ml of air enters the blood chamber. If hypovolaemia occurs, the inlet pressure becomes more negative and pump speed remains constant, however the blood flow rate is decreased. During VA ECMO, a change in systemic vascular resistance changes the relationship between the circuit flow and the speed of the pump. Similarly, pump failure during VA ECMO can result in a reverse of the flow in the circuit [87]. Roller pumps consist of a length of 1/4- to 5/8-inch (internal diameter) tubing, which is compressed by two rollers 180° apart inside a curved raceway. Rollers mounted on a rotating arm progressively compress a segment of tubing pushing blood ahead of the roller and flow rate depends on the diameter of the tubing rate of rotation, the length of the compression raceway, and completeness of compression. A roller pump is usually used in conjunction with a blood-filled

bladder sited between the drainage cannula and the pump to allow continuous pumping despite the alterations in the patient's intravascular effective volume. If hypovolaemia occurs, pump speed and therefore blood flow decrease. Roller pumps are afterload independent. During VA ECMO, a significant change in systemic vascular resistance does not influence blood pumping. Since the driving force of drainage into the bladder is gravity, roller pumps have to be kept below the level of patient, which becomes crucial when transporting patients on ECMO. With roller pumps, there is a direct relationship between pump rate and blood flow; thus, a flowmeter is not required. Roller pumps are cheaper, reliable, safe and have small priming volumes, but can produce high negative pressures and micro-particles shed from compressed tubing (spallation)[150]. Roller pumps are vulnerable to careless operation,back-flow when not in use if rollers are not sufficiently occlusive, excessive pressure with rupture of connections if the return tubing becomes obstructed, tears in tubing, and changing roller compression settings during the operation. Roller pumps, but not centrifugal pumps, are used for sucker systems and for delivering cardioplegic solutions. Centrifugal pumps produce pulseless blood flow and standard roller pumps produce a sine wave pulse around 5 mmHg. The return tubing cannula dampens the pulse of pulsatile pumps, and is difficult to generate pulse-pressures above 20 mmHg within the body during full CPB [151].

The two principles can so far be looked at as being more or less equivalent, even for long-term extracorporeal support. Some centres use two pumps in parallel, thus backing up their unit in case of pump or oxygenator malfunction.

A nonocclusive pump avoids stress to blood components while abolishing negative pressures acting on the drained blood. However, in relation to the pump rate and the patient's intravascular volume, various amounts of blood might be pumped at a time. Using a servo-controlled mechanism is another way to prevent excessive negative pressure. Servo-controlled pumping allows setting of a calculated maximum negative pressure and slows down the rate of the pump when you are close to

the limit [86]. An exciting development was the discovery of intubing pumps which are the miniaturised forms of high-end pumps that are able to pump blood flows between 0 and 10 L/min. These pumps require very small amounts of priming volumes and can be integrated at any location of the ECMO. Inline pumps can support arteriovenous circuits at any time,drive VV orVA circuits; and can be placed at the bedside.

2.5.2 Oxygenators

Membrane oxygenators mimic the human lung by interspersing a thin membrane of either microporous polypropylene hollow fibre (0.3- to 0.8-μm pores) or non-microporous silicone rubber between the gas and blood phases. Membrane oxygenators are safer than bubble oxygenators because they produce less particulate and gaseous microemboli, are less reactive to blood elements, and allow superior control of blood gases [152]. Considering microporous membrane oxygenators, while preventing gas from entering blood, plasma-filled pores also facilitate transfer of both oxygen and carbon dioxide. In order to obtain a sufficient amount of oxygen, blood has to be spread as a thin film over a large area with high differential gas pressures because oxygen is poorly diffusible in plasma whereas carbon dioxide is highly diffusible in plasma so it can easily be removed from the blood. Areas of turbulence and secondary flow increase diffusion of oxygen within blood.

Considering non-microporous membrane oxygenators, O_2 and CO_2 diffuse across thin silicone membranes, which are made into envelopes and wound around a spool to produce a spiral coil oxygenator. Gas passes through the envelope and blood passes between the coil windings. Polypropylene hollow-fibre oxygenators are the standard oxygenators used during CPB. Their priming volumes are small, gas-transfer rates are high and resistance is low so they are at least theoretically superior to silicone membrane oxygenators [153]. However, in the past series, it was discovered that over time, the micropores become permeable to fluid causing plasma to leak into the

gas phase and out the exhalation port resulting in deteriorating gas exchange and developing coagulopathy. Because of protein leakage that deteriorates membrane function, these spiral coil oxygenators are preferred over hollow fibre microporous oxygenators for the prolonged perfusions (>2–3 days) [154].

Peek et al. compared silicone membrane oxygenators with polypropylene hollow-fibre oxygenators and concluded that, silicone oxygenators have excellent biocompatibility and durability but provide less efficient gas exchange, are bulky, are difficult to prime and have high resistance to blood flow [155].

In 2002, Wiesenack et al. tested a new membrane oxygenator featuring a very thin (0.05μm), solid membrane on the blood side of a highly porous support matrix. This membrane reduced the risk of gas emboli and plasma leakage during prolonged CPB, but impaired transfer of volatile anaesthetics [156].

Haworth directed the oxygenator development to the construction of smaller devices with low-priming volumes, high gas transfer rates, and a lower resistance against the streaming blood [153]. Another very interesting development was the introduction of small silicone rubber hollow fibre oxygenators by Motomura et al., reaching gas transfer rates very similar to those of conventional hollow fibre oxygenators [157].

In the early 2000s, a new generation of oxygenator was introduced into clinical practice, containing non-microporous hollow fibres constructed of polymethylpentene (PMP). PMP oxygenators combine the durability of silicone membranes with the ease of use and efficient gas exchange of hollow-fibre construction. In 2005, Khoshbin et al. [155], suggested that, compared with silicone membrane oxygenators, PMP oxygenators are associated with reduced red cell and platelet

transfusion and improved gas change. Compared with polypropylene hollow-fibre oxygenators, PMP oxygenators have improved durability and reduced requirement for blood product transfusion.

2.5.3 Cannulae and Tubing

The tip of the drainage cannula is usually the narrowest part of the perfusion system and inappropriate catheters can produce high pressure differentials and turbulence. To put it simply, the larger the diameter of the cannula, the better the flow. Usually for the adult patients, the drainage cannula should be 23F to 25F, and the return cannula should be 17F to 21F. The various components of the heart–lung machine are connected by polyvinyl tubing and fluted polycarbonate connectors. Medical grade polyvinyl chloride tubing is universally used because it's flexible, compatible with blood, inert, nontoxic, smooth, transparent, and resistant to kinking and collapse, and can be heat sterilised. Bioactive coating of artificial surfaces to decrease the necessity of systemic anticoagulation is another issue that has an important effect on the rate of complications during ECMO procedures [159]. Heparin can be attached to blood surfaces of all components of the extracorporeal circuit by ionic or covalent bonds. There are many reports that have studied the use of heparin-coated circuits but the effectiveness of them remains controversial because studies are contaminated by patient selection, reduced doses of systemic heparin, and washing or discarding field-aspirated blood [160]. Little is known about the use of heparin-coated ECMO units in patients with heparin/platelet factor4 (HPF 4) antibodies, very probably responsible for the development of heparin induced thrombocytopaenia type II (HIT II) [86]. Koster et al., suggested that heparin immobilised on artificial surfaces neither induces HPF 4 antibody formation nor supports its persistence [161]. On the contrary, Cruz et al. pointed out a relation between HIT II development and thromboembolic complications in patients with heparin-coated cardiac stents [162]. In general, heparin as a substance acting late in the coagulation cascade seems not to be the ideal drug to be used for the purpose of biocompatibility.

Direct contact between blood and the ECMO circuit leads to activation of inflammatory mediators, particularly the complement activation pathway [163]. Although a majority of studies indicate that heparin coatings reduce concentrations of C3a and C5b-9 [164,165], the inflammatory response to extracorporeal circulation is not reduced and the evidence for clinical benefit is not convincing [166].

2.5.4 Heat Exchangers

Heat exchangers control body temperature by changing the temperature of blood passing through the perfusion circuit. Hypothermia is preferred in cardiovascular surgery in order to reduce oxygen demand. Gases are more soluble in cold blood so rapid rewarming of cold blood may cause formation of bubbles therefore gas emboli [167]. Most membrane oxygenator circuits incorporate a heat exchanger upstream to the oxygenator to minimize bubble emboli. Blood is not heated over 40°C to prevent denaturation of plasma proteins, and temperature difference within the body and perfusion circuit are limited to 5–10°C to prevent bubble emboli.

