# Left ventricle unloading in extracorporeal life support

# Left Ventricular Unloading in Extracorporeal Life Support

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# Left Ventricle Unloading in Extracorporeal Life Support

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# Chapter 1.

## General introduction

**Abbreviations**

Ea, arterial elastance
ECMO, extracorporeal membrane oxygenation
EDP, end-diastolic pressure
EDPVR, end-diastolic pressure- volume relationship
EDV, end-diastolic volume
Ees, end-systolic elastance
ESP, end-systolic pressure
ESPVR, end-systolic pressure- volume relationship
LV, left ventricle
MVO2, myocardial oxygen consumption
PE, potential energy
PV, pressure-volume
PVA, pressure-volume area
SW, stroke work
V-A ECLS, veno-arterial extracorporeal membrane oxygenation

The ECLS (extracorporeal life support) or ECMO (extracorporeal membrane oxygenation) is an evolution of the heart–lung machines used in cardiac surgery. ECLS exists in two configurations, veno-venous or veno-arterial, which are used to support respiratory function, circulation, or both.
ECLS is not a treatment and does not correct the underlying pathological insult [1].
The final aim of this support consists of bridging patients, either to natural organs recovery, whenever it is possible, or to long-term devices and/or transplantation.

**Brief ECLS History**

After years of pre-clinical research, the first successful extracorporeal cardiopulmonary bypass was performed in 1953, by the surgeon John Gibbon [2]. The duration of extracorporeal circulation was limited, and the support could not be extended over 6 hours, due to the cellular damage caused by the direct exposure of blood to gas [3].
The first successful application of prolonged life support took place in 1971 and it is considered as a landmark achievement in the modern era of Intensive Care Medicine and Surgery. *J. Donald Hill* treated a young patient affected by post-traumatic ARDS for 3 days and saved his life [4]. In 1975, the American surgeon Robert Bartlett and his colleagues at Boston Children's successfully treated the first infant with ECLS, a girl named Esperanza (literally "Hope,") by the nurse's staff [5]. The success of this case led to a great enthusiasm. Therefore, the National Heart, Lung and Blood Institute in the USA developed the first trial of extracorporeal support in patients with respiratory failure. However, the negative results, published in 1979, showed the overwhelming majority of the patients (90%) dying, with no difference between the groups. Consequently, most clinicians stopped offering ECLS [6].
Nevertheless, a minority kept on improving the technique, while others worked on modifying other aspects of the support of respiratory failure patients.
In 1978 Kolobow and Gattinoni introduced a modified extracorporeal gas exchange technique, called extracorporeal carbon dioxide removal [7,8], as a novel method to mitigate the lung insult caused by aggressive mechanical ventilation [9,10].
Only in the recent decade, the worldwide acceptance of the use of ECMO was achieved. On one hand, the H1N1 pandemic led to offer ECLS in a large number of very sick young patients with success support to full recovery [11,12,13]. On the other hand, the encouraging results of a large ECLS prospective trial in patients with acute respiratory distress syndrome were published in The Lancet (the CESAR trial). In fact, this trial showed that transferring patients with acute respiratory distress syndrome to a specialist centre that could offer ECLS if required led to a better outcome [14].
Parallel to the development of ECLS for respiratory injury, ECLS started to be used to support patients with cardiopulmonary failure, in veno-arterial configuration. V-A ECLS was employed almost exclusively as a support for post-cardiotomy cardiogenic shock until recent years.

In the past few decades, V-A ECLS become an advanced treatment for cardiogenic shock and a unique option for refractory cardiac arrest.

**V-A ECLS**

V-A ECLS simultaneously provides a temporary mechanical circulatory support and extracorporeal gas exchange, which can support the cardiorespiratory system [15,16]. The circuits, in veno-arterial configuration, consist of a venous cannula (inflow, drainage), a pump, an oxygenator, and an arterial cannula (outflow, return).

The blood is pumped out of the body, passed through an artificial lung that includes a membrane filter that removes carbon dioxide and adds oxygen, and then blood is returned to the patient via a pump with the same force as the heart, replacing its function.

V-A ECLS can be placed in two different configurations: via peripheral or central access (*Figure 1*). Central V-A ECLS is more often implemented in the operating theater and, therefore, in post-cardiotomy patients unable to wean off from cardiopulmonary bypass [17,18]. Whereas peripheral V-A ECLS is placed percutaneously or by surgical cut-down, outside of the operating room, in patients affected by refractory cardiogenic shock and cardiac arrest [19,20]. Typically, femoral artery and femoral or internal jugular vein are the most used access.

Interestingly, it has recently been adopted a modified cannulation approach promoting patient mobility and faster recovery and to reduce complications associated with femoral arterial cannulation, such as compartment syndrome and peripheral ischemia. This configuration involves cannulation of the subclavian artery through a graft, maintaining the standard venous access [21].

**Indications for V-A ECLS**

The most frequent indication for ECLS in the United States [22] is post cardiotomy shock. The prevalence of ECLS implementation in post cardiotomy setting ranges between 0.4% and 3.65% [23,24,25] and, according to the ELSO Registry, including almost 90,000 ECLS in adults and children, its use has been raising, particularly during the last 2-3 years [26]. Despite the available surgical access (sternotomy or thoracotomy) for a central cannulation, the peripheral approach is more commonly preferred [27,28,29].

Besides post cardiotomy setting, the peripheral V-A ECLS use for refractory cardiogenic shock sharply increased [30,31]. The Extracorporeal Life Support Organization registry collected more than 15000 adults supported with V-A ECLS showing an approximately 40% survival rate to hospital discharge [32].

Peripheral V-A ECLS is also used as a resuscitation strategy for refractory cardiac arrest. The overall survival rate using peripheral V-A ECLS in cardiac arrest is still very poor (29%), although suggestions of improved survival and neurological outcomes have been observed in select patient subgroups [33.34,35]. Lack of clear evidence is caused by the absence of strong randomized controlled studies due to the obvious related logistical, legal, and

ethical issues.
The future perspectives ECLS include a better patient selection, as well as optimize patient care while on ECLS, in particular how to avoid and handle the support complications. The latter concept is crucial since the unsatisfactory outcomes might be explained by a still poor patient-machine management.

**Physiological Basis**
Beyond the above cited patient-machine management, the understanding of the physiological basis of this interaction is pivotal. For this reason, a specific introduction on the heart physiology is more than mandatory.
The heart acts as a muscular pump drawing blood into the arterial system.
Variations of pressure and volume measured into the ventricle describe the ventricular function. A pressure-volume (PV) loop, reporting the volume variation on the x-axis and pressure variation on the y-axis, is obtained by measuring these variations directly into the LV chamber [36, 37].
Experimentally, the PV loop can be measured for each single cardiac cycle.

*PV loop Analysis*
The PV loop is depicted in *figure 1*. From point a, diastole commences, and the blood starts drawing from the left atrium to the left ventricle, physiologically generating a low ventricular pressure. Subsequently, at the point b, isovolumic contraction begins. The muscular fibers strain rises, leading to a pressure increase into the LV without volume expansion.

***Figure 1.***

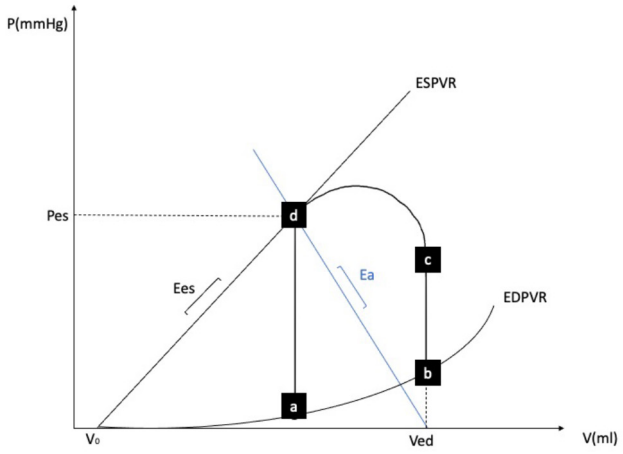


***Figure 1.*** **Pressure volume loop. P,** pressure, V, volume, Ea, arterial elastance; Ees, end-systolic elastance; EDPVR, end-diastolic pressure-volume relationship; ESPVR, end-systolic pressure-volume relationship; V0, diastolic volume at a pressure of zero

The intraventricular pressure increase rate is a common index of LV contractility, which is considered independent from the afterload. This relationship can be described as: dP/dtmax, for its maximum rate or indexed for end-diastolic volume (EDV), to consider the variation induced by preload increases [37].
As soon as intraventricular pressure overcomes the aortic pressure, aortic valve open. Thereafter, the blood is pumped into the Aorta (point c to d) until the end-systolic pressure (ESP) point is reached.
The LV ejection ends, the aortic valve closes, and the isovolumetric relaxation begins, up to point a, when mitral valve opens ventricular filling restarts [37].

*Extrinsic and intrinsic properties*
Each single PV loop is influenced by intrinsic (ventricular) and extrinsic properties of the heart. These strongly affect the PV loop [38]. A dedicated *table 1* listed all these features.
In summary, the intrinsic properties are pictured by two lines which inscribe the PV loop. First, the end-systolic pressure- volume relationship (ESPVR) is a line, whom slope is represented by the ventricular or end-systolic elastance (Ees) [38]. Second, the end diastolic pressure- volume line relationship (EDPVR) is curvilinear and indicates the diastolic properties [39].
Preload and afterload are commonly considered as extrinsic conditions which influence the PV loop. The end-diastolic volume (EDV) is a preload surrogate, and it is strongly determined by the venous return [40].
Whereas the afterload can be defined as the “load” against which the heart ejects blood. Afterload is strongly connected with the concept of arterial elastance, since it influences the slope of the Ea line, that intersects the ESP and the EDV points.
Each beat, the ventricle interacts with arteries producing the external myocardial work (also known as stroke work). This interaction is called ventricle-arterial coupling, defined as the ratio between Ea/Ees, optimal when it approximates [36].
Finally, according to the time-varying elastance model, the entire cardiac cycle can be interpreted as a cycling variation of elastance. In other words, considering multiple PV loops featured by different load conditions and at different instants of cardiac cycle, all the ESP points lies on the same straight line [40].

*Myocardial work and oxygen consumption*
The principal variables related myocardial work and oxygen consumption are listed in *table 2*. The PV area (PVA) is the sum of the external stroke work (SW) and the potential energy (PE). The first represents the work performed by the LV to pump blood into the aorta, whereas PE consists in the residual energy stored in the myofilaments at the end of systole, related to the viscoelastic ventricular properties [41]. Myocardial oxygen consumption (MVO2) is experimentally demonstrated as linearly related to ventricular PVA

[42] However, only approximately 10- 25% of energy is converted to external power, related to the production of cardiac output [43]. The residual energy is dissipated as heat [44]

*PV loop during cardiogenic shock*

The PV loop is a dynamic entity, which is strongly influence by each pathological, as well as loading conditions. With reference to cardiogenic shock, as the common indication for V-A ECLS, the PV loop analysis leads to the following variations [45]. As consequence of the acute myocardial disfunction, PV loop shifts downward and rightward since the ESPVR slope significantly drops, reflecting the decreased LV contractility. The blood, which was filled in the LV, is not successfully pumped by the dysfunctional LV, leading to an end-diastolic pressure (EDP) increase, as well as EDV. Moreover, the poor LV contractility does not generate enough energy, causing a decrease of ESP and aortic pressure, namely perfusion. As a direct consequence stroke volume and, therefore, cardiac output drop. In addition, mild elevation of PCWP may also be seen [46].

Therefore, the overall effect consists of increased PE and reduced SW. This significantly impacts on myocardial work efficiency: less energy becomes external work, more energy is dissipated as heal and, finally, the $MVO_2$ still remains high [47].

*PV loop on peripheral V-A ECLS*

During cardiogenic shock, V-A ECLS primarily support hemometabolic shock by ensuring perfusion into the vital organs and secondarily decreasing the heart's preload, through the venous cannula, which draws blood from the right atrium.

Nevertheless, peripheral V-A ECLS generates an unfavourable increase of LV afterload, imposed to an already failing LV [48,49]. Under a poor LV contractility, the Starling's Law is the only way to overcome the increased afterload. Therefore, LV begins to work under higher volumes, and, as a results, it starts dilating.

Based on increased blood statis and LV distention [50], EDP rises, as well as left atrial pressure and pulmonary capillary wedge pressure, which may cause acute pulmonary oedema [51]. Unfortunately, this cascade is particularly unfavourable since slight EDV increases may cause large increases in EDP.

As an overall effect, the PV loop becomes narrow and taller as compared to non-supported cardiogenic shock, shifting rightward and upward along the end-diastolic pressure-volume relationship [36]. Obviously, the latter changes have a direct reflection in terms of myocardial work and oxygen consumption. In fact, PVA increases mainly due to the rise of PE and despite the SV reduction. Therefore, the poorly oxygenated blood due to pulmonary oedema and the increased myocardial oxygen demand might further worsen the LV function [52].

**The need of unloading the LV**

Based on the previous pathophysiological basis, the LV unloading owns a specific role. Unloading the LV means to reduce the LV mechanical power expenditure and consequentially myocardial oxygen consumption. This may lead to decrease the hemodynamic forces which promote ventricular remodelling.

With reference to hemodynamic and energetic changes, the LV unloading effect has been extensively studied [53,54,55]. First, the PV loop shifts leftward and, therefore, the ventricle works under lower LV volumes and pressures. As a result, the PE drops and the PVA is reduced, as well as MVO2.

Currently, the evidence supporting LV unloading has been sharply raising over the last years [56,57]. It has been well established that LV overload significantly jeopardizes ventricular recovery, particularly in the presence of ischemia-induced myocardial impairment [52]. In fact, LV mechanical unloading applied during the acute phase of myocardial infarction experimentally showed a consistent infarct size (IS) reduction [58].

Moreover, IS is strongly associated to the degree of unloading. Saku et al. clearly showed as a total left ventricular assist device reduced more effectively the MVO2 (% reduction against Control: -56 ± 9%) and IS (infarct area/area at risk: 5.0 ± 3.1%) compared to a partial left ventricular assist device (MVO2 reduction: -21 ± 14%; IS: 29.1 ± 5.6) [59].

LV unloading not only reduces IS, but it may possibly help myocardial recovery [60]. The ESPVR was able to shift back to normal values in human hearts explanted from transplantation recipients, after a period of mechanical circulatory support, introducing the concept of “reverse remodelling” [61].