2.6 ANTICOAGULATION FOR ECMO

The goal of anticoagulation for ECMO is to adjust such an equilibrium between attenuating platelet and thrombin activation to prevent life-threatening thrombosis and providing sufficient clotting to prevent excessive bleeding. Furthermore, an accurate device that has an ability to assess the degree of anticoagulation is not clinically available. Unidentified macroscopic clots cause a variety of thromboembolic events in patients considered adequately anticoagulated [168]. It seems to be that the effectiveness of anticoagulation worsens with the duration of ECMO. Monitoring for anticoagulation is the heart beat of ECMO management. The most popular test to monitor anticoagulation is the activated clotting time (ACT) and ACT still remains the predominant test to manage heparin anticoagulation during ECMO. It measures the integrity of the intrinsic coagulation and common pathways. However, the ACT'scapability to correctly measure the level of anticoagulation has been questioned [169]. The concerns about ACT's accuracy are: test results are affected by coagulopathy, maturity of coagulation system, platelet dysfunction, degree of hypothermia, antithrombin level, age, haemodilution, sample size, and temperature [170,171]. Ongoing synthesis of thrombin is another problem especially in children and may result in inadequate anticoagulation despite high levels of ACT [171–173]. The popular range for the ACT with heparin during ECMOhas been 180–220 s [174]. Baird et al. analysed 604 consecutive paediatric ECMO patients retrospectively for factors that affected outcome [170]. The mean ACT for all patients was 227 ± 50 s but the range of 158–620 s was very broad. They suggested that increased heparin dosing increases survival. The measurement of heparin concentration is an option to manage anticoagulation. Laboratory derived heparin concentration is the gold standard but is not easily or quickly obtained for patients on. The Hepcon (MedtronicPerfusion Systems, Minneapolis, MN) is able to provide heparin concentrations that have relatively good correlation to the laboratory

derived anti-Xa plasma heparin measurements [175] and has demonstrated superior results compared with ACT [174]. More importantly, unlike the ACT, use of heparin concentrations have the benefit of being less sensitive to changes in the patient's platelet and clotting factor levels. However, studies of heparin concentration monitoring for anticoagulation during ECMO are few compared to the ACT so target heparin levels have not been determined. Several centres used viscoelastic tests, such as thromboelastogram (TEG/ROTEM) [176]. The TEG/ROTEM is a device that measures the viscoelastic properties of the blood to examine the whole clotting system instead of isolated parts. It provides ongoing coagulation profiles looking at not only the initiation of clotting but also the strength and dissolution of the clot as in the case of fibrinolysis. The activated partial thromboplastin time (APTT) is universally recognised as a standard monitor for heparin therapy except when high heparin dosing is required as in CPB. In situations that do not require high heparin dosing, such as ECMO, the APTT is a valuable tool to assess anticoagulation. In a comparison between laboratory APTT and ACT, theACT was found to correlate poorly with the APTT [168]. Furthermore, in very ill patients requiring continuous heparin infusion, ACT could not delineate between low and moderate levels of anticoagulation compared with the APTT[177]. The APTT that will prevent thrombus extension with heparin has been reported as 1.5 times baseline APTT [178]. This APTT corresponds to a heparin level of 0.2–0.3 u/mL and does not correlate moderately well with heparin concentrations [179] .Heparin-continues to be the first choice for ECMO because it is rapidly acting, easily reversible, cheap, easily available, and well tolerated by paediatric and adult patients. Biologic activity varies between 30 min and six hours depending on the systemic heparin concentration. Heparin dosing for adults and paediatric patients is different for several reasons. The larger blood volume/weight ratios in neonates compared with adults require greater heparin dosing [168]. The more rapid metabolic rates with neonates and infants may allow greater excretion by the kidneys and therefore affects heparin dosing. Differences between adults and paediatric patients may also derive from the differences in thrombin generation. Traditionally

heparin dosing ranges between 20 and 70 U/kg/h for ECMO. Most agree that the APTT should be 1.5–2.5 times the control. The most recent studies of heparin concentrations suggest a value 0.3–0.7 u/mL[179]. Heparin dosing for an effective anticoagulation is closely connected with antithrombin concentration. Reduced heparin responsiveness is called heparin resistance and for effective inhibition of thrombin, adequate levels of antithrombin are required. It is clear that prolonged durations of ECMO will lead to consumption of antithrombin and the patient may not be capable of maintaining the level. Koster et al., used bivalirudin, a direct thrombin inhibitor, in a patient with myocardial failure after repair of acute type A aortic dissection who developed acute heparin-induced thrombocytopaenia during ECMO and achieved successful results in terms of postoperative blood loss and transfusion requirements [180].

2.7 MANAGEMENT OF ECMO: *Maintenance and Weaning of ECMO*

Achieving the suggested range of anticoagulation and cannulation, ECMO is commenced by unclamping the circuit and slowly increasing flows to the target range. Standard initial settings and goals for ECMO are specified in literature and listed in Figure 6 [87,181]

Table 3 **Initial Settings and Goals for ECMO.**

Circuit flow	50–80 mL/kg/min
Sweep gas flow	50–80 mL/kg/min
Fractional inspired oxygen	100%
Inlet pressure (centrifugal pump)	>100 mmHg
Oxygen saturation (return cannula)	100%
Oxygen saturation (drainage cannula)	>65%
Arterial oxygen saturation	VA: >95% VV: 85–92%
Mixed venous oxygen saturation	>65%
Arterial carbon dioxide tension	35–45 mmHg
pH	7.35–7.45
Mean arterial pressure	65–95 mmHg
Haematocrit	30–40%
Platelet count	>100,000 mm^3

Figure 6: Gokhan Lafc et al.

The basic function of VA-ECMO in supplying mechanical circulatory support is to drain blood from the venous circulation, oxygenate it and then return it to the arterial circulation at physiologic perfusion pressures. Although ECMO does a very good job of unloading the right ventricle, it does not do as good a job of unloading the left ventricle, even though left ventricular preload is significantly reduced by the diminished return from the lungs. For this reason, attempts to improve left ventricular contractility, reducing left ventricular distension and clot formation are of utmost importance. Such measures should include inotropic support and may include intra-aortic-balloon pumping (IABP). Another option in central ECMO is to insert a left ventricular vent to empty the ventricle, splicing this line into the venous line of the ECMO circuit. In peripheral ECMO however,

the use of an IABP can be detrimental as the peripheral arterial flow from the femoral arterial cannula will be competing with the inflated state of the IABP. ECMO flow can be very volume dependent and will drop with hypovolaemia, cannula malposition, pneumothorax and pericardial tamponade. This usually manifests as ‘kicking’ or ‘chatter’ of the venous tubing as well as a drop in output. Management includes a volume challenge, exclusion of intra-abdominal distension or compartment syndrome, cardiac tamponade or pneumothorax. If this does not work, a slight reduction in flows may be helpful or there may be a need to insert another venous cannula. Further, centrifugal pumps in contrast to roller pumps are very afterload dependent and therefore hypertension is another variable that can reduce flows and should be avoided. Whilst on ECMO, the aim is to support and rest the heart and/or lungs. From a respiratory point of view, hypoxia is treated by increasing the flow rate and FiO_2 of the ECMO circuit, not by altering the FiO_2 and PEEP on the ventilator. Attempts should be made to wean the FiO_2 on the ventilator and maintain a PEEP level of 5–10 cmH_2O. A protective lung ventilation strategy with low plateau pressures and low tidal volumes should be aimed for as well as low respiratory rates, unless trying to wean off the ECMO circuit. PCO_2 control should be via the ECMO fresh gas flow to the oxygenator, not by altering the respiratory rate on theventilator. From a cardiac point of view the aim should be to minimise the use of inotropes and thus rest the heart. However, often a low-dose inotrope infusion is maintained to ensure some contractility and adequate emptying of the left ventricle. It is also important to ensure the patient is not hypovolaemic. There are no standardised methods or techniques with regards to weaning ECMO. With regards to VV ECMO, the actual ECMO flows do not need to be altered to assess native respiratory function—this is done by altering gas flow through the ECMO circuit. The patient may be weanable if gas exchange is able to be maintained with a low FiO_2 on the oxygenator (e.g. <30%) and low fresh gas flow rates into the circuit (e.g. <2 L/min) provided that the respiratory rate and PEEP set on the ventilator are not too high (e.g. <25 breaths/min and <15cmH_2O, respectively).With regards to VA ECMO, factors indicating cardiac recovery and thus

a potentially weanable patient include; an increasing blood pressure which may need vasodilators, return of pulsatility or increasing pulsatility on the arterial pressure waveform, falling pO_2 by a right radial arterial line indicating more blood is being pumped through the heart which may be less well oxygenated, and falling central venous and/or pulmonarypressures. Assessment of native cardiac function is performedby reducing flows in the ECMO circuit which requires changes to the ventilator and oxygenator gas flow settings, and an increased dose of heparin due to the increased risk of stasis and thrombosis at low ECMO flows. A trans oesophageal echocardiogram (TOE) is also useful to quantify degree of cardiac recovery and assessing response to reduced flow rates. It would be reasonable to reduce pump flows in 0.5 L decrements to 2 L/min over 36–48 h watching the above variables. Below this flow rate, major concern would exist with clot formation in the circuit. The remainder of the wean generally takes place in the operating room under TOE observation and then the patient can be decannulated in a surgical setting.It is important to note that cardiac outputs from a pulmonary artery catheter are inaccurate in patients on ECMO because most of the circulating blood volume is bypassing the pulmonary circulation (and passing through the ECMO circuit) [182].

2.8 COMPLICATIONS OF ECMO

Not surprisingly, ECMO does have an attendant myriad of possible complications. Complications of ECMO are classified as mechanical or patient related (Figure 7).

Complication	Incidence (%)
Blood clots (oxygenator, pump, tubing, haemofilter)	0.13–22
Bleeding (surgical site, cannulation site, gastrointestinal, intracranial, tracheostomy, haemolysis, DIC)	5.3–79
Pump failure	4.7–30
Oxygenator failure	21–27
Neurologic and musculoskeletal complications (intracranial bleed, stroke, seizure, encephalopathy)	10–33
Limb ischaemia	13–25
Infection	17–49
Renal failure	30–58
Multiple organ dysfunction syndrome	10
Problems during cannulation	0.8–8
Hyperbilirubinaemia	27

Figure 7: Gokhan Lafc et al.

With regards to ***circuit complications***, gas embolism and catastrophic blood loss (tubing rupture, disconnection) are acutely life-threatening. With centrifugal pumps, a large negative pressure (up to 100 mmHg) is generated between the drainage cannula and the pump head [87]. Mostly air enters from this part of the circuit leading to massive gas embolism. The second cause of gas embolism is cavitation. Loss or reduction of circuit flow is a frequent complication usually caused by hypovolaemia. The other causes are cardiac tamponade, tension pneumothorax, and cannula malposition.