Regarding the clinical relevance, the LV unloading prevents blood stasis in the LV and the subsequent increasing risk of thrombus formation, in case of extreme overload and permanent aortic valve closure [62].

***Table 1.***

| Properties | Definition | Effect on PV loop |
|---|---|---|
| **Intrinsic** | | |
| ESPVR | The linear relationship line is termed: ESP = Ees x (ESV – $V_0$). The ESPVR is defined by two main features[1]:<br>- the slope is the Ees, a load-independent LV contractility parameter<br>- the volume–axis intercept V0, the left ventricular volume at the end of the systole | Increase or decrease of cardiac contractility, as when positive or negative inotropes are administered, determine a leftward or rightward shift, respectively, of the ESPVR, whose slope accordingly varies |
| EDPVR | The EDPVR defines only the *passive diastolic properties* of the ventricle. This curvilinear diastolic pressure–volume relationship, according to Walley, can be described as: $P = S \times log\ (Vm-V)/(Vm-Vo)^2$. S represents diastolic myocardial stiffness, *Vm* is the maximum allowed diastolic ventricular volume (set by the pericardium and the cardiac cytoskeleton, and Vo is the diastolic volume at a pressure of zero). Furthermore, Ventricular compliance is defined as: *C = dV/dP, [mL]/[mmHg]* | These properties are influenced by pressure and required sophisticated engineering assumptions. Consequentially, diastolic properties are difficult to apply in practice [8]. |
| **Extrinsic** | | |
| Preload | The degree of ventricular fibers stretch at the end of the diastole. Changes of preload, in the experimental context, are obtained through an inferior vena cava occlusion, that reduces the amount of blood returning to the heart. | Decrease in preload progressively leads to leftward PV loop shift, indicating a lower end-diastolic volume. |
| Afterload | Afterload is defined as the “load” against which the heart ejects blood.<br>It can be described according to the modified Laplace Law, assuming a spherical shape of the LV: $\tau = pr/h$, *( [mmHg]* , τ = wall stress, p = intraventricular pressure, r = chamber radius, h = wall thickness. | Changes in afterload determine a rightward shift of the PV loop, with an increase of both end-systolic pressure and peak chamber pressure and with a decrease of stroke volume. |
| **Vascular** | | |
| Ea | Arterial elastance is defined as: *Ea = ESP/SV*<br>Indeed, after the closure of the aortic valve, the proximal aorta contains a blood volume that equals SV at a pressure that equals ESP<br>The Ea line connects the *EDV* with the end systolic pressure point. The Ea line slope is defined by the ratio between *systemic vascular resistance (SVR)* and the duration of the heartbeat. Therefore, Ea is influenced by the SVR, the *heart rate* and the preload (EDV)[9]. | The rightward shift of the Ea line, with a subsequent increase of its slope, corresponds to an increased afterload and reduces the mechanical efficiency of the heart, as the wasted energy is increased. |

***Table 1.*** **Main Pressure-Volume Loop Features.** Ea, arterial elastance; Ees, end-systolic elastance; EDPVR, end-diastolic pressure-volume relationship; EDV, end-diastolic volume; ESP, end-systolic pressure; ESPVR, end-systolic pressure-volume relationship; ESV, end-systolic volume; PV pressure-volume; SV, stroke volume.

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2 Walley KR. Left ventricular function: time-varying elastance and left ventricular aortic coupling. Crit Care. 2016 Sep 10;20(1):270.
3 Sunagawa K, Maughan WL, Burkhoff D, et al. Left ventricular interaction with arterial load studied in isolated canine ventricle. Am J Physiol 1983;245(5 Pt 1):H773–80.

***Table 2.***

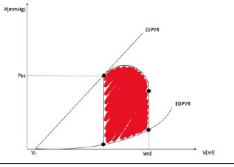
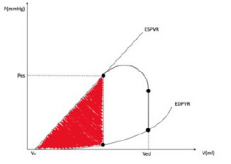
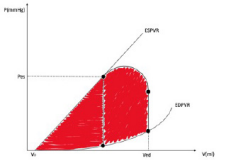
| | Definition | PV loop |
|---|---|---|
| **Stroke Volume** | *Stroke volume*, the amount of blood in milliliters (mL) pumped by the LV into the aorta at each cardiac cycle is defined by EDV – ESV, where EDV = end-diastolic volume and ESV = end-systolic volume | |
| **Stroke work** | *Stroke work* is calculated as SW = $\int_{EDV}^{ESV}$ PdV, where EDV and ESV represent the volume change during systole, P the aortic pressure during systole. |  |
| **Potential Energy** | *Potential Energy* is assessed as PE = $\int_{V0}^{V1}$ ESPVRdV-$\int_{V0}^{V1}$ EDPVR(V)dV where V0 is the intercept of EDPVR with the x-axis. |  |
| **PV Area** | *Pressure Volume Area* can be obtained from the formula PVA = SW + PE, where SW is the external stroke work and PE is the potential energy |  |
| **$MVO_2$** | *According to Suga's model (AM 15, 16), oxygen consumption as MVO2 = a x PVA + b, where a is the slope of the straight line of the $MVO_2$/PVA relationship, and b is the oxygen axis intercept.* | |

***Table 2.*** **Main LV workload features.** EDPVR, end-diastolic pressure-volume relationship; EDV, end-diastolic volume; ESP, end-systolic pressure; ESPVR, end-systolic pressure-volume relationship; ESV, end-systolic volume; MVO2, myocardial oxygen consumption; PE, potential energy; PV pressure-volume; PVA, pressure volume area; SW, stroke work.

1 Suga H: Total mechanical energy of a ventricular model and cardiacoxygen consumption. Am JPhysiol1979;236:H498-H505.
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**LV unloading in clinical daily practise**

The LV overload on V-A ECLS is currently based on local consensus and a common shared definition is lacking.

The gold standard to diagnose LV distention should be the direct measurement of end-diastolic LV pressure. However, it can be measured directly in the operating room or the catherization lab, or through a pigtail inserted in the LV from a peripheral arterial access [63]. Therefore, this leads to find indirect signs of LV overload.

Consequently, the clinical presentations range from severe pulmonary edema and LV distention on echocardiography, to hemodynamic thresholds based on pulmonary artery catheter, refractory ventricular arrhythmias and LV thrombosis [64].

For instance, Schrage et al in their retrospective analysis of a cohort of patients supported with ECLS in association with Impella were not able to detail any definition of LV overload [56]. Yet, two years later, the authors in their international multicenter cohort study could not provide any standard criteria for unloading the LV. Since their observations were retrospective, they could simply declare that patients were treated at the discretion of the local investigators and per local guidelines [57].

On the contrary, Truby et al. defined the LV distension as pulmonary edema on chest radiography and increased pulmonary artery diastolic blood pressure (>25 mmHg) [65], which is a surrogate of the wedge pressure evaluated in SHOCK trial [66].

These differences in definitions may account for the high variability of LV overload rate ranging from 2% to 68% in the literature. Camboni et al. reported a rate of LV decompression only in 2% of more than 600 cases [67]. They managed the LV distension with a restrictive fluid management and a careful reduction of ECLS flow.

In the cohort investigated by Truby et al, the clinical and subclinical (not requiring immediate decompression) LV distension occurred in 7% and 22% of patients, respectively [65]. Again, in a young population raging from 1 day to 22 years old, Fiser at al reported the 68% of patients supported with V-A ECLS who were undergone to transcatheter septostomy for cardiac decompression [68]. Accordingly, in the most recent evidence from Schrage et al, the rate of unloading with Impella was 49% [57].

Despite all evidences, the strategy, namely venting the LV during V-A ECLS, has not systematically showed to impact on the major outcomes yet. On one hand, although several LV venting techniques are nowadays available, scanty data have been provided regarding their real effectiveness. On the other hand, the lack of consensus on LV overload definition as well as the available venting strategies don't allow to effectively compare such difference experiences mainly based on local expertise. In addition, the presence of several confounding factors (i.e. comorbidities and other pre-existing conditions) might not help the evaluation of a new strategy in Intensive Care Medicine. To conclude,

considering that V-A ECLS alone might not be an effective therapy for failing hearts, *which are the best strategies? May the "hemodynamic cosmesis" really impact on the major outcomes?*

**General aims and outline of the thesis**

The research presented in this thesis has two main aims.

The first aim is to provide solid data regarding the most promising LV venting techniques, deeply discussing the hemodynamic and physiological meaning, based on preclinical data derived from a swine cardiogenic shock model. Additionally, the second aim is to explore whether selected populations might benefit from an active LV unloading strategy the most.

After this general introduction, ***chapter 2*** reviews the current approaches to vent the LV during V-A ECLS, with a selection of papers published between 1993 and 2016. The venting techniques are systematically revised and classified, focusing on each advantage and shortcoming.

The need of a common LV overload definition is firstly introduced in ***chapter 3***. In a population of 184 adult patients supported with peripheral V-A ECLS at the Maastricht University Medical Center from January 2007 to January 2018, the primary aim was to assess the impact of IABP in patients with protracted aortic valve closure. The latter, as an early marker of increased LV afterload, may lead to an evident subsequent overload. A new multiparametric definition of LV overload is proposed, considering invasive and non-invasive tools.

In ***chapter 4***, a porcine model of cardiogenic shock is used to study whether percutaneous transaortic suction device or trans-pulmonary drainage, among the most promising LV venting techniques, is superior to the other in supplying an effective unloading associated with V-A ECLS. Additionally, a detailed PV loop analysis of both strategies gives the unique opportunity to report an extensive hemodynamic and bioenergetic phenotypization.

The satisfactory experimental results obtained with the transaortic suction device led to a further discussion and description, which is outlined in ***chapter 5***. This is a journey, starting from the solid pathophysiologic basis of this strategy and ending to a full treatise of the combined configuration of V-A ECLS and Impella (also called ECPella) and its significant clinical applications.

The ***chapter 6*** investigates the role of balloon atrial septostomy in a swine experimental study of cardiogenic shock managed by V-A ECLS. The experiment fully analyzed the impacts on LV overload and workload, as well as on the overall ECLS-related end-organ perfusion. Furthermore, to the best of the authors' knowledge, this work provides a comprehensive quantification of the BAS effects for the first time.

A population of congenital heart disease children and neonates is chosen in ***chapter 7*** to examine the clinical impact of LV decompression, mainly obtained through atrial septostomy. The almost absence of any pre-existing conditions in 90 patients supported with V-A ECLS allows to make important considerations. Among all, the prognostic value of LV unloading can be tested and judged in a such unique population.

The ***chapter 8***, finally, condenses the growing knowledge and experience in a decision-making algorithm, which may drive the clinicians in their daily

practice. Different clinical scenarios are treated, providing the current authors' clinical approach on LV unloading during V-A ECLS.
To conclude, ***chapter* 9** discusses the major results of the above-mentioned studies and integrates them in a broader scientific and clinical perspective.

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# Chapter 2.

## Modalities and effects of left ventricle unloading on extracorporeal life support: a review of the current literature

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**Abbreviations**
BBAS, balloon atrial septostomy
BiVAD, biventricular assist device
CS, cardiogenic shock
ECPR, extracorporeal cardiopulmonary resuscitation
IABP, intra-aortic balloon pump
LA, left atrial
LV, left ventricle
LVAD, left ventricular assistance device
TACV, trans-aortic catheter venting
V-A ECMO, veno-arterial extracorporeal membrane oxygenation

**Abstract**

**Introduction/Aim**

Veno-arterial extracorporeal membrane oxygenation (V-A ECMO) support is increasingly used in refractory cardiogenic shock and cardiac arrest, but is characterized by a rise in afterload of the left ventricle (LV) which may ultimately either further impair or delay cardiac contractility improvement. The aim of this study was to provide a comprehensive overview regarding the different LV venting techniques and results currently available in the literature.

**Methods**

A systematic literature search was performed in the PubMed database: 207 articles published between 1993 and 2016 were included. Papers dealing with pre-clinical studies, overlapping series, and association with other assist devices were excluded from the review, with 45 published papers finally selected. Heterogeneous indications for LV unloading were reported. The selected literature was divided into subgroups, according to the location or the performed procedure for LV venting.

**Results**

Case reports or case series accounted for 60% of the papers, while retrospective study represented 29% of them. Adult series were present in 67%, paediatric patients in 29%, and a mixed population in 4%. LV unloading was performed percutaneously in 84% of the cases. The most common locations of unloading were the left atrium (31%), followed by indirect unloading (intra-aortic balloon pump) (27%), trans-aortic (27%), LV (11%), and pulmonary artery (4%). Percutaneous trans-septal approach was reported in 22%. Finally, the unloading was conducted surgically in 16%, with open chest surgery in 71%, and minimally invasive surgery in 29% of surgical cases.

**Conclusion**

Nowadays, only a few data are available about left heart unloading in V-A ECMO support. Despite the well-known controversy, IABP remains widely used in combination with V-A ECMO. Percutaneous approaches utilizing unloading devices is becoming an increasingly used option. However, further studies are required to establish the optimal LV unloading method.

**Introduction**

Peripheral or central veno-arterial extracorporeal membrane oxygenation (V-A ECMO) may represent the final option for patients in severe cardiogenic shock (CS) refractory to medical therapy. Alternatively, it is used during resuscitation in cardiac arrest, described as extracorporeal cardiopulmonary resuscitation (ECPR), and shown to significantly increase the survival rate in such a setting [1]. The predicted mortality rate before ECMO was developed exceeded 90%. Currently, even when ECMO is utilised, survival in cardiogenic shock remains poor [2,3]. The usefulness of V-A ECMO in this setting, therefore, is still under debate and its efficacy is variable, as the outcome can be influenced by numerous factors [4].

**Why is Left Ventricular Venting Potentially Important During V-A ECMO?**

One of the most important concerns in V-A ECMO therapy is the effect of retrograde flow in the aorta towards the left ventricle (LV). This unwanted effect can cause a marked increase in LV afterload and thus may impact LV function. In the presence of acute severe LV dysfunction, the LV may be unable to sustain such an increased afterload, thus further impairing its performance [5]. The consequences of LV pressure overload may account for LV dilatation, increases in left atrial (LA) pressure, and pulmonary oedema. Furthermore, LV overload increases wall stress and myocardial oxygen consumption, jeopardizing ventricular recovery particularly in the presence of ischemia-induced myocardial impairment. If the overload is extreme and LV contractile impairment significant, situation observed at high V-A ECMO flow, the aortic valve may remain closed even during systole, causing blood stasis in the LV, making the left cardiac chambers a predisposing milieu for thrombi formation [6]. This cascade of events has been well demonstrated in animal models and has been confirmed in human studies [7].