With regards to ***patient complications***, haemorrhage, particularly from cannulation and surgical sites is the most frequent complication, which can rapidly become life-threatening. Less common, but potentially more serious, is gastrointestinal, tracheostomy, and intracranial bleeding. Haemorrhage appears to be out of proportion to the degree of coagulopathy and patient platelet count. ECMO is well known to cause coagulopathy. Causes of coagulopathy include heparin, thrombocytopaenia, fibrinolysis, uraemia and hepatic dysfunction [87]. Continuous activation of the contact and fibrinolytic systems by the circuit as well as consumption and dilution of factors occur within minutes of initiation of ECMO [163]. The duration of ECMO is very important by means of haematologic complications.

Haemolysis is another well-recognised complication of ECMO with an incidence between 5% and 8% [183].Thromboembolism, caused by thrombus formation within the extracorporeal circuit is an infrequent but serious complication, and is more likely to occur with VA than VV ECMO, because, with the latter, the oxygenated blood is returned to the systemic arterial circulation. In addition, aortic thrombosis has been described when blood flows retrograde towards the heart (oxygenated blood is returned to the systemic circulation via femoral arterial access in peripheral ECMO), and stagnates there in the setting of low left ventricular output [184]. Local complications, particularly at the site of peripheral insertion of VA-ECMO can occur, of which the most concerning is leg ischaemia. A down-flow cannula into the superficial femoral artery can be inserted during percutaneous cannulation of the common femoral artery. In open procedures, a Dacron graft can be sutured onto the common femoral artery and the cannula inserted into the graft without compromising the artery [185]. Fasciotomy for severe leg ischaemia can be required in 6% of the patients [186]. Another patient complication is infection. Infection occurs more frequently in ECMO patients than other surgical intensive care unit patients. However, sites of infection (bloodstream, lower respiratory tract, urinary tract, wound) and causative microorganisms (gram-

negative bacilli and staphylococci) are similar [187]. Patients who suffer from post-cardiotomy cardiogenic shock are more vulnerable to nosocomial infections than other ECMO patients [188]. Haemodynamic instability can be seen in both ECMO modalities with different causes. VA ECMO totally supports the circulation, so hypotension during VA ECMO implies reduced vascular tone. VV ECMO does not have any direct effect on haemodynamics, so hypotension during VV ECMO may be caused by reduced vascular tone, reduced preload, or cardiac dysfunction. Severe sepsis can lead to marked hypotension and venous desaturation, despite full VA ECMO support. LV distention may occur during VA ECMO, particularly in patients with mitral and aortic valve regurgitation. The complication is often identified by the presence of alveolar oedema on the chest radiograph or oedema fluid frothing up the endotracheal tube shortly after the institution of ECMO. Increasing pump flows reduces pulmonary blood flow and may ameliorate this problem. Failing this, the left heart must be vented, either surgically or in the catheter laboratory by percutaneous atrial septostomy [189]. Fatal arrhythmias can be seen due to electrolyte imbalance or hypoxaemia. Hypoxaemia is another patient complication. VA ECMO, usually provides adequate SaO_2. But, the presence of significant left ventricular ejection and impaired lung function can result in upper-body hypoxaemia. This situation most commonly occurs when VA ECMO is inappropriately used for treating isolated respiratory failure or when VA ECMO has been used appropriately for cardio-respiratory failure and cardiac function has recovered. The most common cause of hypoxaemia during VV ECMO is inadequate circuit flow. The other causes include sepsis, inadequate sedation, iatrogenic overheating, overfeeding, seizures, or recirculation. The most common neurologic complication associated with ECMO is intracranial haemorrhage. The reported incidence varies between 1.6% and 18.9% [190-193]. The other neurologic complications are ischaemic stroke and seizures [193]. Intracranial haemorrhage and/or ischaemic stroke occur due to systemic heparinization, thrombocytopaenia, the ligation of carotid artery and jugular vein, coagulopathy or systemic hypertension. Renal failure is another complication that is not uncommon. Oliguria is

frequently seen in the early stages of ECMO. Acute tubular necrosis may require haemofiltration or haemodialysis.

2.9 OUTCOMES OF ECMO

The results of ECMO support are fairly consistently related to the indication for institution of such therapy.

The Extracorporeal Life Support Organization (ELSO) established in 1989 and located at the University of Michigan, maintains a registry of all known cases in which ECMO was used. Over 250 international centres have contributed data to the registry. Currently there are over 65,000 cases in the Registry including over 34,000 newborns, 16,000 children and 14,000 adults. In the adult population (>18 years), 7,008 cases of ECMO support for respiratory failure were reported of which 57% survived to discharge. 5,603 patients were supported for cardiac failure of which only 41% survived to discharge. A separate category of patients requiring urgent deployment of ECMO for established or impending cardiopulmonary arrest are presented in the report. Of the 639 cases reported 28% survived to discharge (Figure 8).

Unfortunately, good quality randomised controlled trials of ECMO outcomes in the adult population are lacking.

2.10 CONCLUSIONS

Although controversial, ECMO may be of benefit in selected adult patients with cardiopulmonary failure. Due to its complexity, patients requiring ECMO are best served in centers which use this technique regularly. However, all intensivists should be familiar with the principles and methods of ECMO both to optimize its use and also to facilitate education for staff, patients, and families.

ECLS Registry Report

International Summary

January, 2015

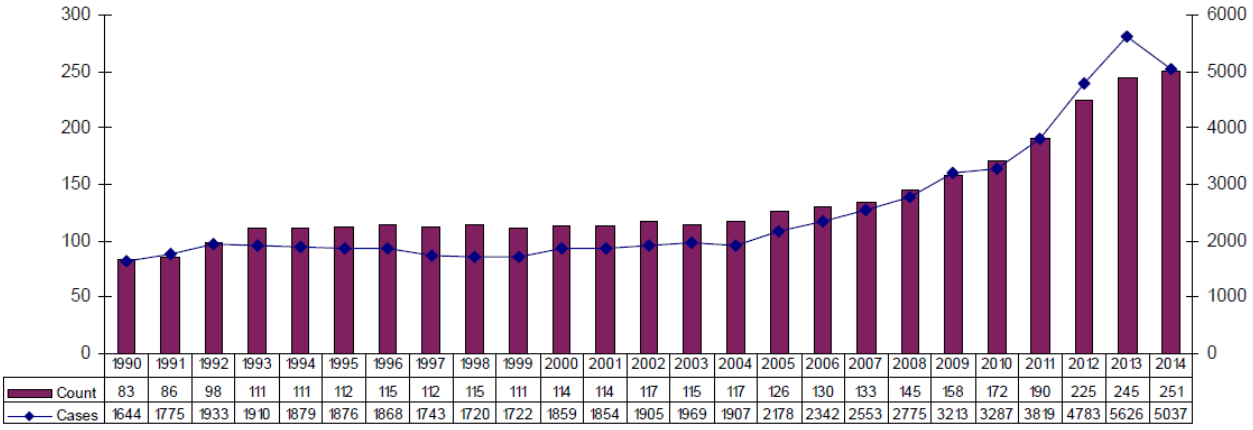
Extracorporeal Life Support Organization
2800 Plymouth Road
Building 300, Room 303
Ann Arbor, MI 48109

Overall Outcomes

	Total Patients	*Survived ECLS*		*Survived to DC or Transfer*	
Neonatal					
Respiratory	27,728	23,358	84%	20,592	74%
Cardiac	5,810	3,600	62%	2,389	41%
ECPR	1,112	712	64%	449	40%
Pediatric					
Respiratory	6,569	4,327	66%	3,760	57%
Cardiac	7,314	4,825	66%	3,679	50%
ECPR	2,370	1,313	55%	976	41%
Adult					
Respiratory	7,008	4,587	65%	4,026	57%
Cardiac	5,603	3,129	56%	2,294	41%
ECPR	1,657	639	39%	471	28%
Total	65,171	46,490	71%	38,636	59%

Centers

Centers by Year



	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014
Count	83	86	98	111	111	112	115	112	115	111	114	114	117	115	117	126	130	133	145	158	172	190	225	245	251
Cases	1644	1775	1933	1910	1879	1876	1868	1743	1720	1722	1859	1854	1905	1969	1907	2178	2342	2553	2775	3213	3287	3819	4783	5626	5037

Figure 8: ELSO REGISTRY

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3. EXTRACORPOREAL MEMBRANE OXYGENATION (ECMO) IN REFRACTORY CARDIOGENIC SHOCK: IMPACT OF ACUTE VERSUS CHRONIC ETIOLOGY ON OUTCOME

3.1 INTRODUCTION

Acute cardiogenic shock is a condition that continues to have a very high mortality despite advances in medical therapy [1-3]. Conventional treatment typically comprises inotrope infusions, vasopressors and intra-aortic-balloon-pump (IABP) [1, 4]. When circulatory instability is refractory to these treatments, mechanical circulatory support represents the only hope for survival, as indicated by current guidelines [3, 4]. As most of these patients present with critical circulatory instability requiring urgent or emergent therapy, the chosen mechanical assistance should be rapidly and easily implanted. For this reason ExtraCorporeal Membrane Oxygenation (ECMO) represents the ideal "bridge-to-life" and increasingly it is used to keep the patient alive while the optimal therapeutic management is determined (bridge-to-decision). Management may then follow one of three courses: "bridge-to-recovery": patient recovery, and weaning from ECMO; "bridge-to-transplant": direct orthotopic heart transplantation; "bridge-to-bridge": placement of ventricular-assist-device or total artificial longer-term support [5, 6] There have been several large reports on the use of ECMO as a mechanical support in post-cardiotomy patients [3,7-9] but relatively few, mostly small case-series focusing on its role in primary acute cardiogenic shock outside of the post-cardiotomy setting [10-13].

We present the results of our centre's experience (Padova) in the treatment of primary acute cardiogenic shock with the PLS-Quadrox ECMO system (Maquet) as a bridge to decision.

Furthermore, we evaluated the impact of etiology on patient outcomes by comparing acute primary refractory CS secondary to acute myocardial infarction (AMI), myocarditis, pulmonary embolism (PE) and post-partum cardiomyopathy (PPCM) with acute decompensation of a chronic cardiomyopathy, including dilated cardiomyopathy (DCM), ischemic cardiomyopathy (ICM) and grown-up-congenital-heart-diseases (GUCHD). We also analyzed whether duration and magnitude of support may predict weaning and survival.

3.2 MATERIALS AND METHODS

3.2.1 Patients

Between January 2009 and March 2013, a total of 249 patients were treated with ECMO in our center. We prospectively analyzed 64 patients implanted with the PLS^{TM} ECMO system for treatment of cardiogenic shock refractory to maximal inotropic and vasopressor therapy and IABP, excluding postcardiotomy, pediatric and respiratory supports. We divided patients in two groups according to etiology: 37 were assigned to the "Acute" group (A-PCS), where the primary cause was an acute event in a previously healthy heart, including 26 AMI, 4 myocarditis, 6 PE, 1 post-partum cardiomyopathy; 27 to the "Chronic" group (C-PCS), in whom the etiology was an acute deterioration of a chronic cardiomyopathy, including 20 DCM, 5 ICM, 2 GUCHD (Table 1). Written informed consent was obtained for all patients.

Table 1. Etiologies leading to ECMO implantation, in the overall population, A-PCS group, and C-PCS group.

Etiology	**Overall (n=64)**	**A-PCS (n=37)**	**C-PCS (n=27)**
AMI	26 (41%)	26 (70%)	0
Myocarditis	4 (6%)	4 (11%)	0
Pulmonary embolism	6 (9%)	6 (16%)	0
Post-partum CM	1 (2%)	1 (3%)	0
DCM	20 (31%)	0	20 (74%)
ICM	5 (8%)	0	5 (19%)
Congenital	2 (3%)	0	2 (7%)

AMI: acute myocardial infarction; CM: cardiomyopathy; DCM: dilated CM; ICM: ischemic CM.

3.2.2 Criteria for ECMO installation

Patients who met the criteria of profound CS due to pump failure were candidates for ECMO. Profound shock was defined as systolic blood pressure less than 75 mm Hg, cardiac index ≤ 1.8 L/minute/m^2, with left ventricular end-diastolic pressure >20 mmHg, despite receiving multiple high-dose intravenous inotropic agents (dopamine ≥10 μg/kg/minute, dobutamine ≥10 μg/kg/minute, epinephrine ≥0,1 μg/kg/minute, norepinephrine ≥0,1 μg/kg/minute) and/or IABP, associated with clinical signs of pulmonary congestion, and impaired end-organ perfusion (renal, respiratory and hepatic failure and altered mental status) [14]. The diagnosis of impaired end-organ function required at least one of the following: altered mental status; cold, clammy skin and extremities; oliguria with urine output of less than 30 ml per hour; respiratory failure was defined as PaO_2 <60 mmHg and/or $PaCO_2$ >45 mmHg (type I-II) or need for mechanical ventilation in the setting of cardiogenic shock (type IV); serum lactate level higher than 2.0 mmol per liter; bilirubin or transaminases > three times the upper normal limit set by the local laboratory; multi-organ-failure (MOF) was defined as failure of two or more organs, in addition to cardiac dysfunction. [4,15] The only absolute contraindication to ECMO was the presence of severe neurologic involvement after arrest (significant anisocoria and signs of decerebration or focality); age > 75 years and severe peripheral vascular disease (PVD) were considered relative contraindications. [6]

3.2.3 ECMO system

The system used in our institute was the PLS^{TM} ECMO (Maquet, Cardiopulmonary AG, Hirrlingen, Germany) [7,16]. This system has a portable, "all-in-one" design including oxygenator (Quadrox D^{TM}), centrifugal pump (Rotaflow^{TM}), and heparin-coated tubes as well as an optional heat exchanger, with specific features to minimise thrombotic risk [7,16]. Furthermore it has obtained CE approval for 14 days of support.

3.2.4 ECMO placement

In our institute, when feasible, we opted to implant ECMO with the patient awake and breathing independently, with local anaesthetic, at the bedside. Cannulation was performed using a percutaneous veno-arterial Seldinger technique, with venous drainage cannula placed in the femoral vein (18F to 28F) and arterial return cannula placed in the femoral artery (18F to 22F). When this strategy was unsuccessful or contra-indicated (eg. significant peripheral vascular disease, small femoral vessels) the patient was taken to theatre, sedated and intubated. At the surgeon's discretion, a choice between one of the following cannulation techniques was made: subclavian or inguinal dissection and anastomosis of an 6 to 10 mm Dacron vascular graft onto the subclavian or femoral artery for cannulation, or, in a single case, sternotomy and central cannulation (venous cannula in right atrium and arterial cannula in ascending aorta). Limb ischemia subsequent to percutaneous femoral arterial cannulation was dealt with distal cannulation using a smaller cannula (either percutaneous or surgical) or by shifting the cannulation site.

3.2.5 Anticoagulant management

Before placement of cannulae, a heparin bolus of 70 U/Kg (usually 5000 units) was administered to obtain an ACT of 180 s. We then performed aPTT, INR and antithrombin assays 4 times per day and platelet counts, fibrinogen and d-dimer assays once daily. Patients were kept anticoagulated with heparin maintaining and aPTT in the range of 50 – 60 sec. When d-dimer was elevated or there were haemorrhagic or thrombotic complications, a thromboelastometry was carried out and targeted therapy, based on these results, was commenced.

3.2.6 Management of ECMO

ECMO is intended as a bridge-to-life, and at first all patients need full-flow support (patient's estimated required cardiac output (CO), calculated as BSA*2.4 l/min). In this phase stabilization is obtained, with cardiac function totally replaced by ECMO, which guarantees circulatory support and organ perfusion.

After this phase, some pulsatility may be observed, and this would be a sign of an initial recovery of cardiac function. In this second phase, we maintain inotropic support and IABP when already present prior to ECMO implantation; we wake the patient to guarantee sympathetic tone; we perform weaning from mechanical ventilation, achieving extubation as soon as possible, to reduce pulmonary resistance; we start to reduce support, monitoring pulsatility and organ perfusion (lactate, urine output, central venous pressure, pulmonary capillary wedge pressure). We maintain inotrope therapy, to help the native heart to open the aortic valve and empty the left ventricle (LV), thus eliminating the need for a vent. If the patient remains stable, the third phase is commenced, which consists of a weaning protocol.

3.2.7 Weaning trial

After obtaining hemodynamic stabilization and improvement of organ function (either neurologic, respiratory, renal and hepatic), ECMO support was progressively decreased to 1 L per minute. Standard management involved serial echocardiograms during this phase, but we mostly relied on persistence of satisfactory hemodynamics and organ function on low-to-medium dose inotropic support, to assess the feasibility of weaning from ECMO. In detail, we performed echocardiographic evaluation of ventricular function (LV EF >35%, good RV contractility) and volume (absence of excessive ventricular distension, or severe tricuspid regurgitation), as well as clinical parameters such as normal systemic pressure (systolic >85mmHg) and central venous pressure, normal blood lactate level and urine output.

3.2.8 Data Analysis

Continuous variables are expressed as means ±SD, median (range). Categorical variables are summarized by reporting absolute frequency distribution and percentage, and were compared using the χ^2-test or Fisher's exact test as appropriate. Student t test (for unpaired data) or the Mann-Whitney test were used to compare continuous variables, as appropriate (normal distribution was assessed by the Shapiro-Wilk normality test). Overall survival and survival after discharge were estimated by the Kaplan-Meier method. Statistical findings were considered significant if the critical level was less than 5% ($p<.05$). Statistical analysis was performed using STATA software (release 10.0 for Windows; Stata Corporation LP, College Station, Tex).

Table 2. Preoperative characteristics.

Preoperative characteristics	Overall (n=64)	A-PCS (n=37)	C-PCS (n=27)	*p* *(A vs C)*
Age (y)	50 ± 16	52 ± 15	48 ± 17	0.38
Sex (female)	12 (19%)	10 (27%)	2 (7%)	0.004
BSA (m^2)	1.8 ± 0.2	1.9 ± 0.2	1.8 ± 0.1	0.001
Malignant arrythmia	29 (45%)	18 (49%)	11 (41%)	0.04
CPR within 72h	32 (50%)	26 (70%)	6 (22%)	<0.0001
N. of inotropes	1.9 ± 1	1.7 ± 1	2.1 ± 1.1	0.009
IABP	25 (39%)	19 (51%)	6 (22%)	0.001
Respiratory failure	55 (86%)	32 (86%)	23 (85%)	0.04
Mechanical ventilation	46 (72%)	29 (78%)	17 (63%)	0.01
Renal failure	32 (50%)	14 (38%)	18 (67%)	0.001
CVVH	8 (13%)	4 (11%)	4 (15%)	0.71
Hepatic failure	20 (31%)	7 (19%)	13 (48%)	0.0007
MOF	24 (38%)	12 (32%)	12 (44%)	0.32
APACHE IV score - predicted mortality	61% ± 16%	58% ± 16%	65% ± 17%	0.38

3.3 RESULTS

Preoperative characteristics, implantation technique, mechanical support data and outcomes are reported in Tables 2, 3, 4 and 5 respectively. Mean age was 50 ± 16 years with no differences between A-PCS and C-PCS groups. In A-PCS group there was a higher incidence of malignant arrhythmias (A-PCS: 49% vs C-PCS: 41%), CPR either in the previous 72 hours (A-PCS: 70% vs C-PCS: 22%) or during ECMO implantation (A-PCS: 38% vs C-PCS: 11%), IABP (A-PCS: 51% vs C-PCS: 22%), and mechanical ventilation (A-PCS: 78% vs C-PCS: 63%). In C-PCS group we observed a greater rate of end-organ dysfunction, demonstrated by the higher number of inotropes (C-PCS 2.1 vs A-PCS 1.7), renal (C-PCS 67% vs A-PCS 38%) and hepatic failure (C-PCS 48% vs A-PCS 19%). The Acute Physiology and Chronic Health Evaluation (APACHE) IV score indicated a 61% ±16% predicted mortality, with no differences between the two groups (Table 2).