The underlying cardiac illness may play an additional role in such a vicious circle: in chronic heart failure, concomitant severe mitral valve regurgitation may be associated due to ventricular dilatation, likely worsen LA overload and ultimately leading to pulmonary oedema [8]. On the other hand, in acute heart disease (i.e. in acute myocardial infarction), the distension of the LV possibly due to V-A ECMO may worsen the ongoing myocardial damage by inducing arise in LV pressure and hence generating sub-endocardial ischemia [9].

Based on the above-mentioned mechanisms, it is clear that unloading the LV during V-A ECMO may either provide an actual LV functional rest or avoid or reduce the shortcomings due to counterflow generated by the temporary cardiocirculatory support. Notewithstanding, such adverse effects of V-A ECMO are not always present, or, at time, only slightly evident, with the majority of the supported patients not showing clear hemodynamic or structural disadvantages from the V-A ECMO-related assistance [10].

Prevention and treatment of LV overload in V-A ECMO may, therefore, prove useful in a number of situations, but, at the same time, the optimal technique and the target patient population who will actually benefit from venting

procedures remains unclear. In addition, these procedures are invasive, thus increasing bleeding risk and complication rate, and therefore the risk/benefit should be carefully assessed.

**Literature search and selected articles**

A systematic literature search was performed in the PubMed database. PubMed search used MeSH terms and free terms. The search used the following terms: *(Extracorporeal membrane oxygenation[MeSH Terms]) AND (venting OR left ventricle decompression OR left ventricle unloading OR unloading OR Impella OR Left atrial venting OR Left ventricle venting OR Tandem heart OR Intra aortic balloon pump OR Pulmonary artery drainage OR Atrial septostomy OR Percutaneous left ventricle support devices OR Tandem Heart).*

***Figure 1.***

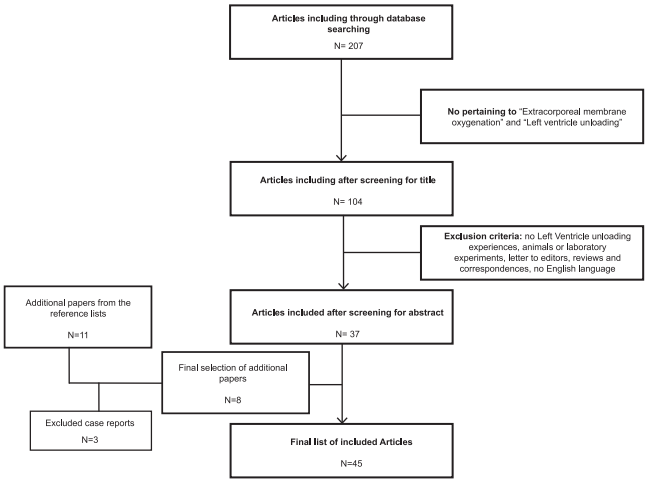


***Figure 1.*** Flowchart of systematic literature search in PubMed and study selection

No restrictions for publication date or publication status were selected. A three-phase process was carried out, which led to the final list included in this review (*Figure1*). Firstly, an initial literature search was conducted. Secondly, the results of this search were screened, and finally the eligibility of the articles selected throughout the screening process was checked. All articles describing ECMO and LV unloading in the clinical setting were found to be eligible.

All titles were screened. In this phase, the exclusion criteria was the absence of the title's pertinence with "Extracorporeal membrane oxygenation" and "Left ventricle unloading".

The resulting abstracts were then checked, and those which reported no LV unloading experiences, or described animals or laboratory experiments were excluded. Furthermore letters to editors, reviews and correspondences were

also excluded. Moreover, only English literature was taken into consideration. In cases of uncertainty, full-text reports were read to assess eligibility. Finally, the research was integrated by manually searching reference lists of selected articles, adding 9 additional papers. However, three case reports were not included because they were less exhaustive than those included on the same topics. This review discusses the current approaches to vent the LV during V-A ECMO, with a selection of 45 papers published between 1993 and 2016. Although the statistical calculation was carried out on the total amount of papers, we have reported only 33 articles, excluding case reports that would not have added additional information to our description *(Table 1)*.

**Surgical Venting of the Left Ventricle**

**Surgical techniques**

Implant of a LV venting catheter may be achieved through a surgical approach. This is usually adopted intra-operatively or immediately after cardiac surgery procedures. Post-cardiotomy heart failure occurs in approximately 0.5%–3% of cardiac surgery patients and continues to be associated with significant morbidity and mortality. Furthermore, ECMO is becoming increasingly used, but mortality rate is apparently worsening during the most recent years [11]. Among the several causes for such unfavorable trend, lack of cardiac recovery or occurrence of multi-organ failure represent the most frequent causes of dismal outcome [11]. LV venting has been claimed to represent an enhanced patient management in this setting [11]. Simple placement of the catheters and the capacity to provide dual heart and pulmonary support make this approach the preferred therapeutic modality after cardiac surgery [12]. ECMO can be implanted either in a peripheral or a central configuration. The peripheral ECMO is commonly used, especially if LV unloading is not a priority [11]. This approach is less invasive and simpler than the central configuration. However, if the LV becomes overloaded the central configuration of ECMO is required, which is achieved by the implantation of cannula in the right atrium and aorta or axillary artery.

During the central configuration of ECMO, the LV venting catheter is usually obtained by inserting a cannula through the right superior pulmonary vein either in the LA or LV, and connected with a Y-connector to the venous line on the extracorporeal life support circuit.

Sandrio et al. presented an experience of 8 children who received LV unloading with a cannula placed in this manner. No patient died whilst on support and 7 patients were successfully weaned, with one patient bridged to a biventricular assist device. Interestingly, 4 patients were not post-cardiotomy patients [13] The same surgical approach was used by Weymann et al. in 12 patients with a mean age of 31.6 ± 15.1 years. All patients received central ECMO and there were no post-cardiotomy patients. The weaning rate was 100% and the survival at discharge was 58.3%. The authors thus strongly recommend LV decompression in refractory cardiogenic shock [14], indicating the usefulness of this technique even when central ECMO is placed in the

non-post-cardiotomy setting. Another opportunity is to place the LV venting cannula in the pulmonary artery trunk.
In the pediatric patient population, other techniques have been developed due to the fact that the pulmonary veins are small and therefore introducing a vent might cause problematic narrowing of the vessels. Pulmonary venting during ECMO support, therefore, may be a valid option in pediatric patients. Kimura et al. presented a case of a 14-year-old boy treated after resuscitation from near-drowning. Firstly, a biventricular assist device (BiVAD) with an oxygenator was put in place. However, the increase in pulmonary vascular resistance, caused by lung failure, required central ECMO with right atrium, pulmonary artery and LV drainage, and ascending aorta aortic return. The patient was weaned from the oxygenator on day 16. However, BiVAD support was prolonged because both left and right cardiac function did not recover completely [15]. In addition, Kotani et al. studied 23 children, 16 of whom received LA decompression by means of transthoracic LA cannulation, with either a straight or right-angled venous cannula, placed via the right-side LA approach. Removal of the cannula was achieved in 81.3% of them [16]. In another pediatric experience Hacking et al. decompressed the LA via a cannula inserted into the dissected Waterston groove in 39 children [17]. To summarize, different approaches can be chosen, with variable outcomes, to vent the LV in patients with an open chest and central ECMO configuration.

***Table 1.***

| | Author | Year | Experience | Approach | Location | Patient(s) | Mechanism of unloading | Technique |
|---|---|---|---|---|---|---|---|---|
| Pediatrics | | | | | | | | |
| | Kotani | 2013 | Retrospective Study | Surg | LA | 23 | LA unloading | right-side LA cannula***(OC) |
| | Hacking | 2015 | Retrospective Study | Surg | LA | 51* | LA unloading | LA cannula (dissected Waterston groove ) *** (OC) |
| | Sandrio | 2014 | Case series | Surg | LV | 8 | LV unloading | Cannula (right superior Vein) in LV (OC) |
| | Kimura | 2013 | Case report | Surg | LV/PA | 1 | Indirect and direct LV unloading | PA and LV drainage (OC) |
| | Guirgis | 2010 | Case report | Surg | LV | 1 | LV unloading | Cannula in the cardiac apex (MI) |
| | Fouilloux | 2011 | Case report | Perc | PA | 1 | Indirect LV unloading | PA drainage |
| | Cheung | 2003 | Case report | Perc | LV | 1 | LV unloading | BBAS, cannula via ASD |
| | Vlasselaers | 2006 | Case report | Perc | LV | 1 | LV unloading | Impella |
| Adults | | | | | | | | |
| | Eudailey | 2015 | Case report | Surg | LV | 1 | LV unloading cannula | Cannula in the cardiac apex (MI) |
| | Weymann | 2014 | Prospective Study | Surg | LV | 12 | LV unloading cannula | Cannula (right superior Vein) in LV (OC) |
| | Alkhouli | 2016 | Case series | Perc | LV | 4 | LV cannula | Transseptal puncture ± balloon dilatation |
| | Haynes | 2009 | Case report | Perc | LA | 1 | ASD Shunt | ASD with stenting |
| | Avalli | 2011 | Case report | Perc | PA | 1 | Indirect LV unloading | PA drainage |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Barbone | 2011 | Case report | Perc | LV | 1** | LV unloading | Trans-AO Cannula |
| Hong | 2016 | Retrospective Study | Perc | LV | 7 | LV unloading | Trans-AO Cannula |
| Fumagalli | 2004 | Case report | Perc | LV | 1 | LV unloading | Trans-AO Cannula |
| Doll | 2004 | Prospective Study | Perc | Aorta | 144 | Reduced LV afterload and LVEDP | IABP |
| Ma | 2014 | Retrospective Study | Perc | Aorta | 54 | Reduced LV afterload and LVEDP | IABP |
| Park | 2014 | Retrospective Study | Perc | Aorta | 41 | Reduced LV afterload and LVEDP | IABP |
| Santise | 2014 | Retrospective Study | Perc | Aorta | 13 | Reduced LV afterload and LVEDP | IABP |
| Yang | 2014 | Prospective Study | Perc | Aorta | 12 | Reduced LV afterload and LVEDP | IABP |
| Cheng | 2015 | Meta-Analysis | Perc | Aorta | 1517 | Reduced LV afterload and LVEDP | IABP |
| Ro | 2014 | Retrospective Study | Perc | Aorta | 60 | Reduced LV afterload and LVEDP | IABP |
| Gass | 2015 | Retrospective Study | Perc | Aorta | 56 | Reduced LV afterload and LVEDP | IABP |
| Petroni | 2014 | Prospective Study | Perc | Aorta | 12 | Reduced LV afterload and LVEDP | IABP |
| Samadi | 2015 | Retrospective Study | Perc | Aorta | 3 | Reduced LV afterload and LVEDP | IABP |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Lin | 2016 | Retrospective Study | Perc | Aorta | 302 | Reduced LV afterload and LVEDP | IABP |
| | Cheng | 2013 | Retrospective Study | Perc | LV | 5 | LV unloading | Impella |
| | Pappalardo | 2016 | Retrospective Study | Perc | LV | 34 | LV unloading | Impella |
| | Koeckert | 2011 | Case report | Perc | LV | 1 | LV unloading | Impella |
| | Li | 2013 | Case series | Perc | LA | 5 | LA unloading | TandemHeart |
| Mixed | | | | | | | | |
| | Seib | 1999 | Retrospective Study | Perc | LA | 10 | ASD Shunt | BBAS |
| | Aiyagari | 2006 | Case series | Perc | LA | 7 | LA unloading | Transseptal puncture+ LA cannula |

**Table1. Included studies.** Legend: Perc, percutaneous; Surg, surgical; LV, Left Ventricle, LA, left Atrium; AO, aorta; IABP, Intra-Aortic Balloon Pump; PA, pulmonary artery, LVEDP, Left Ventricle End Diastolic Pressure, BBAS, blade and balloon Septostomy; ASD, Atrial Septal Defect; OC, Open Chest; MI, Minimal Invasive

* 51 cases, 49 patients, ** the Authors treated 3 patients treated, only one was described, ***Mixed tech

**Minimally invasive surgical techniques**

In case of application of a peripheral V-A ECMO configuration, LV unloading may be performed using minimally invasive techniques. There are two main surgical techniques: the subxiphoidal approach and the anterolateral approach. The subxiphoidal technique was described by Guirgis et al.; firstly, the left apex must be exposed, thus this technique is mostly reserved for patients after cardiac surgery, who have already received a median incision. After the apex is exposed, a 16-20 French cannula or sump suction is implanted in the LV, and the tunnelled through a subxiphoidal incision to the extracorporeal side [18]. Conversely, Cheung et al proposed the left anterolateral thoracotomy. This approach might be particularly useful when peripheral ECMO is utilised. The vent cannula is placed in the apex by means of fluoroscopy or under echocardiographic guidance [19].

Finally, Eudailey et al reported a singular approach characterized by cannulation with a transdiaphragmatic LV venting [20].

All of these procedures are not technically simple and expose the patient to a number of potential complications including laceration of the myocardial wall or damage to the epicardial coronary arteries.

**Percutaneous Venting of the Left Ventricle**

LV decompression can also be achieved by a percutaneous approach, using several techniques: anterograde venting of the left ventricle through the pulmonary artery drainage or retrograde venting through the aortic valve and atrial septostomy. The vent cannula is usually connected to the inflow section of the ECMO circuit.

**Pulmonary Artery drainage**

Pulmonary drainage consists in the placement of a venous cannula into the main pulmonary artery, connected to the inflow ECMO cannula [21] [22].

Avalli et al. described a case of a 43-year-old woman, connected to ECMO for refractory cardiogenic shock after pneumonia and severe sepsis. Trans-oesophageal echocardiography clearly demonstrated the overload of the dilated left ventricle with an intraventricular clot. For these reasons, a 15F venous cannula was placed percutaneously in the pulmonary artery and connected to the venous limb of the ECMO circuit to unload the left ventricle. The cannula was then removed via the superior vena cava on day 9. Subsequently, the ECMO was suspended on day 16 and the patient, was successfully discharged after 30 days from admission showing signs of myocardial recovery [21].

Fouilloux et al. reported a case of a two-year-old girl affected by restrictive cardiomyopathy. LV unloading was obtained with a 10F cannula inserted into the pulmonary trunk through the inferior vena cava with a femoral approach. The procedure was fluoroscopy guided and complication free. A few hours later, the transthoracic echocardiography showed successful unloading of the left ventricle, with the pulmonary artery cannula removed five days later [22].