Table 3. Implantation technique.

Implantation technique	Overall (n=64)	A-PCS (n=37)	C-PCS (n=27)	*P (A vs C)*
Bedside	31 (48%)	21 (57%)	10 (37%)	0.11
Salvage CPR	17 (27%)	14 (38%)	3 (11%)	0.02
Peripheral F-F	51 (80%)	32 (86%)	19 (70%)	0.11
Peripheral S-F	12 (19%)	4 (11%)	8 (30%)	0.1
Upgrade F-F to S-F	9 (14%)	4 (11%)	5 (19%)	0.48
Central	1 (1%)	1 (3%)	0	0.04

BSA: body surface area; CPR: cardio-pulmonary-resuscitation; CVVH: continuous-veno-venous hemofiltration; F-F: femoro-femoral; IABP: intra-aortic-balloon-counterpulsation; MOF: multi-organ-failure; S-F: subclavian-femoral.

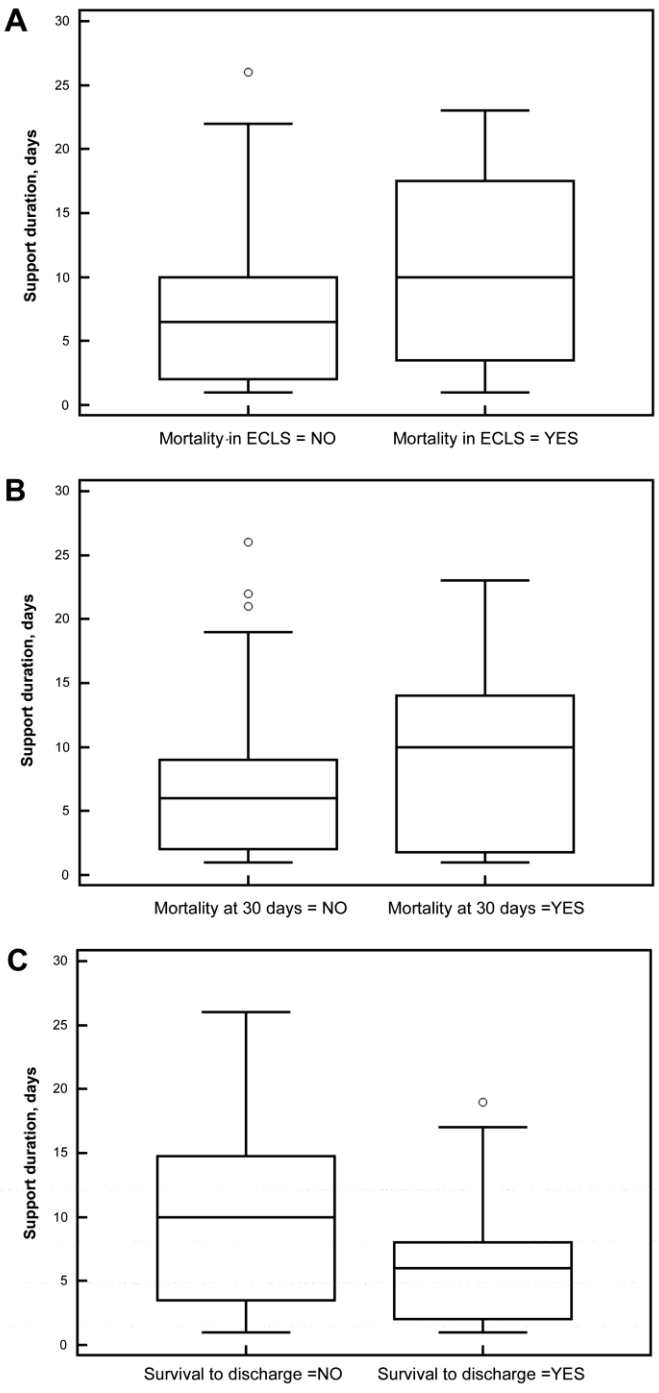

Figure 1: Analysis of support duration vs: (A) mortality on ECMO (p=0.06); (B) 30-day mortality (p=0.05)]; (C) survival to discharge (p=0.002).

V-A ECMO was implanted peripherally in all but one case. Fifty-one patients were treated with F-F cannulation, and 12 with S-F ECMO. Nine patients required shifting of cannulation site from femoral to subclavian artery, because of limb ischemia or issues in femoral cannulation (Table 3).

Mean duration of ECMO support was 9±9 days (range, 1–46), with no differences between the two groups. Mean percentage of theoretical flow was 61 ±15%. Patients in C-PCS group required higher support compared with A-PCS (67% vs 57%) to achieve adequate organ perfusion, as confirmed by the absence of difference in serum lactates (expressed as the average of the peak lactate on a daily basis). As expected, given the greater frequency of AMI in the A-PCS group, peak troponin was significantly greater in this group (Table 4). The outcomes of ECMO support differed significantly between the two groups. In C-PCS group, 23 patients were bridged to either a left-ventricular-assist-device (52%) or heart-transplantation (33%). Conversely, in A-PCS group ECMO was used as bridge-to-transplantation in 3 patients (8%), bridge-to-bridge in 9 patients (24%), and bridge-to-

recovery in 18 patients (49%). One patient in both groups was bridged to conventional surgery. Recovery of cardiac function was achieved only in A-PCS group (18 vs 0 pts, p=0.0001). In terms of mortality during ECMO support (16% in A-PCS vs 11% in C-PCS), hospital discharge (59% in A-PCS vs 56% in C-PCS) and survival at 4-years follow-up (49% in group A-PCS vs 44% in C-PCS), the two groups were comparable; only 30-day mortality differed between the groups being significantly greater in the C-PCS group (26% in C-PCS vs 16% in A-PCS, p=0.02). (Table 5). Complications during support were similar in the two groups (Table 6).

Table 4. Details of ECMO support.

Parameter	Overall (n=64)	A-PCS (n=37)	C-PCS (n=27)	*p (A vs C)*
Duration (days)*	7 (2-11.5)	7 (2.75-10.25)	7 (2-12.75)	0.86
Flow (% of theoretical CO)	61 ±15	57 ±13	67 ±15	0.004
N. of inotropes (mean)	2.6 ±1.1	2.2 ±1.1	3.1 ±0.8	<0.001
Serum lactates (mmol/L)*	2.55 (1.7-3.6)	2.3 (1.55-3.25)	2.85 (1.9-4.3)	0.14
TnI peak (µg/L)*	3.75 (0.33-100)	53 (2.2-231.9)	0.47 (0.15-1.98)	0.0007

*Legend: CO: cardiac output . *median (IQR)*

Table 5. Outcomes of ECMO support.

Outcome	Overall (n=64)	A-PCS (n=37)	C-PCS (n=27)	*p (A vs C)*
BTD	9 (14%)	6 (16%)	3 (11%)	0.72
BTR	18 (28%)	18 (49%)	0	<0.0001
BTS	2 (3%)	1 (3%)	1 (4%)	0.04
BTB	23 (36%)	9 (24%)	14 (52%)	0.001
BTT	12 (19%)	3 (8%)	9 (33%)	0.001
Mortality in ECMO	9 (14%)	6 (16%)	3 (11%)	0.72
Mortality 30-day	13 (20%)	6 (16%)	7 (26%)	0.02
Discharged from hospital	37 (58%)	22 (59%)	15 (56%)	0.75

Legend: BTD: bridge-to-decision; BTR: bridge-to-recovery; BTS: bridge-to-conventional surgery; BTB: bridge-to-bridge; BTT: bridge-to-transplant.

Analysis of support duration revealed that duration tends to affect mortality on ECMO and also at 30 days [Figure 1A (p=0.06); figure 1B (p=0.05)], and is a significant predictor of hospital discharge (Figure 1C, p=0.002). We have also shown that a support duration of less than 8 days predicts improved outcomes [mortality in ECMO (p=0.05), 30-day mortality (p=0.01), hospital discharge (p=0.002)]. Analysis of flow rates has demonstrated that in the A-PCS group, the required percent of support is a significant predictor of recovery [Figure 2A (p=0.03)]. In fact, we have shown that flow rates less than 60% correlate with probability of recovery (p=0.02). A subgroup of particular interest is represented by patients suffering AMI, in whom this phenomenon is particularly accentuated [Figure 2B (p=0.01)] (Figure 2).

Table 6. Complications during ECMO support.

Complications during ECMO	Overall (n=64)	A-PCS (n=37)	C-PCS (n=27)	*p (A vs C)*
Neurological	12 (19%)	8 (22%)	4 (15%)	0.49
Limb ischemia	9 (14%)	6 (16%)	3 (11%)	0.72
Leg amputation	0	0	0	1.00
Bleeding	13 (20%)	8 (22%)	5 (19%)	0.76
Hemolysis	1 (2%)	1 (3%)	0	1.00
Renal failure	25 (39%)	12 (32%)	13 (48%)	0.20
CVVH	22 (34%)	10 (27%)	12 (44%)	0.14
Oxygenator change	14 (22%)	5 (14%)	9 (33%)	0.06
Malfunction	4 (6%)	2 (5%)	2 (7%)	1.00
ARDS/Pulmonary congestion	5 (8%)	1 (3%)	4 (15%)	0.15
Sepsis	9 (14%)	3 (8%)	6 (22%)	0.15
MOF post	14 (22%)	8 (22%)	6 (22%)	0.95

Legend: ARDS: acute respiratory distress syndrome; CVVH: continuous veno-venous hemofiltration; MOF: multi-organ-failure.