**Trans- aortic Left Ventricular Unloading**

Trans-aortic catheter venting (TACV) is an alternative percutaneous venting method, performed during V-A ECMO, in which the venting cannula is usually connected to the ECMO venous line.

Hong et al. retrospectively reviewed 7 patients who underwent both ECMO and TACV. This technique consisted of the insertion of a 5–6 French pigtail trans-aortic catheter directly into the LV cavity, across the aortic valve using a trans-femoral approach under trans-thoracic echo guidance.

Finally, the TACV was connected to the venous limb of the ECMO circuit. No procedure related complications were reported. The survival rate was 58% and a significant difference between pre- and post-TACV LV end-diastolic diameter was identified, demonstrating that TACV might be an acceptable alternative to venting procedures [23].

LV unloading, with a 7 French pigtail catheter inserted by means of a trans-aortic route into the LV via the femoral artery contralateral to the arterial outflow cannula, was performed by Barbone et al in 3 patients with car¬diogenic shock due to acute myocardial infarction.

The procedure was performed in the catheterization laboratory at the time of V-A ECMO initiation. This approach resolved LV distension and prevented lung congestion without major complications [24].

Fumagalli et al. proposed an alternative percutaneous approach. Using a J-tipped wire, inserted into the left ventricle via the subclavian artery, a 17 French pediatric cannula was placed into the LV through the aortic valve under fluoroscopic guidance.

Blood drained from the LV was thereafter pumped into the femoral artery. LV unloading was successfully achieved and pulmonary oedema was finally solved. Heart transplantation was performed after 7 days of ECMO support [25].

**Trans-septal Venting**

The presence of a left-to-right shunt due to atrial communication (for example, as a result of atrial septal defects or patent foramen ovale) may positively influence the hemodynamic balance in the setting of V-A ECMO support associated with LV overloading representing a favourable exit route in the presence of increased left-side pressure as in cardiogenic shock or cardiac arrest.

Atrial communication can be artificially induced using percutaneous techniques and, as such, used as protective mean to reduce left heart overloading.

Aiyagari et al. presented their approach, characterized by V-A ECMO with a LA drain, incorporated into the ECMO venous circuit. This technique consisted of performing a trans-septal puncture and placing a LA drain (8-15 French). Seven patients (age range from 8 months to 28 years) with cardiac failure and LA hypertension were treated. The procedure was feasible and free from major complications in all patients. Five patients showed echocardiographic improvement in LA dilation. Four patients were successfully weaned and

three subsequently survived to hospital discharge. The authors stressed the importance of an adequately sized LA cannula for satisfactory unloading [26]. Other possibilities to unload the LA are blade or balloon septostomy [16, 27]. Seib et al. for example, reported a series of 10 patients with severe LV failure who required V-A ECMO support.
Left heart decompression with blade and balloon atrial septostomy (BBAS) was performed in 9 cases, while one patient had a patent foramen ovale. The feasibility was 100% and the procedure led to LV decompression and pulmonary decongestion. The survival rate was 70% [27].
Kotani et al. depicted dramatic improvement in LA pressure immediately after balloon atrial septostomy in four patients on ECMO support who required LV decompression [16]. In addition, there are several cases in the literature describing the use and efficacy of these techniques, either in isolation or in combination with additional venting options [28, 29] .
Atrial communication patency can be maintained by means of atrial stenting. The major advantages of this procedure are the possibility to define the size of the atrial shunt and, obviously, the preservation of flow over time. Atrial stenting is, however, not free from complications such as stent malposition which is dangerous for the adjacent anatomical structures. Furthermore, in order to close the defect surgical correction is usually required [30].

**Indirect Left Ventricular Unloading through Intra-Aortic Balloon Pump**
The Intra-aortic balloon pump (IABP) is able to decrease LV afterload and increase arterial diastolic pressure, concomitantly increasing coronary blood flow [31]. Its use is controversial, in particular the SHOCK II trial didn't demonstrate any survival benefits derived from the application of the IABP in patients suffering from cardiogenic shock [32].
The role of counter-pulsation in V-A ECMO support seems even more controversial. Starting from animal models, Sauren et al. showed that ECMO support with the addition of IABP counterpulsation may improve LV performance [33]. On the contrary, Bělohlávek et al. concluded their elegant study declaring that the combination of V-A ECMO/IABP with femo-femoral approach may impair coronary perfusion [34].
Despite these findings, IABP in combination with ECMO is still being widely used in clinical practice. Doll et al, for example, treated 144 patients after cardiac surgery with IABP during V-A ECMO. The use of IABP was associated with a significantly higher survival rate and the use of IABP was ultimately an independent predictor of in-hospital survival [35].
Moreover, Gass et al. studied 135 patients in such a setting; overall in-hospital survival was 57.8%. Prior IABP use was an independent predictor of a reduction in-hospital mortality, as well as a reduced risk of both stroke and vascular injury [36].
Accordingly, Ma et al described improvements in several hemodynamic parameters in 54 adults with acute heart failure who received V-A ECMO and IABP support [37]. Santise at al. reported the outcomes of V-A ECMO support

in patients after heart transplantation who developed primary graft failure. The weaning rate and survival were both higher in the group with additional IABP support [38].
Despite these results, the positive role of IABP has not been consistently confirmed. Ro et al., for example, illustrated that there was an increase in successful extra corporeal life support weaning rate associated with IABP use, however this did not translate into an improvement in survival [39].
Additionally, Park et al. did not find any differences in in-hospital survival in 96 patients with acute myocardial infarction complicated by cardiogenic shock, treated with this combination strategy [40].Again, the same conclusions were reported by Lin et al. in 529 patients (227 used ECMO alone and 302 combined IABP plus V-A ECMO)[41].
Finally, the largest data set currently available regarding the use of V-A ECMO plus IABP has been derived from a meta-analysis performed by Cheng et al. which included a total of 1517 patients. The use of IABP on top of ECMO support did not appear to be associated with a relevant or significant change in survival outcomes, even in the acute myocardial infarction subgroup or when it was placed prior to ECMO initiation [42].

**Devices Related to Left Ventricular Unloading**
Minimally invasive implanted extracorporeal left ventricular Assistance device (LVAD) provides the unique possibility to completely or significantly unload the LV. Impella (Abiomed Inc, USA) is a catheter-based transaortic axial flow pump, placed percutaneously through a femoral approach. The device is available in different sizes, in relation to their capacity to guarantee different L/min support (ranging from 2,5 to 5 L/min). Its usefulness in cardiogenic shock is well known, although a very recent study showed that there was no benefit of the Impella device over conventional IABP in patients experiencing cardiogenic shock in the setting of acute myocardial infarction [43].
Some case reports have previously been published about the concomitant use of Impella and V-A ECMO support, also in paediatric patients [9, 44] .
Recently Pappalardo et al. reported about 157 patients treated with V-A ECMO, 34 of whom received concomitant treatment with the Impella device. After propensity score matching, 21 patients treated with V-A ECMO and Impella were analyzed. The V-A ECMO and Impella group showed significantly lower in-hospital mortality (47% vs. 80%, $P < 0.001$) and a higher rate of successful bridging to either recovery or further therapy (68% vs. 28%, $P < 0.001$] compared to V-A ECMO alone patients [45].
Cheng et al described a decreased LV end-diastolic diameter, measured by echocardiography, in 5 patients undergoing V-A ECMO together with Impella implantation. Four of the five patients were successfully transitioned to HeartMate II LVAD [46].
The main and well known limitation of Impella is represented by hemolysis [47]. This was confirmed by Pappalardo et al. In fact, the V-A ECMO and Impella group clearly showed an increased hemolysis (76% vs. 33%, P =

0.004). However, no differences were found in the rates of major bleeding [45]. TandemHeart (Cardiac Assist, Inc., Pittsburgh, PA) may represent another option to decompress the LV ventricle. This device has two cannulas: the inflow cannula drains blood from the left atrium and the other pumps blood into the aorta via a femoral access point. The inflow cannula is trans-septally placed into the LA via the femoral vein. Li et al previously reported a case series of 5 patients treated with TandemHeart and V-A ECMO, however only two survived at the time of discharge [48].

**Concluding Remarks and Perspectives**

Percutaneous V-A ECMO is increasingly placed in patients with refractory cardiogenic shock[49]. The majority of the selected papers confirmed such a growing interest in this option over time, except if LV unloading is required after cardiac surgery.A previous or concomitant open-chest condition predisposes to surgical LV unloading techniques. In fact,16% of our papers reported surgical LV venting, using open chest surgery (71%) or minimally invasive techniques (29%).According to the classification of unloading techniques [10], the most common locations of unloading were the LA (31%), followed by the Aorta/IABP (27%) and trans- aortic (27%).The LV itself (11%) and the pulmonary artery (4%) were also used for unloading (*Figure 2*).

***Figure 2.***

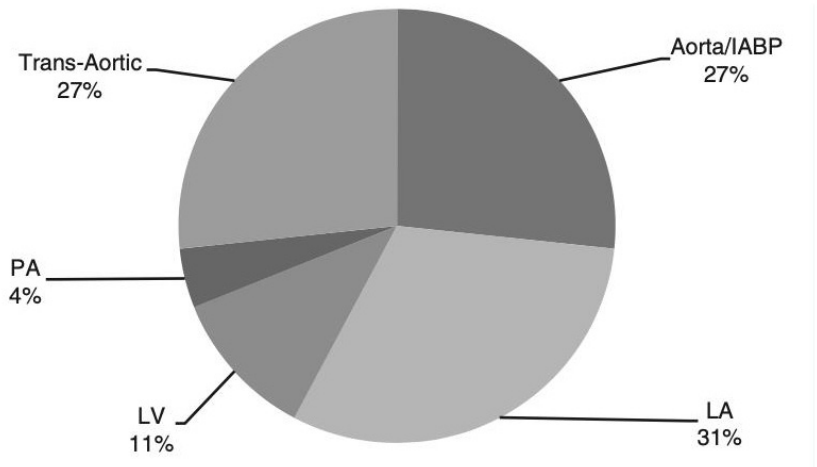


***Figure 2.*** **Location of LV Unloading.** LV, Left Ventricle, LA, left Atrium; IABP, Intra-Aortic Balloon Pump; PA, pulmonary artery

Overall, two considerations should be made. Firstly, despite the well-known controversies, IABP remains widely used in combination with V-A ECMO. Recently, Cheng et al. showed that this combination is not associated with relevant and significant changes in survival outcomes [42] .
However, Petroni et al showed that adding an IABP to peripheral V-A ECMO was associated with improved LV function.
Moreover, discontinuation of IABP was associated with smaller LV dimensions and lower pulmonary artery pressures but did not affect microcirculation. In other words, IABP seemed to provide additional support to LV function or at least to enhance LV unloading during V-A ECMO support [50].
On the contrary, the IABP's influence on the cerebral circulation appears to be negative.
Yang et al, for example, showed that IABP significantly decreased mean cerebral blood flow during myocardial stunning [51] and, similarly, Samadi et al. described 3 cases of spinal cord infarction during concomitant circulatory support with IABP and V-A ECMO [52]. These findings might explain the absence of influence on survival found in the other published studies However further randomized control studies would be required to show the true benefit of the combination of the two modalities.
In conclusion, 60% of the selected papers evaluated in this study were case reports or case series, demonstrating that the evidence available on this subject remains very limited. LV venting is becoming increasingly important or applied.
Thus, we strongly believe that adding a specification of the venting modality into the nomenclature of ECMO configuration should be advisable. The agreed method to add this specification might be a relevant task for ELSO and related organizations.
Lack of knowledge cannot lead us to better define this dilemma. Grounded data are therefore needed regarding the hemodynamic and physiological changes deriving from each method, and therefore raises the question of the need for further basic research in this domain using suitable animal or simulation models.

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# Chapter 3.

## Protracted aortic valve closure during peripheral veno-arterial extracorporeal-life support: is intra-aortic balloon pump an effective solution?

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**Abbreviations**
AV, aortic valve
DBP, diastolic arterial blood pressure
ECG, electrocardiogram
HR, heart rate
IABP, intra-aortic balloon pump
LV, Left ventricular
LVAD, left ventricular LV assistance device
SBP, blood pressure, systolic
TVP, transvalvular pressure
V-A ECMO, veno-arterial extracorporeal membrane oxygenation
VTI, velocity time integral

**Abstract**

**Background**

Left ventricular (LV) afterload increase with protracted aortic valve (AV) closure may represent a complication of veno-arterial extracorporeal membrane oxygenation (V-A ECMO).

The aim of the present study was to assess the effects of intra-aortic balloon pump (IABP) to overcome such a hemodynamic shortcoming in patients submitted to peripheral V-A ECMO.

**Methods**

Among 184 adult patients who were treated with peripheral V-A ECMO support at Medical University Center Maastricht Hospital between 2007 ad 2018, patients submitted to IABP implant for protracted AV closure after V-A ECMO implant were retrospectively identified. All clinical and hemodynamic data, including echocardiographic monitoring, were collected and analyzed.

**Results**

During the study period, 10 subjects (mean age 60 years old, 80% males) underwent IABP implant after peripheral V-A ECMO positioning due to the diagnosis of protracted AV closure and inefficient LV unloading as assessed by echocardiographic and an absence of pulsation in the arterial pressure wave. Recovery of blood-pressure pulsatility and enhanced LV unloading were observed in 8 patients after IABP placement with no significant differences in the main hemodynamic parameters, inotropic therapy, or in the ECMO flow (p=0,48). The weaning rate in this patient subgroup (mean ECMO duration 8 days), however, was only 10%, with another patient finally transplanted, leading to a 20% survival-to-hospital discharge.

**Conclusion**

IABP placement was an effective solution in order to reverse the protracted AV closure and impaired LV unloading observed during peripheral V-A ECMO support. However, the impact on the weaning rate and survival needs further investigations.