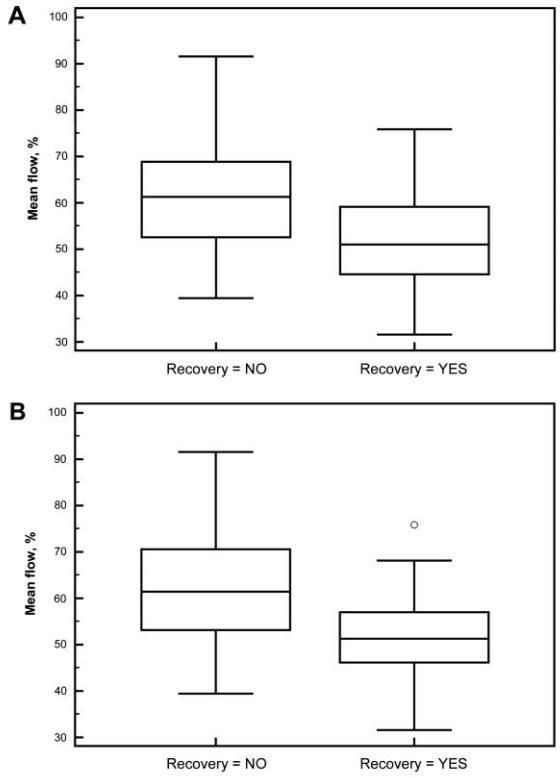

Figure 2: Analysis of mean flow vs. (A) recovery in A-PCS group (p=0.03); (B) recovery in AMI group (p=0.01).

Overall survival did not differ between the two groups (A-PCS 73% vs C-PCS 70% at 1 month, A-PCS 57% vs C-PCS 56% at 6 months, A-PCS 51% vs C-PCS 55% at 1 and 4 years) (Figure 3A). The overall actuarial survival of the cohort after discharge was 89% at 1-year and 86% at 4-year follow-up (Figure 3B). A result of particular interest was the survival of those patient who recovered cardiac function, which was 83% at 4-years follow-up (Figure 3C).

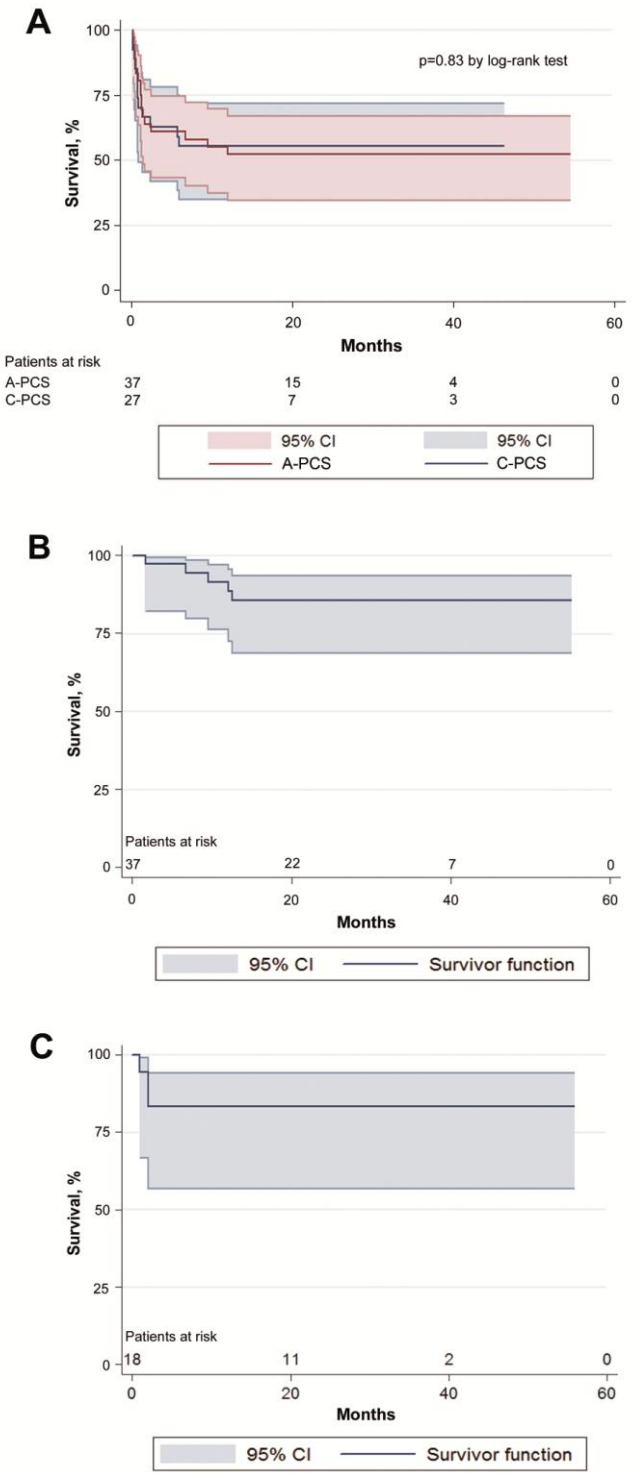

Figure 3: Kaplan-Meier estimates of actuarial survival in different populations: (A) overall; (B) discharged patients; (C) bridge-to-recovery subgroup after discharge.

3.4 COMMENT

The aim of this study was to evaluate the impact of etiology – in particular acute vs chronic – on the outcome of patients in acute cardiogenic shock treated with ECMO.

The outcomes assessed were death during ECMO support, 30-day mortality, hospital discharge, survival at follow-up, both overall and in the two aetiology groups. The two groups were comparable in terms of their pre-implantation condition and post-implantation complications. Differences between the groups could be attributed to the differing etiology of cardiogenic shock: in the chronic group, shock represents the end-stage of a progressive decline in cardiac function with chronic structural damage, a picture not seen in group A-PCS, where the most common cause of cardiogenic shock was AMI. In the analysis of primary end points the only difference between the groups was the greater 30-day mortality in the chronic group when compared to the acute group. This data is consistent with the recent series published by Bermudez et al [6], but differs regarding long-term survival. Indeed in our series the two groups were comparable in terms of mortality during support, hospital discharge and even survival at follow-up. When considering all patients, the outcomes are in line with the existing literature, as is overall survival [13,18]. In light of these results it is possible to say that the use of ECMO allows survival to be maximized in patients who are otherwise untreatable and face an extremely severe prognosis, independent of etiology of the shock and hence also their study group. Indeed, in our experience, unlike Bermudez et al [6], patients in a chronic setting can also benefit from ECMO as a bridge to candidacy for VAD or transplant.

As secondary end points we have looked at the proportion of patients who had recovery of cardiac function (bridge-to-recovery) to determine if the duration and magnitude of support are predictors of recovery and survival.

In keeping with the markedly different profiles of the two groups, was the fact that the recovery occurred only within the acute group. This difference was highly significant and reinforced the idea that cardiogenic shock, in the context of chronic progressive cardiac failure, represents the terminal stage of the disease which is not possible to remedy without replacing the heart's pump function. As a result, in group C-PCS, ECMO acted essentially as either a bridge to VAD or bridge-to-transplant. Conversely in group A-PCS, ECMO support temporarily rests the damaged myocardium allowing it to recover functionality [19]. In patients with refractory shock secondary to an acute aetiology ECMO offers a substantial chance of recovery, often representing, after failed PCI, the only therapy required.

In patients with the best outcomes in terms of mortality during support and at 30 days, the duration of ECMO was significantly inferior; the same relationship was seen in hospital discharge: specifically a duration of support of less than 8 days is a significant predictor of improved chance of survival and hospital discharge. Potentially the shorter duration of support reflects, at least partly, a less substantial systemic compromise.

Another part of this study is related to the management of the flow rates. In our experience, after the first phase of "resuscitation" at full-flow, we aimed to reduce the support, whenever possible. Specific strategies make this possible. Firstly, the use of ECMO reduces venous return and hence the preload of the LV, thus reducing the work it is required to do. Secondly, ECMO provides most of the splanchnic circulation, while not increasing the afterload on the left ventricle as much as full support would. Finally, with the help of inotropes, the native heart is often able to open the aortic valve and emptying the left ventricle (LV), thus eliminating the need for a vent, and also providing most of the coronary and cerebral perfusion. Within the acute group, analyses of flow rates demonstrate that the maintenance of support at <60% of theoretical requirement was significantly associated with recovery of cardiac function, likely reflecting a less severe initial myocardial

condition and a greater degree of reversibility. Of particular interest within the acute group is the subgroup of patients with AMI, both for its epidemiological significance and its high frequency in the acute group (n=26). In this subgroup the proportion of patients who recover cardiac function is very promising, totaling 42%. These results are comparable to existing literature and in particular to studies reporting specifically the results of patients with cardiogenic shock secondary to AMI [18]. It is reasonable to propose that in this group ECMO helps to contain the damage caused by ischemia-reperfusion injury and evolution of the infarcted area by directly reducing the afterload against which the heart has to work and hence reducing the oxygen demand of the myocardium [19]. In this subgroup it was also seen that the degree of ECMO support was a predictor of cardiac function recovery: patients who experienced recovery had mean flows of 55% of theoretical predicted requirement.

When analysing all patients as a single cohort, an interesting finding was survival both short and long term. In our study 30-day survival was around 80% and discharge from hospital was around 60%. A particularly encouraging result was the 89% survival at 2-years follow-up seen in patients discharged from hospital. The subgroup with shock due to AMI was consistent with these findings, but peculiar in so far as ECMO was the only necessary treatment after failed PCI for 42% of the patients, and provided a long-term survival in the order of 80%. These results would support the use of ECMO in PCS, where treatment with IABP was recently shown to confer no benefit in terms of mortality [20].