**Introduction**

Veno-arterial extracorporeal membrane oxygenation (V-A ECMO) has been widely employed for refractory cardiogenic shock and cardiac arrest. V-A ECMO may be quickly assembled and implanted, has limited costs as compared to other mechanical circulatory support devices, and allows the attending physicians to temporarily stabilize the compromised hemodynamic conditions while providing a bridge to recovery or to other more durable treatments [1,2]. V-A ECMO, therefore, is a useful circulatory support system but has shortcomings. One of these is the effect of retrograde aortic flow from the ECMO system on the left ventricle (LV) afterload and unloading. This counter-stream blood flow variably increases the afterload of the already impaired LV [3]. This can lead to reduced LV ejection and dilatation, higher pressure within the LV, left atrium and pulmonary veins, leading to stasis in the left cardiac chambers with thrombosis and clot formation, and pulmonary oedema [4]. In the worst cases, the LV will be unable to overcome the ECMO generated counter-flow and pressure leading to a protracted closed aortic valve (AV). Based on these aspects, LV unloading during V-A ECMO may represent, therefore, either a critical aspect to be monitored or an indication for adjunctive unloading procedures [5]. Echocardiographic monitoring is a cornerstone of V-A ECMO management, and, besides the information of ongoing LV function, is paramount to assess LV unloading and define the extent of blood stasis in the left cardiac cavities (echo contrast, named “smoke-like” effect), thereby indicating the need of ancillary unloading maneuvers [6,7,8,9]. Nowadays here are several techniques, of varying aggression and complexity, which aim to unload the LV [5]. Those are classified either according to their surgical/percutaneous approach or considering the anatomical unloading location. However, the optimal technique and the target patient population who will actually benefit from venting procedures remain unclear [5].The majority of patients who are supported with V-A ECMO do not apparently require LV unloading although the actual prevalence and the potential benefit of a widespread use of the use of LV unloading techniques might be relevant,but are currently are unknown [10].Since the Extracorporeal Life Support Organization Guidelines for Adult Cardiac Failure recommend that the intra-aortic balloon pump (IABP) should be placed as an additional support to ECMO, it is used and are routinely placed at the initiation of ECMO at many medical centers [11,12,13,14,15]. From the physiological point of view, IABP should support positively the myocardial ejection by reducing the increased afterload. However, many studies have not shown a consistent effect on survival and thus the evidence for the additive benefit of IABP therapy is limited or controversial [16,17]. Despite the lack of clarity, the practice of adopting concomitantly the IABP with ECMO is widespread [18], but no evidence is available about the effect of IABP on AV function, particularly in the situation of absence of valve opening. The aim of the present study, therefore, was to assess the impact of IABP in patients submitted to peripheral V-A-ECMO presenting protracted AV closure with or without clear sign of LV stasis and increased pressure in the left cardiac chambers due to increased LV afterload.

**Methods**

*Patient series*

In the period from January 2007 to January 2018 at the Maastricht University Medical Center, peripheral V-A ECMO support was implanted in 184 adult patients for severely impaired cardiovascular conditions. All patient data were analyzed in relation to etiology of cardiovascular illnesses, clinical and hemodynamic conditions at ECMO implant and thereafter, ECMO management and in-hospital outcome. Particularly, echocardiographic and blood pressure curve evaluation soon after temporary support placement and subsequent examinations were reviewed in order to highlight the presence of an effective or partial AV opening, or the confirmation of a permanent closure of the same valve or any other hemodynamic as well as radiographic signs of blood stasis. Efficacy of LV ejection was also assessed by velocity time integral (VTI) assessment. The patient informed consent was waived in this study based on the retrospective nature of the research, by the patient status at the time of data recordings (patients intubated and sedated), and by the used of routine parameter recording and diagnostic tool.

*IABP and ECMO placement Method and Management*

For all patients, the contra-lateral femoral artery of the V-A ECMO cannulation site was cannulated for balloon placement (Seldinger method). If feasible (no major resistance at IABP passage through the small skin incision), a sheathless technique was used to reduce the incidence of leg ischemia. The tip of the balloon was placed 1 cm distal to the junction with the left subclavian artery, as assessed by echocardiographic assessment and by mobile chest x-ray system at bed-side.Either the electrocardiogram (ECG) or the aortic blood pressure curve was used as a trigger; for the ECGs, the descending section of the R wave (representing closing of the AV) was used to calibrate the counter-pulsation interval, with an IABP ratio of 1:1. If the patient showed low dependence on positive inotropic drugs, the IABP ratio was gradually reduced to 1:3 accompanied by half an hour of observation; if circulation was steady, the IABP was removed. The Rotaflow (Getinge, Hirrlingen, Germany) was the centrifugal ECMO pump used in all patients who underwent peripheral V-A ECMO.

*Hemodynamic Data Collection*

Hemodynamic parameters were collected at the following time points: a few hours before, and just prior to and after a few minutes after IABP placement. The following data were collected: pulsatility of arterial systemic blood pressure, mean arterial blood pressure, systolic (SBP) and diastolic arterial blood pressure (DBP), heart rate (HR), ECMO flow and echocardiographic evaluation of the AV closure. The pre-IABP ECMO Flow and the inotropic therapy reflected the average of the last six hours. By contrast, the post IABP ECMO flow was recorded simultaneously with the echocardiographic evaluation.

*Statistical Analysis*
The SPSS 23.0 (IBM Corp., Armonk, NY, USA) statistical program was utilized for statistical analysis. Continuous variables at different time points were examined with paired t-tests, with $P < 0.05$ considered statistically significant.

**Results**
From the overall peripheral V-A ECMO population, 44 patients received combined IABP and V-A ECMO. Of these patients, 10 subjects underwent IABP implant after variable time from V-A ECMO positioning due to the diagnosis of protracted AV closure as assessed by echocardiographic evidence of the AV dysfunction and inefficient LV unloading, as well as absence of pulsatility at blood pressure curve monitoring. Patient demographic data are shown in *table 1*.
The mean age was 60 years old and 80% were males. Patient etiologies included 3 post-cardiotomy and 2 Out Hospital Cardiac Arrest.

***Table 1.***

| | Age | Gender | Etiology | ECMO access | ECMO duration | Wean-ing | In-l CU survival |
|---|---|---|---|---|---|---|---|
| **1** | 69 | F | OHCA,STEMI | Peripheral | 2 | No | Died |
| **2** | 74 | M | CS, Rupture papillary muscle | Peripheral | 9 | No | Died |
| **3** | 59 | M | PC, Endocarditis | Peripheral | 3 | No | Died |
| **4** | 54 | M | OHCA, CAD | Peripheral | 2 | No | Died |
| **5** | 52 | M | CS,Endocarditis | Peripheral | 19 | No | Died |
| **6** | 67 | M | Type A dissection | Peripheral | 3 | No | Died |
| **7** | 61 | M | Lymph Myocarditis | Peripheral | 21 | Yes | Discharged |
| **8** | 70 | M | PC, Aortic disease | Peripheral | 7 | No | Died |
| **9** | 45 | M | AHF, ARVC | Peripheral | 1 | No | Discharged |
| **10** | 52 | F | PC,David procedure | Peripheral | 17 | No | Died |

***Table 1.* Demographic data.** Legend: F, female; M,male; OHCA, out hospital cardiac arrest; STEMI, ST elevation myocardial infarction; CS, cardiogenic shock; Lymph, lymphocitic; PC, post cardiotmoy; CAD, coronary artery disease; AHF, acute heart failure; ARVC, arrhythmogenic right Ventricular cardiomyopathy

*Table 2* illustrates the parameters collected exactly before and subsequent to the IABP placement. No significant differences (p>0,05) were found neither in the hemodynamic parameters, such as mean systemic arterial blood pressure and HR or in the inotropic therapy, nor in the ECMO flow details as recorded just pre- and immediately after IABP implant (p=0,48).

As shown in *Table 2*, IABP implant was able to reverse 80% of the cases of protracted AV closure, as confirmed by recovery of systemic arterial blood pressure pulsatility and restored AV opening at echocardiographic assessment performed after IABP placement.

Only two patients showed no benefit from IABP implant regarding AV function. Both patients required immediately a further LV unloading due to rapid progression to frank pulmonary oedema, solved by placing an additional draining cannula in the pulmonary artery.

In addition, another patient, despite an initial successful restoration of the AV opening after IABP implant, required the positioning of the cannula into the pulmonary artery after 48 hours for a new evidence of protracted AV closure and echocardiographic signs of intraventricular blood stasis.

***Table 2.***

| | Pre MAP | HR | post SBP | post DBP | Post HR | pre ECMO flow | Post ECMO flow | Inotropes | Pre AV | post AV | Further Unloading |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **1** | 72 | 90 | 85 | 40 | 91 | 3,5 | 3,4 | NOR 0,9 | Close | Open | |
| **2** | 71 | 105 | 80 | 41 | 90 | 3,9 | 3,7 | NOR 0,18 | Close | Open | |
| **3** | 40 | 92 | 78 | 51 | 89 | 3,8 | 4,1 | ADRE 5<br>NORA 0,7 | Close | Close | PA |
| **4** | 67 | 92 | 112 | 62 | 92 | 3,3 | 3,1 | NORA 0,1 | Close | Open | |
| **5** | 49 | 86 | 101 | 40 | 86 | 3,8 | 5,4 | NORA 1,1 | Close | Open | |
| **6** | 70 | 95 | 126 | 59 | 95 | 3,1 | 3,1 | DOBU 10<br>ADRE 0,3<br>NOR 0,5 | Close | Open | |
| **7** | 50 | 72 | 80 | 50 | 64 | 4,2 | 4,2 | NOR 0,25 | Close | Open | |
| **8** | 58 | 80 | 70 | 40 | 80 | 5,0 | 4,1 | NOR 0,8 | Close | Close | PA |
| **9** | 77 | 127 | 95 | 47 | 85 | 3,1 | 4,3 | NOR 0,08 | Close | Open | |
| **10** | 42 | 90 | 70 | 35 | 96 | 4,2 | 4,2 | MIL 0,5<br>NOR 1 | Close | Open | PA |

***Table 2.*** **Parameters pre and post IABP placement.** SBP, DBP (mmHg), HR (bpm), flow (L/min), inotropes ( mcg/kg/min)
Legend: Pre, before IABP insertion; Post. After IABP insertion; SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure; HR, Heart Rate; AV, aortic valve; NOR, noradrenaline; ADRE, adrenaline; DOBU, dobutamine; PA, pulmonary artery cannula.

Mean V-A ECMO duration was 8 days (1-21 days). As expected, the resolution of the permanent closure of the AV was shown not to represent the only factor for favorable in-hospital patient outcome. As shown in *table 1*, the V-A ECMO-weaning rate in this patient subgroup was only 10%, with one patient eventually transplanted at another center, leading to a final survival-to-hospital discharge of 20%.

**Discussion**

The case series presented in this study is unique since it is the first collection of data regarding the onset and detection of a clear hemodynamic shortcoming of V-A ECMO, namely the protracted AV closure due to the combination of poor LV function and retrograde flow generated by the ECMO system towards the AV.

Furthermore, we were able to demonstrate that the IABP insertion is capable of overcoming such a relevant adverse event, although such a positive effect was not obtained in all cases.

The resolution of such a hemodynamic ECMO-related drawback is only one of many factors which lead to the favorable or unfavorable patient outcome and the IABP effect on AV function.

During peripheral V-A ECMO, LV afterload significantly increases. Such a condition may be poorly tolerated by an already dysfunctional LV, leading to AV dysfunction and left cardiac chamber distension [19].

Evidence from patients undergoing LV assistance device (LVAD) implant indicate the

biomechanics of the AV is often altered in this condition with the appearance of AV insufficiency [20,21,22]. LVAD-related continuous flow may also induce protracted AV closure which, if present for months, may ultimately lead to leaflet fusion and, therefore, to irreversible AV closure [22]. This pathophysiological condition is similar to what it is observed in V-A ECMO patients regarding protracted AV closure. The ECMO pumps blood directly into the aorta, increasing the aortic pressure. This leads to increased pressure difference between the aortic root and the LV, also known as the transvalvular pressure (TVP) of the AV [ 22,23].
The valve opens when the TVP is near zero and closes under pressure load. The continuous increased aortic pressure from the V-A ECMO raises the TVP, consequently if the LV function is poor the AV opening will be impaired. As a result, the latter is an early sign of insufficient LV unloading. Obviously, the usual short duration of V-A ECMO is not sufficient to induce structural valve changes as observed in LVAD patients but may still lead to dangerous pre or post-valvular blood stasis in the extreme cases of protracted AV closure. Echocardiography can detect and help manage such complications and hemodynamic alterations that may arise during ECMO support [24,25,26]. We propose the echocardiographic evaluation of LV loading should have two components. First, the anatomic evaluation should briefly check the AV, the LV and the LA distensions and the vena cava inferior dilation. Second, discrete parameters should be collected. The velocity time integral might be measured at the LV out flow tract. An estimation of the pulmonary artery pressure should be recorded by defining the maximal jet velocity of the tricuspid backward flow [6]. Nevertheless, taking all into consideration, we speculate that AV function may allow classification of the degree of the LV overload *(table 3)*.

***Table 3.***

| Method | Factor | Grade of severity | | |
|---|---|---|---|---|
| **Arterial line** | | | | |
| | Arterial Pulsatility | Mild weakness | Moderate weakness | Almost Pulseless |
| **Central venous Line** | | | | |
| | $ScvO_2$ | 75-55% | 55-45% | <45% |
| | CVP (mmHg) | 8-12 | 12-16 | > 20 |
| **Echocardiogram** | | | | |
| | AV | Opening every 2 bpm | Opening every 3-4 bpm | Closure |
| | LV distension | Mild | Moderate | Severe |
| | LA distension | Mild | Moderate | Severe |
| | "Smoke like" effect | Mild | Moderate | Severe |
| | IVC dilatation[1] (cm) | 1.5 to 2.5 | >2.5 | >2.5 |
| | IVC collapse[2] | <50% | <50% | No change |
| **Swan Ganz Catheter** | | | | |
| | PCWP(mmHg) | 13-18 | 18-25 | > 25 |
| **Chest X-ray** | | | | |
| | Congestion[3] | Alveolar edema | Interstitial edema | Redistribution |

***Table 3.*** **Definition of left ventricle overload.**
Legend: ScvO2, Central venous blood oxygen saturation; CVP, central venous pressure, AV, aortic valve; bpm, beats per minute; LV, left ventricle; LA, left atria, PCWP, post capillary wedge pressure.
1 IVC diameter in inspiration (Hallemat (2013) Crit Dec Emerg Med 27(10): 14-2)
2 IVC collapse in expiration (Hallemat (2013) Crit Dec Emerg Med 27(10): 14-2)
3 classification according to Ravin CE Radiographic analysis of pulmonary vascular distribution: a review. Bull N Y Acad Med. 1983 Oct;59(8):728-43.