3.5 CONCLUSIONS

ECMO is intended as a bridge-to-life and should be considered as a first line of support in patients with refractory cardiogenic shock. In the setting of a chronic decline in cardiac function, ECMO

represents a bridge to implantation of VAD or orthotopic heart transplant. In patients with refractory shock due to acute aetiologies, ECMO offers a substantial chance of recovery, often representing, after failed PCI, the only necessary treatment. In our experience the magnitude and duration of the ECMO support significantly impacts the chance of weaning and also of survival, reflecting a less severe initial myocardial condition and a greater degree of reversibility. Maintaining flows at around 60% of the theoretical requirement and minimising the duration of support appears to be the strategy which offers the best chance of survival.

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inglese	B2	B2	B2	B2	B2

Livelli: A1/A2: Livello base - B1/B2: Livello intermedio - C1/C2: Livello avanzato
Quadro Comune Europeo di Riferimento delle Lingue

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50. **Cellular, molecular, genomic changes occurring in the heart under mechanical circulatory support.**
Michele Gallo, Vincenzo Tarzia, Laura Iop, Jonida Bejko, Giacomo Bortolussi, Roberto Bianco, Tomaso Bottio, Gino Gerosa.
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51. **Clinical psychological and neuropsychological issues with left ventricular assist devices (LVADs).**
Daniela Mapelli, Annachiara Cavazzana, Chiara Cavalli, Tomaso Bottio, Vincenzo Tarzia, Gino Gerosa, Bianca Rosa Volpe.
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54. **Jarvik 2000: evolution of surgical implantation from conventional to minimally invasive technique.**
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DR. VINCENZO TARZIA: PERSONAL CONTRIBUTION DURING THE PH.D. PERIOD (2012-2014)

ARTICOLI (I anno 2012)

1) **Nitinol Flexigrip Sternal Closure System and Chest Wound Infections: Insight From a Comparative Analysis of Complications and Costs.**
   Bejko J, Tarzia V, Franceschi MD, Bianco R, Castoro M, Bottio T, Gerosa G.
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2) **Descending aorta-to-coronary artery bypass graft imaging by means of multislice computed tomography.**
   Tarzia V, Dal Lin C, Bottio T, Testolin L, De Biasio V, Gerosa G.
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3) **Development of artificial neural network-based algorithms for the classification of bileaflet mechanical heart valve sounds.**
   Bagno A, Licciardello C, Tarzia V, Bottio T, Pengo V, Gerosa G.
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4) **Carpentier-Edwards Magna ease versus Magna valves: a comparison of in-vitro valve hydrodynamic performance.**
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5) **Occult gastrointestinal bleeding in patients with a left ventricular assist device axial flow pump: diagnostic tools and therapeutic algorithm.**
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6) **In vitro comparison of different mechanical prostheses suitable for replacement of the systemic atrioventricular valve in children.**
   Bottio T, Dal Lin C, Lika A, Rizzoli G, Tarzia V, Buratto E, Gerosa G.
   J Thorac Cardiovasc Surg. 2012 Mar;143(3):558-68.

ABSTRACTS E PRESENTAZIONI A CONGRESSI (I anno 2012)

I. ISHLT 32nd Annual Meeting & Scientific Sessions April 18-21, 2012 Prague, Czech Republic

1) **Low infection rates in Jarvik 2000 LVAD. Are post-auricular cable and pump configuration playing a positive effect?**
Vincenzo Tarzia, Ugolino Livi, Gabriele Di Giammarco, Guido Sani, Massimo Maccherini, Mauro Rinaldi, Francesco Alamanni, Michele De Bonis, Fabrizio Gazzoli, Attilio Renzulli, Giuseppe Mazzesi, Giorgio Arpesella, Germano Di Credico, Mario Zogno, Alberto Costantino and Gino Gerosa

II. HeartWare Regional Users' Meeting. Milan, Italy, 24-25 Jun, 2012

1) **Real World Anti-Coagulation and Anti-Platelet Regimen**
Dr. Vincenzo Tarzia

III. 26 th EACTS Annual Meeting, Barcellona, Spain, 27-31 October 2012

1) **The impact of transcatheter aortic valve implantation on patient profile and on outcomes of aortic valve surgery programmes: a multi-institutional appraisal**
A. D'Onofrio, O. Alfieri, F. Alamanni, M. Fusari, V. Tarzia, G. Rizzoli, G. Gerosa

2) **Nitinol flexigrip sternal closure system and standard sternal steel wiring: insight from a matched comparative analysis**
J. Bejko, T. Bottio, V. Tarzia, M. Gallo, M. De Franceschi, R. Bianco, M. Castoro, G. Gerosa

IV. 26 th National Congress SICCH, Rome, Italy, 10-13 November 2012

1) **Preoperative INTERMACS scale and outcomes of "all-comers" undergoing LVAD implantation: results from the Jarvik 2000 Italian Registry.**
M. Maiani, V. Tarzia, G. Di Giammarco, G. Sani, M. Maccherini, M. Rinaldi, F. Alamanni, M. De Bonis, F. Gazzoli, A. Renzulli, G. Mazzesi, G. Arpesella, G. Di Credico, M. Zogno, A. Costantino, G. Gerosa, U. Livi.

2) **Jarvik 2000 System Implant: Psychological and Neurocognitive Assessment**
D. Mapelli, B. Volpe, A. Cavazzana, C. Cavalli, V. Tarzia, T. Bottio, G. Gerosa

V. Approccio multidisciplinare alle infezioni sternali e mediastiniti postchirurgiche: diagnosi, terapia e prevenzione.
Vicenza, 21 Novembre 2012

1) **Il sistema VAC nella esperienza della cardiochirurgia di Padova**
Dr. Vincenzo Tarz

CAPITOLI DI LIBRI (I anno 2012)

I. **Dawn and Evolution of Cardiac Procedures: Research Avenues in Cardiac Surgery and Interventional Cardiology**
1)Surgical treatment of atrial fibrillation
Gino Gerosa, Carlo Dal Lin, Vincenzo Tarzia

II. **Trattamento chirurgico della patologia dell'aorta toracica. Piccin**
1) ***Chirurgia dell' arco aortico : Tecniche di protezione cerebrale***
Vincenzo Tarzia, Carlo Dal Lin, Gino Gerosa

ARTICOLI (II anno 2013)

1. **Ultrasound phonocardiography for detecting thrombotic formations on bileaflet mechanical heart valves.** Melan G, Bellato A, Susin FM, Bottio T, Tarzia V, Pengo V, Gerosa G, Bagno A. J Heart Valve Dis. 2013 Nov;22(6):828-36.

2. **Less invasive surgical and perfusion technique for implantation of the Jarvik 2000 left ventricular assist device.** Gerosa G, Gallo M, Tarzia V, Di Gregorio G, Zanella F, Bottio T. Ann Thorac Surg. 2013 Aug;96(2):712-4. doi: 10.1016/j.athoracsur.2013.01.086.

3. **First quantification of alpha-Gal epitope in current glutaraldehyde-fixed heart valve bioprostheses.** Naso F, Gandaglia A, Bottio T, Tarzia V, Nottle MB, d'Apice AJ, Cowan PJ, Cozzi E, Galli C, Lagutina I, Lazzari G, Iop L, Spina M, Gerosa G. Xenotransplantation. 2013 Jul-Aug;20(4):252-61.

4. **Cardiac autonomic dysfunction in the early phase after left ventricular assist device implant: Implications for surgery and follow-up.** Compostella L, Russo N, Setzu T, Tursi V, Bottio T, Tarzia V, Compostella C, Covolo E, Livi U, Gerosa G, Sani G, Bellotto F. Int J Artif Organs. 2013 Jun 25;36(6):410-8.

5. **The impact of transcatheter aortic valve implantation on patients' profiles and outcomes of aortic valve surgery programmes: a multi-institutional appraisal.** D'Onofrio A, Alfieri OR, Cioni M, Alamanni F, Fusari M, Tarzia V, Rizzoli G, Gerosa G. Interact Cardiovasc Thorac Surg. 2013 May;16(5):608-11.

ABSTRACTS E PRESENTAZIONI A CONGRESSI (II Anno 2013)

I. Patologia dell' aorta toracica: Trattamento chirurgico ed endovascolare, Camisano Vicentino (VI), 2 Febbraio 2013.

1) **Trattamento chirurgico della patologia dell' aorta toracica: tecniche di protezione cerebrale.**
V. Tarzia, G. Gerosa

II. ISHLT 33rd Annual Meeting & Scientific Sessions April 24-27, 2013 Montréal, Québec, Canada

1) **Long Term Results with Total Artificial Heart: Is It Prime Time for Destination Therapy?**
G. Torregrossa, G. Gerosa, V. Tarzia, V. Vida, D. Duveau, F. Arabia, P. Leprince, V. Kasirajan, F. Beyersdof, A. Loforte, F. Musumeci, R. Hetzer, T. Krabatsch, J. Gummert, M. Morshuis, J. Copeland

2) **Age Is No Boundary to Long Term Survival on Permanent MCS: A Multicentre Experience.**
V. Tarzia, T. Bottio, U. Livi, M. Maiani, G. Di Giammarco, G. Sani, M. Maccherini, M. Rinaldi, F. Alamanni, M. De Bonis, F. Gazzoli, A. Renzulli, G. Arpesella, G. Gerosa

3) **Different Impact on the Coagulation System of Two Continuous Flow LVADs: Axial Versus Centrifugal Flow.**
V. Tarzia, F. Vasques, G. Bortolussi, J. Bejko, M. Gallo, M. Carrozzini, M. Comisso, E. Buratto, M. De Franceschi, E. Campello, L. Spiezia, P. Simioni, T. Bottio, G. Gerosa

III. 27 th EACTS Annual Meeting, Vienna, Austria, 5-9 October 2013

1) **Efficacy and safety of paravertebral block analgesia versus general anaesthesia for ventricular assist device implantation: a single-centre experience**.
T. Bottio, J. Bejko, G. Bortolussi, M. Comisso, M. Carrozzini, R. Bianco, V. Tarzia, G. Gerosa

2) **Impact of vacuum-assisted closure therapy on outcome of sternal wound dehiscence**
V. Tarzia, M. Carrozzini, G. Bortolussi, J. Bejko, M. Comisso, M. De Franceschi, T. Bottio, G. Gerosa

3) **Extracorporeal membrane oxygenation in primary cardiogenic shock: the impact of acute versus chronic aetiology on outcome**
V. Tarzia, G. Bortolussi, R. Bianco, A. Marzari, L. Cacciavillani, S. Iliceto, T. Bottio, G. Gerosa

IV. First International Padua Meeting on Severe Bleeding Management, Padua, Italy, 12 November 2013

1) **From theory to practice: what would you have done?**
   Clinical Cases in Cardiac Surgery
   V. Tarzia

CAPITOLI DI LIBRI (II Anno 2013)

The Globesity Challenge to General Surgery: A Guide to Strategy and Techniques.
Cardio-thoracic and Vascular

Gino Gerosa, Marco Schiavon, Giuseppe Marulli, Vincenzo Tarzia, Federico Rea

ARTICOLI (III anno 2014)

58. **HeartWare ventricular assist device as bridge to transplant in children and adolescents.** Padalino MA, Bottio T, Tarzia V, Bortolussi G, Cerutti A, Vida VL, Gerosa G, Stellin G. Artif Organs. 2014 May;38(5):418-22

59. **Less-invasive off-pump ventricular assist device implantation in regional paravertebral analgesia.** Bottio T, Bejko J, Falasco G, Bortolussi G, Gallo M, Tarzia V, Gerosa G.J Artif Organs. 2014 Sep;17(3):275-7.

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61. **HeartWare LVAD implantation in a patient with a rare ARVD: Carvajal syndrome.** Bottio T, Bejko J, Tarzia V, Gerosa G. Int J Artif Organs. 2014 Jul 31;37(7):563-6.

62. **The Danger of Using a Sledgehammer to Crack a Nut: ROTEM-Guided Administration of Recombinant Activated Factor VII in a Patient With Refractory Bleeding Post-Ventricular Assist Device Implantation.** Tarzia V, Buratto E, Bortolussi G, Paolini C, Bejko J, Bottio T, Gerosa G. Artif Organs. 2014 Jul 28.

63. **Results with Syncardia Total Artificial Heart Beyond One Year.** Torregrossa G, Morshuis MJ, Varghese R, Hosseinian L, Vida V, Tarzia V, Loforte A, Duveau D, Arabia FA, Leprince P, Kasirajan V, Beyersdorf F, Musumeci F, Hetzer R, Krabatsch T, Gummert J, Copeland JG, Gerosa G. ASAIO J. 2014 Aug 25.

64. **Colchicine for prevention of postpericardiotomy syndrome and postoperative atrial fibrillation: the COPPS-2 randomized clinical trial**. Imazio M, Brucato A, Ferrazzi P, Pullara A, Adler Y, Barosi A, Caforio AL, Cemin R, Chirillo F, Comoglio C, Cugola D, Cumetti D, Dyrda O, Ferrua S, Finkelstein Y, Flocco R, Gandino A, Hoit B, Innocente F, Maestroni S, Musumeci F, Oh J, Pergolini A, Polizzi V, Ristic A, Simon C, Spodick DH, Tarzia V, Trimboli S, Valenti A, Belli R, Gaita F; COPPS-2 Investigators. JAMA. 2014 Sep 10;312(10):1016-23.

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66. **Cellular, molecular, genomic changes occurring in the heart under mechanical circulatory support.** Michele Gallo, Vincenzo Tarzia, Laura Iop, Jonida Bejko, Giacomo Bortolussi, Roberto Bianco, Tomaso Bottio, Gino Gerosa. Ann Cardiothorac Surg. 2014 Sep;3(5).

67. **Clinical psychological and neuropsychological issues with left ventricular assist devices (LVADs).** Daniela Mapelli, Annachiara Cavazzana, Chiara Cavalli, Tomaso Bottio, Vincenzo Tarzia, Gino Gerosa, Bianca Rosa Volpe. Ann Cardiothorac Surg. 2014 Sep;3(5).

68. **The Jarvik-2000 ventricular assist device implantation: how we do it**. Fabio Zucchetta, Vincenzo Tarzia, Tomaso Bottio, Gino Gerosa. Ann Cardiothorac Surg. 2014 Sep;3(5).

69. **Implantation of the HeartWare HVAD: from full sternotomy to less invasive techniques.** Vincenzo Tarzia, Edward Buratto, Michele Gallo, Giacomo Bortolussi, Jonida Bejko, Roberto Bianco, Tomaso Bottio, Gino Gerosa. Ann Cardiothorac Surg. 2014 Sep;3(5).

70. **Jarvik 2000: evolution of surgical implantation from conventional to minimally invasive technique.** Vincenzo Tarzia, Edward Buratto, Carlo Dal Lin, Michele Gallo, Giacomo Bortolussi, Jonida Bejko, Tomaso Bottio, Gino Gerosa. Ann Cardiothorac Surg. 2014 Nov;3(6):621-3.

71. **Surgical implantation of the CardioWest Total Artificial Heart.** Vincenzo Tarzia, Edward Buratto, Michele Gallo, Giacomo Bortolussi, Jonida Bejko, Carlo Dal Lin, Gianluca Torregrossa, Roberto Bianco, Tomaso Bottio, Gino Gerosa. Ann Cardiothorac Surg. 2014 Nov;3(6):624-5.

72. **Haemorrhage and thrombosis with different LVAD technologies: a matter of flow?** Vincenzo Tarzia, Edward Buratto, Giacomo Bortolussi, Michele Gallo, Jonida Bejko, Roberto Bianco, Tomaso Bottio, Gino Gerosa. Ann Cardiothorac Surg. 2014 Nov;3(6):582-4.

73. **Nitinol flexigrip sternal closure system and standard sternal steel wiring: insight from a matched comparative analysis.**
Bejko J, Bottio T, Tarzia V, De Franceschi M, Bianco R, Gallo M, Castoro M, Bortolussi G, Gerosa G.
J Cardiovasc Med (Hagerstown). 2015 Feb;16(2):134-8

ABSTRACTS E PRESENTAZIONI A CONGRESSI (III Anno 2014)

I. ISHLT 34th Annual Meeting & Scientific Sessions April 10-13, 2014 San Diego, USA

1) **From Bench To Bedside: Can the Improvements in LVAD Design Mitigate Adverse Events and Increase Survival Rate?;**
   V. Tarzia, G. Di Giammarco, M. Maccherini, T. Bottio, V. Tursi, M. Maiani, S. Bernazzali, M. Foschi, S. M. Diso, U. Livi, G. Sani, G. Gerosa.

2) **Efficacy and Safety of Paravertebral Block Analgesia Versus General Anaesthesia for Ventricular Assist Device Implantation: A Single-Centre Experience**
   J. Bejko, T. Bottio, G. Bortolussi, M. Carrozzini, V. Tarzia, D. Pittarello, G. Di Gregorio, G. Gerosa.

3) **Fortuity or Causality: Relation Between Outflow Graft Site of Anastomosis on Aorta and Cerebral Ischemic Events in LVAD Implantation**
   J. Bejko, T. Bottio, G. Bortolussi, V. Tarzia, R. Bianco, G. Rizzoli, G. Gerosa.

II. 5th Jarvik 2000 LVAD Users Meeting. Petriolo September 27th, 2014

1) **When anticoagulation gets tough: case reports & strategy**
   V. Tarzia

2) **Telemedicine "TELEMACO" project**
   V. Tarzia

III. 28 th EACTS Annual Meeting, Milan, Italy, 11-15 October 2014

1) **Are all continuous flow left ventricular assist devices equal on platelet activation and inflammatory response? A comparison of centrifugal versus axial flow pump.**
   V. Tarzia, G. Bortolussi, V. Penzo, J. Bejko, M. Gallo, R. Bianco, T. Bottio, G. Gerosa.

2) **Minimally invasive surgical and anaesthetic approach for ventricular assist device implantation: A single-centre experience.**
   T. Bottio, J. Bejko, G. Bortolussi, R. Bianco, G. Falasco, D. Pittarello, V. Tarzia, G. Gerosa.

IV. ATBV 2014 Congresso Nazionale. Hot-Topics in tema di terapia antitrombotica. Le sfide in tema di terapia antitrombotica. Milano 24-25 Ottobre 2014

1) **La trombosi…altrove. La chirurgia cardiaca.**
   V. Tarzia

V. SICCH. 27th National Congress, Rome. November, 28-30th 2014.

1) **Outcome of sternal wound dehiscences in diabetic patients: Can vac therapy play a role?**
   V. Tarzia

2) **Impact of different LVAD technologies on the coagulation system: Axial versus Centrifugal flow.**
   V. Tarzia

CAPITOLI DI LIBRI (III Anno 2014)

I. **Chirurgia per le professioni sanitarie (Mario Lise) (Piccin)**

Cuore e Pericardio

Vincenzo Tarzia, Michele Gallo, Gino Gerosa

II. **Trattato di Cardiochirurgia (Luigi Chiariello)**

Trattamento chirurgico dello scompenso cardiaco refrattario a terapia medica

Vincenzo Tarzia, Gino Gerosa

III. **Manuale di Malattie Cardiovascolari *(Società Italiana di Cardiologia)***

VAD e Trapianto Cardiaco

Gino Gerosa, Vincenzo Tarzia

PROGETTI DI RICERCA SANITARIA FINALIZZATA 2014

Regione Veneto

I. **Applicazione della sanità digitale in Cardiologia**

Responsabile scientifico:Vincenzo Tarzia

EACTS QUIP ADULT CARDIAC DATABASE

V. Tarzia, G. Gerosa