In the presence of severely impaired function or protracted closure of the AV, it is mandatory to timely act in order to prevent or limit related complications [5]. According to our experience, the IABP insertion might be considered as the first step in case of AV opening impairment and absence of arterial blood pressure pulsatility. However, the concomitant presence of other LV overloading signs, such as LV distension, smoke like effect or severe pulmonary congestion, should drive the decision-making towards more aggressive LV unloading techniques. Although the sample size is limited, our findings indicate that IABP has the ability to promote the AV opening.
Pulsatility was resumed in almost all patients, indicating that IABP may represent a valuable solution [27,28].
De Uil and colleagues showed a positive effect of IABP in a patient submitted to

V-A ECMO and surgically implanted venting [29]. Although some other studies experienced a positive IABP effect on the final outcomes [30,31], these were not consistently achieved in our study and one patient required an additional LV unloading technique. Little is known about the meaning of AV dysfunction during V-A ECMO, and how this might be considered as an early stage of the “overload continuum”. The latter could begin with a mere hemodynamic impairment, following by LV structural and anatomic alterations, ending up with irreversible complications, such as thrombosis and pulmonary edema. Therefore, preventing these V-A ECMO drawbacks should be an appropriate goal. Yet it is still unclear which LV unloading technique is indicated at what stage [5].
Further studies are urgently needed in order to define the actual rate of severey impaired LV unloading, the benefit of various venting maneuvers, the impact of LV unloading on timing and efficacy of LV functional recovery, and the influence of such a factor of ultimate patient outcome.

**Limitations of the study**
This study represents a retrospective analysis of a 10-year single-centre experience with a peripheral V-A ECMO configuration. The conduct of patient monitoring and hemodynamic recording, including AV assessment and detection of any sign of impaired LV unloading, received a gradual increase of attention and report during the study period. It is therefore likely the actual extent and rate of protracted AV closure, or partial opening, as well as incidence of blood stasis phenomena, have been underestimated. Some patients received already a LV venting (post-cardiotomy) and this may have reduced the blood stasis formation, although not impacting the AV behaviour. Patient causes of death were due to neurologic complication, multi-organ failure or sepsis. As well known, ECMO patient course and outcome is influenced and impacted by numerous events and mechanisms, making therefore extremely difficult any relationship between AV behaviour and ultimate patient outcome.

**Conclusion**
In conclusion, we were able to demonstrate that in a limited number of patients, the ECMO-related flow, with or without the association of an extremely poor LV function, may completely impede forward trans-aortic flow, thereby inducing a protracted closure of the valve leading to blood stasis upstream or just downstream of the AV itself. Besides several clinical and radiographic clues, the diagnosis of such an adverse event is made by lack of blood pressure curve pulsatility, followed by transthoracic or transesophageal echocardiography, in association with other clinical or diagnostic clues. The IABP implant will restore AV valve opening in in the majority of cases. Resolution of AV dysfunction, however, may not influence patient prognosis and needs further investigations.

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# Chapter 4.

## Trans-aortic or pulmonary artery drainage for left ventricular unloading and veno-arterial extracorporeal life support: a porcine cardiogenic shock model

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**Abbreviations**

CCO, continous cardiac output
CS, cardiogenic shock
ESPVR, end-systolic pressure-volume relationship
F, french
IABP, intra- aortic balloon pump
LA, left atria
LV, left ventricle
LVEDP, left ventricle end diastolic pressure
LVEDV, left ventricle end diastolic volume
LVESP, left ventricle end systolic pressure
LVESV, left ventricle end systolic volume
MCS, mechanical circulatory support
mPAP, mean pulmonary artery pressure
PA, pulmonary artery
PaCO2, arterial carbon dioxide pressure
PaO2, arterial oxyigen pressure
PCWP, post capillary wedge pressure
PE, potential energy
PVA, pressure-volume area
SW, stroke work
Tau, left ventricle isovolumic relaxation constant
V-A ECLS, veno-arterial extra- corporeal life support

**Background**
The peripheral veno-arterial extracorporeal life support (V-A ECLS) in cardiogenic shock increases afterload, therefore jeopardizing left ventricle (LV) recovery, leading to blood stasis and pulmonary edema. The aim of this study was to compare a trans-aortic suction device (Impella, ABIOMED Inc., Danvers, Massachusets) and pulmonary artery (PA) drainage, for LV unloading efficacy during V-A ECLS a porcine cardiogenic shock (CS) model.
**Methods**
A dedicated CS model included twelve swine (21± 1.8-weeks old and weighing 54,3 ± 4,6 kg) supported with V-A ECLS and randomized to Impella or PA-related LV drainage. LV unloading and end-organ perfusion were evaluated through the pulmonary artery catheter and LV pressure/volume analysis.
**Results**
Impella resulted in a marked drop of LVEDV compared to a slight decrease in the PA cannula group, resulting in an overall stroke work (SW) and Pressure-Volume Area (PVA) reductions with both techniques. However, SW reduction was more significant in the Impella CP group (V-A ECLS 3998.8±2027.6 mmHg x mL vs V-A ECLS + Impella 1796.9±1033.9 mmHg x ml, p value 0,016), leading to a more consistent PVA reduction (Impella reduction 34.7% vs PA cannula reduction 9.7%) In terms of end organ perfusion, central and mixed O2 saturation improved with V-A ECLS, and subsequently, remaining unchanged with either Impella or PA cannula as unloading strategy.
**Conclusions**
Trans-aortic suction and PA drainage provided effective LV unloading during V-A ECLS while maintaining adequate end-organ perfusion. Trans-aortic suction device provides a greater LV unloading effect and reduces more effectively the total LV stroke work.

**Background**

The use of mechanical circulatory support (MCS) has increased dramatically over the last 15 years. However, mortality in cardiogenic shock (CS) did not change in the same period, remaining at approximately 50% in affected patients [1,2]. One of the most frequently applied MCS in this setting is veno-arterial extracorporeal life support (V-A ECLS) [3]. Despite marked advances in this technology, several complications and inherent shortcomings may reduce the potential benefits of V-A ECLS. Among these side effects, increased afterload to the left ventricle (LV) represent a critical threat. This complication appears more frequently in peripheral V-A ECLS and may lead to LV dilatation, increases of LV and atrial (LA) end-diastolic pressures, and pulmonary oedema [4]. This LV and LA maladaptive change jeopardize LV recovery, particularly in the presence of ischemia-induced myocardial impairment. and, moreover, V-A ECLS negative hemodynamic effect on LV performance is flow dependent [5] justifying close LV function monitoring and early intervention [6]. In case of extreme overload and severe LV dysfunction, such a condition may lead to protracted aortic valve closure even during systole, causing blood stasis in the LV, LA, and aortic root, thus increasing the risk of thrombi formation [7]. It is therefore clear that the extent of LV unloading, and aortic valve opening should be continuously monitored to timely alert the attending personnel about such a potential negative impact of V-A ECLS on LV performance and indicate the actual need for less or more aggressive maneuvers to facilitate LV decompression [8].

Several approaches promoting LV unloading are being used clinically, non-invasive approaches like pharmacological interventions. More sophisticated strategies include surgical (invasive or minimally invasive) or percutaneous techniques.

The evidences regarding some of the most common techniques, such as intra-aortic balloon pump (IABP), Tandem-Heart, trans-septal venting, are extremely limited and variable [4]. Tandem Heart [9] and septostomy [10] reports include mostly case series, whereas a comprehensive meta-analysis performed by Cheng showed how the use of IABP in association with V-A ECLS did not associate with a significant change in survival outcomes [11]. Overall, the actual timing and effect on the patient outcome, as well as the different impact of the available type of interventions, however, remain unclear [4]. The use of trans-aortic suction device represents one of the most frequently adopted tool to achieve effective LV unloading in V-A ECLS [12]. Another promising technique accounts for an indirect LV unloading procedure by draining blood from the pulmonary artery (PA). Both techniques represent appealing tool since may be achieved with a percutaneous approach, but the actual difference in extent and impact on LV unloading and performance is still unknown [13,14].

Therefore, we designed an experimental study of CS managed by V-A ECLS in which the two techniques were randomly applied to assess the effects of both techniques on LV decompression and workload, together with the impact on overall ECLS-related end-organ perfusion.

**Method**

The study was approved by Charles University, First Faculty of Medicine Institutional Animal Care and Use Committee and was performed at the university laboratory in accordance with Act No 246/1992 Coll. on the protection of animals against cruelty that is harmonized with EU directives on the protection of animals used for scientific purposes.

*Instrumentation*

Briefly, twelve female swine, approximately 21± 1.8 weeks old, weighing 54.3 ± 4.6 kg, were randomized to transaortic suction device or PA cannula as LV unloading technique. The whole procedure was carried out under total i.v. anesthesia (propofol, midazolam, morphine). Initially, hemodynamic and oximetry monitoring systems, including cardiac pressure-volume catheter, were introduced. Then the V-A ECLS circuit was inserted in femoro-femoral percutaneous approach - arterial 15F HLS (Maquet), and 21F venous (Multi-hole, Maquet) accompanied by selected venting system: either Impella (Impella CP, Abiomed, Danvers, MA, USA) via contra-lateral femoral artery, or PA cannula (19F, 50 cm Biomedicus VR 9670-019, Medtronic, Minneapolis, MN, USA) via internal right jugular vein and connected to a Y-piece inserted info venous arm of extracorporeal membrane oxygentation (ECMO) circuit. Then, cardiogenic shock was induced by percutaneous coronary artery balloon-occlusion. Subsequently, stepwise ECLS-support protocol with and without LV unloading was performed. At the end of the protocol the support was withdrawn resulting in hemodynamic collapse thus confirming the severity of CS.

*Experimental protocol*

Both groups, PA and Impella, underwent identical protocol (see *figure 1*) with subsequent phases: baseline (BL), cardiogenic shock induction, stabilization, cardiogenic shock 1 (CS1) and cardiogenic shock 2 (CS2).Primary data were collected at phase BL and CS1 (or CS2), each lasting 100 min. In each of these phases, ECMO flow was stepwise increased every 20 minutes in increments of 20 ml/kg/min from minimum of 20 ml/kg/min up to the target maximum of 100 ml/kg/min (if achievable) yielding 5 flow levels. At each ECMO flow level, 10 minutes were not unloaded, followed by 10 minutes of LV unloading by respective method (PA of Impella). For PA unloading, the PA cannula was fully opened. For Impella unloading, the console was set to P4-P6 to achieve flow of 2 lpm. Thus, a total of 10 steps per each phase were performed.

***Figure 1.***

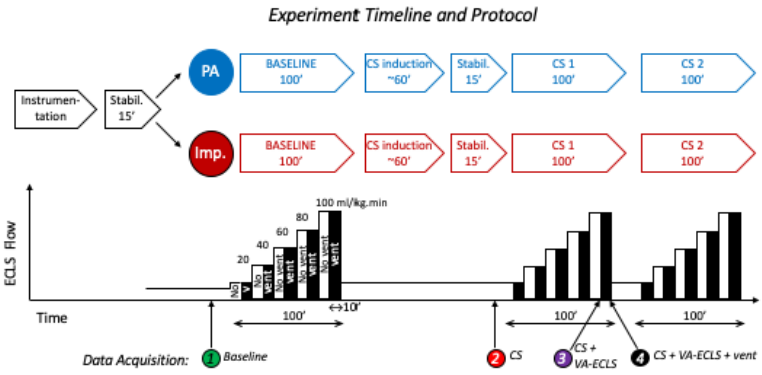


***Figure 1.*** **Experimental timeline and protocol.** Data acquisition consists in 4 main time point: baseline, no supported cardiogenic shock, cardiogenic shock supported with veno-arterial extracorporeal life support, and, finally, the support obtained with veno-arterial extracorporeal life support in association with individual left unloading methods.

At all times, V-A ECLS oxygenator flow and $FiO_2$ were set in order to keep target $PaO_2$ (120-150 mmHg) and $PaCO_2$ (≈ 40 mmHg). Norepinephrine was continuously administered whenever MAP dropped below 50 mmHg and was discontinued once MAP increased over 60 mmHg.

*Cardiogenic Shock model*

Proximal/middle left anterior descending coronary artery was occluded by a regular percutaneous coronary compliant balloon (4 x 20 mm). The balloon was kept inflated for at least 45 minutes (maximum 60 minutes).

The aim was to achieve a profound CS, defined as cardiac output < 50 ml/kg/min and/or a mixed venous oxygen saturation ≤50%. If the animal developed ventricular fibrillation during the induction phase, V-A ECLS flow was instituted in order to maintain a mean arterial pressure (MAP) at around 50 mmHg. At the end of the CS induction, in case of the presence of sustained ventricular malignant arrhythmia, defibrillation was performed (200J biphasic repeated as necessary) in order to restore sinus rhythm.

Circulation was always stabilized for at least 15 minutes and ECLS support was reduced to 20 ml/kg/min or minimum tolerated before CS protocol was initiated. In case that heart failure was recovering unexpectedly fast, ischemia induction was repeated.

*Data acquisition*

All parameters were continuously recorded by means of LabChart Pro (ADInstruments) software. Hemodynamic parameters as well as V-A ECLS data and PV relationships (LVEDP and LVEDV, PVA, ESPVR, Tau, SW, LV output) were extracted from continuous data at preset time points: 1. baseline, 2. CS (with minimum ECMO support), 3. CS with maximum V-A ECLS support alone and, 4. CS with maximum support plus Impella or PA cannula unloading.

Additionally, post-capillary wedge pressure (PCWP) and echocardiogram were acquired at end of each step.
In case that CS1 data were unavailable or unreliable due to technical issues, CS2 data were used instead.

*LV pressure-volume measurements*
A pressure-volume (PV) catheter 7F or 5F VSL (Transonic Systems Inc., Ithaca, USA) was percutaneously inserted through a 7-French sheath in the left carotid artery, advanced retrogradely into the LV, and connected to an ADV 500 PV System. The PV system was connected to a PowerLab 16/35 (ADInstruments, Dunedin, New Zealand) and the PV measurements were continuously recorded in LabChart Pro (ADInstruments). The conductance catheter acquired the following data: LV pressure, LV volume, phase, magnitude, while the LabChart Pro provided the calculations of multiple PV parameters: end-diastolic pressure (LVEDP, mmHg), LV end-diastolic volume (LVEDV, mL), LV stroke work (SW, mmHg×mL), LV end systolic pressure (LVESP, mmHg), LV end-systolic pressure-volume relationship (ESPVR, representing contractility), the LV isovolumic relaxation constant (Tau, representing ventricular relaxation) and pressure-volume area (PVA, mmHg×mL). PV data were extracted at the end of each step during expiration period, PV loops were averaged from three cycles.
The gold standard for estimating ESPVR and PVA is by preload reduction. However, this was not carried out in the current study for two reasons: first, the unsupported profound CS leading to severely compromised hemodynamics didn't allow any further pre-load reductions; second, preload changes during V-A ECLS support would cause a significant impact on ECMO device performance.
As a result, the latter may potentially influence device-derived afterload, making it difficult to define clearly whether ESPVR and PVA changes were influenced by the heart or by the device.
Therefore, Vo (the theoretical volume when no pressure is generated) was arbitrarily assumed as 0 in each animal and was kept as a constant throughout the study to generate single-beat estimations of ESPVR and PVA (see *figure 2*) [15,16].

***Figure 2.***

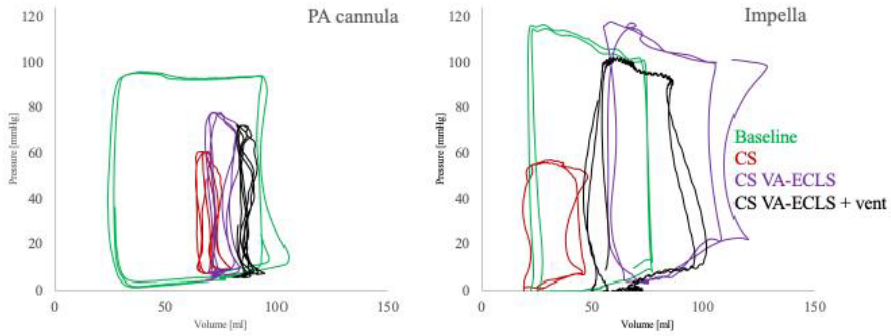


***Figure 2.*** **Different impact of pulmonary artery drainage and Impella on pressure/volume loops in two representative animals.** Impella is able to generate a more effective circulatory support and reduces the left ventricular overload. Pressure/volume loops at different protocol time points: baseline, cardiogenic shock (CS), V-A ECLS support (CS V-A ECLS) and its association with one of the left ventricular unloading techniques (CS V-A ECLS + vent).

*Statistical analysis*

The primary outcomes were LV performance, mainly defined as PVA, SW and potential energy (PE), and end-organ perfusion, described by the central and mixed O2 saturation.

Data are presented as mean (95% confidence interval) with error bars in the two figures of LVEDV and LVEDP over time representing standard error of the mean. Given the uncertainty of absolute values for LV volume using the conductance method, in order to better underline the specific unloading effect, a comparison between LV venting techniques was performed in terms of relative change from the CS state only supported with V-A ECLS.

Given the small sample size, the Wilcoxon rank-sum test was used to assess individual variable differences between the Impella or PA cannula and V-A ECLS at different time points. Statistical analyses were performed with SAS/STAT (SAS Institute inc., Cary, North Carolina, USA). A p-level ≤0.05 was considered statistically significant.

## Results

*Baseline characteristics*

There were no differences between Impella and PA cannula groups in the measured variables at baseline or at induced CS state.

***Table 1.***

| | Support | Max dosage (mcg/h) | Details |
|---|---|---|---|
| **Impella** | | | |
| **1** | Norepinephrine | 1600 | Suction |
| **2** | Norepinephrine | 50 | |
| **3** | | | Extra-beats, Tricuspid regurgitation |
| **4** | | | |
| **5** | | | |
| **6** | | | |
| **PA cannula** | | | |
| **1** | Norepinephrine | 1 | |
| **2** | Norepinephrine | 200 | |
| **3** | | | |
| **4** | Norepinephrine/Dopamine | 50/20 | Hemodynamic unstable Junction Rhythm |
| **5** | Norepinephrine | 500 | |
| **6** | Norepinephrine | 600 | |

***Table 1.*** **Experimental details in each animal.**

Two animals in the Impella group and five animals in the PA cannula group required norepinephrine (max dosage 1600 mcg/h) to maintain a mean arterial pressure (MAP) >50 mmHg after CS was established and fully supported by V-A ECLS in addition with one of the venting strategies.

Furthermore, one animal in the PA cannula group required dopamine (20 mcg/h) in addition to norepinephrine due to junctional rhythm leading to further hemodynamic instability (*Table 1*). V-A ECLS maximum flow did not significantly differ in both groups (4,0 ±0,1 L/min and 3,8±0,9 L/min -p-value>0,05, in Impella and PA cannula groups, respectively).

Complete circulatory collapse with pulseless electrical activity developed within a few minutes after withdrawal of MCS in all animals.

*Hemodynamics and end-organ perfusion*

V-A ECLS alone was able to increase significantly MAP during CS in all animals.

Mean PAP (mPAP) dramatically dropped by approximately 50% with PA cannula (V-A ECLS alone mPAP 24,3±11.2 mmHg vs V-A ECLS + PA cannula mPAP 12,4±5,0 mmHg, p value 0,015), whereas no significant decrease was recorded with Impella (V-A ECLS alone mPAP 23,6±6.4 mmHg vs VA ECMO + Impella mPAP 22,0±6.9 mmHg, p value 0,677). Both configurations led to a

modest (not significant) reduction in PCWP.
Finally, central and mixed O2 saturation, as markers of end-organ perfusion, improved with V-A ECLS, and subsequently remained stable steady in both groups throughout the experiment *(Table 2)*.

***Table 2.***

| | | V-A ECLS (mean±SD) | V-A ECLS +Vent (mean±SD) | p-value V-A ECLS vs V-A ECLS + vent | p-value Impella vs PA cannula |
|---|---|---|---|---|---|
| **MAP (mmHg)** | Impella | 74.9±15.7 | 71.6±11.8 | 0.680 | **0.603** |
| | PA cannula | 78.2±22.6 | 75.8±15.1 | 0.843 | |
| **HR (bpm)** | Impella | 99.3±36.8 | 97.0±31.8 | 0.908 | **0.669** |
| | PA cannula | 89.8±16.9 | 89.9±25.5 | 0.994 | |
| **SVcO2 (%)** | Impella | 85.2±4.6 | 87.0±5.0 | 0.552 | **0.209** |
| | PA cannula | 78.2±15.3 | 81.8±8.1 | 0.610 | |
| **SVmO2 (%)** | Impella | 86.0±5.8 | 87.8±5.8 | 0.623 | **0.342** |
| | PA cannula | 82.5±10.7 | 82.5±11.3 | 1.000 | |
| **PCWP (mmHg)** | Impella | 6.3±3.1 | 4.6±2.5 | 0.390 | **0.649** |
| | PA cannula | 6.7±2.4 | 5.3±0.9 | 0.339 | |
| **mPAP (mmHg)** | Impella | 23.6±6.4 | 22.0±6.9 | 0.677 | **0.005** |
| | PA cannula | 24.3±11.2 | 12.4±5.0 | **0.015** | |
| **cCO (L/min)** | Impella | 4.0±1.0 | 3.3±0.8 | 0.270 | **0.568** |
| | PA cannula | 2.8±1.0 | 2.9±1.2 | 0.886 | |

***Table 2.* V-A ECLS alone and its association with LV venting:** Hemodynamics and venous oxygen saturations. Bold value represents significance of p-value.

Mean PAP (mPAP) dramatically dropped by approximately 50% with PA cannula ( V-A ECLS alone mPAP 24,3±11.2 mmHg vs V-A ECLS + PA cannula mPAP 12,4±5,0 mmHg, p value 0,015), whereas no significant decrease was recorded with Impella (V-A ECLS alone mPAP 23,6±6.4 mmHg vs VA ECMO + Impella mPAP 22,0±6.9 mmHg, p value 0,677). Both configurations led to a modest (not significant) reduction in PCWP.
Finally, central and mixed O2 saturation, as markers of end-organ perfusion, improved with V-A ECLS, and subsequently remained stable steady in both groups throughout the experiment *(Table 2)*.

**Left ventricular unloading**
PV data are summarized in *Table 3*. After V-A ECLS implant and start, LVEDV, SW and PVA increased. Impella resulted in an immediate drop in LVEDV compared to a slight decrease in the PA cannula group, resulting in an overall SW and PVA reductions with both techniques (*see figure 3*).

However, SW reduction was significant only in the Impella group (V-A ECLS 3998.8±2027.6 mmHg x mL vs V-A ECLS + Impella 1796.9±1033.9 mmHg x ml, p value=0.015), leading to a more consistent PVA reduction (Impella reduction 34.7% vs PA cannula reduction 9.7%,). Furthermore, potential energy (PE) decreased by 14.8% with Impella support, whereas the PA cannula effect was negligible, showing an increasing trend (PE percentage reduction -1.2%). Two representative PV loops regarding Impella and PA cannula groups are shown in *figure 2.*

***Table 3.***

| | | V-A ECLS (mean±SD) | V-A ECLS + Vent (mean±SD) | p-value V-A ECLS vs V-A ECLS + vent | % change Vent | p-value Impella vs PA cannula |
|---|---|---|---|---|---|---|
| **LVEDV (ml)** | Impella | 143.6±67.4 | 123.9±75.7 | 0.633 | 13,7 | 0.855 |
| | PA cannula | 134.1±39.9 | 130.1±34.7 | 0.853 | 3,0 | |
| **LVESV (ml)** | Impella | 96.3±64.9 | 91.4±64.1 | 0.895 | 5,0 | 0.730 |
| | PA cannula | 96.4±34.0 | 101.1±25.0 | 0.785 | -4,9 | |
| **LVEDP (mmHg)** | Impella | 13.3±8.5 | 7.9±6.3 | 0.250 | 40,9 | 0.143 |
| | PA cannula | 12.9±4.7 | 13.4±5.7 | 0.880 | -3,8 | |
| **LVESP (mmHg)** | Impella | 87.5±15.9 | 73.5 ±16.9 | 0.135 | 16,1 | 0.884 |
| | PA cannula | 79.3±22.3 | 74.9±16.3 | 0.696 | 5,5 | |
| **PVA (mmHg x mL)** | Impella | 8092.3±3805.1 | 5283.7±3061.8 | 0.154 | 34,7 | 0.941 |
| | PA cannula | 5730.4±2071.5 | 5177.2±1702.9 | 0.613 | 9,7 | |
| **SW (mmHg x mL)** | Impella | 3998.8±2027.6 | 1796.9±1033.9 | **0.016** | **55,1** | 0.457 |
| | PA cannula | 1961.9±1054.0 | 1361.7±1000.8 | 0.309 | 30,6 | |
| **PE (mmHg x mL)** | Impella | 4093.5±2784.9 | 3486.8±2868.3 | 0.710 | 14,8 | 0.797 |
| | PA cannula | 3768.5±1379.7 | 3815.5±1243.8 | 0.951 | -1,2 | |
| **$E_{ES}$ (mmHg/ml)** | Impella | 1.4±0.9 | 1.2±0.7 | 0.667 | 13,6 | 0.174 |
| | PA cannula | 0.9±0.4 | 0.8±0.2 | 0.583 | 16,6 | |
| **Tau (ms)** | Impella | 50.9±16.1 | 50.0±12.4 | 0.914 | 1,8 | 0.231 |
| | PA cannula | 57.4±10.1 | 58.2±10.0 | 0.895 | -1,4 | |

***Table 3.*** V-A ECLS alone and its association with LV venting: LV PV variables.

Impella resulted in an immediate drop in LVEDV compared to a slight decrease in the PA cannula group, resulting in an overall SW and PVA reductions with both techniques (see *figure 3*). However, SW reduction was significant only in the Impella group (V-A ECLS 3998.8±2027.6 mmHg x mL vs V-A ECLS + Impella 1796.9±1033.9 mmHg x ml, p value=0,015), leading to a more consistent PVA reduction (Impella reduction 34.7% vs PA cannula reduction 9.7%). Furthermore, potential energy (PE) decreased by 14.8% with Impella support, whereas the PA cannula effect was negligible, showing an increasing trend (PE percentage reduction -1.2%). Two representative PV loops regarding Impella and PA cannula groups are shown in *figure 2.*

## Discussion

The use of Impella or PA cannula, in association with V-A ECLS, were able to unload the LV in a large closed-chest porcine model of profound CS. However, Impella provided more effective LV unloading than PA cannula, whereas no marked difference between the two V-A ECLS configurations was observed with regards to end-organ perfusion.

### Effect of peripheral V-A ECLS on LV unloading

Our study confirmed what has been repetitively demonstrated, namely that V-A ECLS in CS is associated with PVA increase [17,18]. Indeed, V-A ECLS leads to LV afterload increase, thereby moving the Ea line to the right (if we consider TPR and LV contractility as constants). In this condition, overcoming the afterload is only achievable via the Starling 's Law, that is rising LVEDV[19]. As a consequence, LVEDP, LA pressure, and PCWP increase. The global effect is the shifting of PV loop area rightward and upward along the EDPVR line, becoming progressively narrower and taller. Translating these changes into hemodynamic terms: PVA increases, increasing subendocardial pressure and myocardial oxygen demand [20], all well-known negative factors for an injured myocardium. In the extreme circumstances, unloading the LV during V-A ECLS support becomes mandatory.

***Figure 3.***

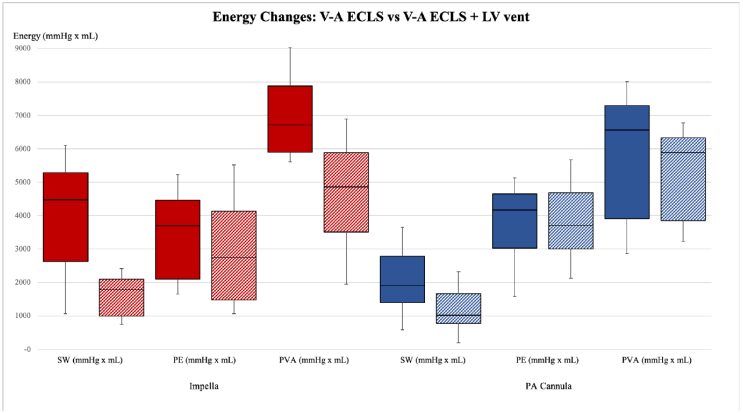


***Figure 3.*** **Energy Changes occurred with PA cannula or Impella in association with veno-arterial extracorporeal life support during cardiogenic shock.** Impella reduces either the stroke work (SW) or the potential energy (PE), thus the Pressure Volume Area (PVA) decrease resulted higher compared with pulmonary artery drainage.

**Unloading mechanisms of the added devices to V-A ECLS**

Our study showed that both direct LV unloading with Impella and indirect LV unloading with PA drainage in combination of right-sided V-A ECLS unloading, led to more effective decompression as compared to V-A ECLS alone.

***Impella***

Impella decompresses LV by pumping continuously blood from the LV to the aorta. Losing the isovolumetric periods, PV loops attains a triangular shape and shifts gradually leftwards, according to the flow generated by Impella [8] (see *figure 2*). In this animal series, we observed a decremental trend in LVEDV, LVEDP and slightly in PCWP. These findings are consistent with the effects on the pulmonary and circulatory physiology founded in other animal studies [21,22,23]. In addition, Lim et al. confirmed this hemodynamic impact in a single-center study of six consecutive patients on V-A ECLS support who received LV unloading with Impella [24]. The current study showed how Impella is able to impact effectively on PCWP rather than on mean PAP, therefore on the overall pulmonary circulation. On one hand, Yourshaw et al showed how the maximum Impella effect on PCWP was recorded 12 hours later from the device implantation [25]. This may lead to consider a slow hemodynamic adaptation which might not be seen in the short data capture interval used in our protocol. On the other hand, the PCWP is most reliable parameter indicating the LV loading features and certainly more influenced by the percutaneous left ventricle positioned device. To summarize, our findings showed and confirmed how Impella had major effects on PCWP and LVEDV. This was found also in a simulation study performed by Donker and collaborators in a closed-loop real-time computer model of CS [13].

***Pulmonary artery drainage***

PA drainage with percutaneous cannulation has been recently reported [26,27]. Scanty data, however, are available regarding its actual hemodynamic impact in V-A ECLS. Von Segesser et al. first reported the potential advantages of pulmonary cannulation in five bovine model of CS. The placement of a pulmonary arterial cannula allowed LV decompression. In fact, mean PAP sharply dropped. This latter hemodynamic change led to lower LV pressure and higher aortic pressure [28]. Our experience confirmed these findings, since mean PAP dramatically decreased by approximately fifty percent as soon as PA cannula-related drainage was activated. However, this action seems to have a limited impact in terms of LV volume reduction, as suggested by the slight LVEDV decrease.

***Unloading effectiveness***

Our study aimed at analyzing two techniques for unloading the LV in combination with V-A ECLS, considering PVA as a satisfactory LV overload estimator.

PVA linearly correlates with myocardial oxygen consumption, independently

from the heart rate [29]. Impella and PA cannula were able to reduce PVA in this animal model of CS and, therefore, both strategies represent effective means to unload the LV during peripheral V-A ECLS, in case of need. PVA is the total mechanical energy performed by the ventricle per heartbeat, which is the sum of SW (external active forces) and potential energy (PE, internal passive forces) [8]. In terms of external forces, SW significantly dropped by more than fifty percent with Impella, whereas this reduction was 30,6 % in PA cannula group. Furthermore, the impact of PA cannula and Impella on internal passive energy was extremely different. While PA cannula showed to have not consistent impact on the potential energy of the LV, PE dropped remarkably in the Impella group.
Therefore, taking into account that PVA reduction is more than three times higher with Impella, the latter technique seems to be more effective in terms of unloading, being able to reduce both PVA components - either internal or external energy. Drainage through the PA cannula, instead, seems to influence only the external force generated by the LV.

***End-Organ Perfusion***

A satisfactory treatment of CS aims at interrupting the vicious cycle of myocardial dysfunction leading to low cardiac output and hypotension [30], and restoring end-organ perfusion [31].
In our study, mixed and central venous oxygen saturation were considered adequate surrogates of end-organ perfusion [32]. Indeed, mean arterial pressure and venous oxygen saturation clearly improved just with the institution of V-A ECLS support.
This improvement occurred at the expense of LV loading due to higher LVEDV, LVEDP and PVA and thereby increased myocardial oxygen consumption secondary to the higher afterload generated by the retrograde ECLS-related flow. The start of the two unloading techniques, end-organ perfusion parameters (as MAP and $ScVO_2$ or $SVmO_2$) were successfully kept stable in association with LV unloading. PVA and consequently myocardial oxygen consumption dropped with both techniques, indicating that LV unloading with the added devices might protect the myocardium against further ischaemic injury or enhance, and make more expeditious, the myocardial recovery during ECLS support [33]. Furthermore, the fact that five out of six animals supported with PA cannula required norepinephrine to maintain a MAP >50 mmHg is probably due to the adjunctive contribution of the Impella to the circulatory support in association with V-A ECLS assistance, contribution which it is absent in case of PA drainage.

**Clinical implications**

LV overload assessment should be carefully evaluated in each patient supported with V-A ECLS due to CS. The combination of clinical, echocardiographic and instrumental parameters is crucial in this assessment [8]. As shown in the current study, PA drainage and Impella are differently able to influence specific

conditions occurring when LV is overloaded. Since the PA cannula seemed to be more effective on mean PAP, patients with high pulmonary pressure and congestive X-ray might receive more benefit with this LV venting strategy. On the contrary, a very stunning dilated LV ventricle with closed aortic valve might be the optimal setting for placing Impella, which is able to dramatically reduce the myocardial oxygen demand and empty the LV. However, the frequent LV thrombus coexisting with the latter condition might contraindicate its use [34]. Finally, another critical and not negligible issue, not strictly related to the hemodynamic effects, is represented by the different cost between the two devices.

**Limitations**

First, this is a study designed on acute immediate term effects of the Impella and PA cannula on top of V-A ECLS and it is unknown if the loading effects would become greater with long-term monitoring. Secondly, venous oxygen saturations were the only biochemical parameters of end-organ perfusion. The lack of lactates in our experience might represent a weakness when perfusion was evaluated. Third, pigs have a short ascending aorta, thereby the Impella outflow might be placed in the aortic arch/descending aorta, possibly jeopardizing the device impact understanding. Another limitation to our study is the impossibility to assess the LV unloading strategy effects at a longer-term, as well as defining infarct size, as the microcirculation is obstructed, or the time-to-recovery, or the overall extent of LV functional recovery, being this an acute experiment. Fourth, the gold standard for estimating ESPVR and PVA is by preload reduction which was not applicable in this study as we mentioned in methods section. Further, V0 was arbitrarily set as 0 ml in all animals and therefore might influence subsequently the absolute values of the relative derived variables.Baseline cardiac output considerably differed without reaching any statistical significance. This might obviously be a weakness which does not allow any comparison with baseline parameters. However, since our study was focused on the evaluation between V-A ECLS support and its association with LV venting strategies, this might not influence the overall results. Finally, Impella and PA cannula are only two among several LV venting techniques nowadays available [8]. Little is known how their different combinations with V-A ECLS affect the LV and end-organ perfusion, indicating the need for further studies.

**Conclusions**

This is the first study which directly compared the effects of two different modalities (one direct and one indirect) of LV unloading during peripheral V-A ECLS. In this large animal model with profound CS due to complete balloon-based proximal/middle left anterior descendent occlusion, the Impella and PA cannula, in association with V-A ECLS, provided effective LV unloading maintaining adequate end-organ perfusion. Impella seems to guarantee a stronger LV unloading effect, reducing more effectively the total LV mechanical energy.

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# Chapter 5.

## ECPella: concept, physiology and clinical applications

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**Abbreviations**

ECPella, veno-arterial membrane oxygenation and Impella
IABP, intra-aortic balloon pump
LV, left ventricle
MVO2, myocardial oxygen consumption
PVA, pressure-volume area
PVL, pressure-volume loop
SVR, systemic vascular resistance
VA -ECMO, veno-arterial membrane oxygenation
LVAD, left ventricular assist device
CO2, carbon dioxide

Veno-arterial membrane oxygenation (VA-ECMO) commonly is used to support patients with refractory cardiac arrest or cardiogenic shock [1,2,3] mainly via percutaneous cannulation [4]. This strategy may cause left ventricle (LV) distention that compromises myocardial recovery [5]. Direct LV unloading provided by Impella was associated with lower mortality in patients with cardiogenic shock supported with VA-ECMO in a recent international multicenter study [6]. The present paper has a specific purpose to provide a complete overview of this strategy, starting from a solid pathophysiologic approach. Then, the rationale for unloading the LV and the related available techniques is discussed. Finally, the combined configuration of VA-ECMO and Impella (ECPella) is fully treated, providing its significant clinical applications.

## Pathophysiologic Background

*Left Ventricle Pressure-Volume Loop*

***Figure 1.***

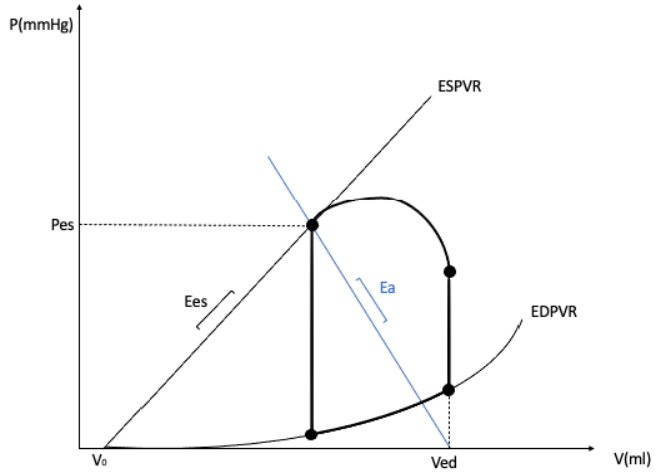


***Figure 1.*** **Pressure Volume Loop. Pressure Volume Loop is bounded by the end-systolic pressure–volume relationship (ESPVR) and end-diastolic pressure–volume relationship (EDPVR).** Pes, end systolic pressure, Ved, end diastolic volume; P, pressure; V, volume, Ees, end-systolic elastance, Ea, arterial elastance

The mechanical and hemodynamic properties of the heart are shown by the ventricular pressure-volume loop (PVL). The PVL describes the four phases of the cardiac cycle, respectively: (1) isovolumic contraction, (2) ejection, (3) isovolumic relaxation, and (4) filling. Typically, the PVL is characterized by the intrinsic (ventricular) properties of the myocardium and by the influence of the extrinsic vascular conditions.

The ventricular intrinsic properties are represented by two lines that inscribe the PVL shape. The end-systolic pressure- volume relationship is linear [7]. On the contrary, the end-diastolic pressure-volume line is a nonlinear relationship and reflects the diastolic properties [8].

***Table 1.***

| | |
|---|---|
| **Intrinsic Properties** | |
| **ESPVR** | The linear relationship is defined by two main features[7]:<br>- the slope is the end-systolic elastance *(Ees)*, a load-independent LV contractility parameter. Therefore, different loading conditions lead to distinct PVLs which move along the same ESPVR line defined by identical *Ees*.<br>- the volume–axis intercept *Vo* |
| **EDPVR** | The nonlinear relationship defines only the *passive diastolic properties* of the ventricle and represents diastolic stiffness. These properties are influenced by pressure and required sophisticated engineering assumptions. Consequentially, diastolic properties are difficult to apply in practice [8]. |
| **Extrinsic Properties** | |
| **Ved** | The end diastolic volume (*Ved*) defines the pre-load which is strongly determined by the venous return[9]. |
| **Ea** | The arterial elastance (*Ea*) connects the *Ved* with the end systolic pressure volume. The Ea line slope is defined by the ratio between *systemic vascular resistance (SVR)* and the duration of the heartbeat. Therefore, Ea is influenced by the *SVR*, the *heart rate* and the preload (*Ved*)[9]. |
| **Others** | |
| **SV** | The stroke volume (*SV*) is the width of the loop. The product between SV and heart rate is the cardiac output. |
| **Pes** | The *Pes* (ventricular end-systolic pressure) represents the height of the loop |

***Table 1.*** **Main pressure volume loop features related to *figure 1*.**

Differently, the extrinsic conditions mainly are defined by the concepts of preload and afterload. The end-diastolic volume (and, therefore, pressure) indicate the preload, which is a surrogate of the sarcomere length. Differently, the afterload can be depicted on the pressure-volume plane by the “effective arterial elastance” line, influenced by the systemic vascular resistances, the heart rate, and, finally, the preload [9] (see *Table 1 and Figure 1*).
Finally, the PVL defines the determinants of myocardial oxygen consumption [8] The most important determinant is the pressure-volume area (PVA). The PVA is the sum of the external stroke work and the potential energy, which represents the residual energy stored in the myofilaments at the end of systole. Myocardial oxygen consumption (MVO2) is linearly related to ventricular PVA; therefore, any increase in PVA corresponds to a linear increase in MVO2 [10] (see *Figure 2*).

***Figure 2.***

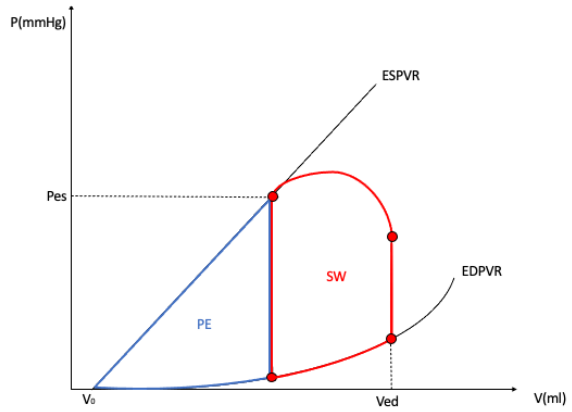


***Figure 2.*** **Left Ventricular Energetics.** The sum of the stroke work (SW) and potential energy (PE) is called Pressure–volume area (PVA).

**Pressure-Volume Loop on Peripheral VA-ECMO**

During cardiogenic shock, VA-ECMO primarily alleviates the hemo-metabolic shock associated with low-output state, supporting the cardiopulmonary system and secondarily reducing the heart's preload, by drawing blood from the right atrium.However, a direct hemodynamic consequence after peripheral VA-ECMO implantation is the increase of LV afterload, moving the arterial elastance line to the right. In this condition, only the LV volume increase allows overcoming the high generated afterload through the Starling's Law. As a result, the subsequent LV distention leads to increased LV end-diastolic pressure, left atrial pressure and pulmonary capillary wedge pressure that may cause pulmonary edema. Indeed, this mechanism is particularly unfavorable because slight LV volume increases may cause large increases in end-diastolic pressure. The global effect is the shift of PVL rightward and upward along the end-diastolic pressure-volume relationship, becoming progressively narrow and taller (see *Figure 3*).

Translating these changes in hemodynamic terms: PVA increases despite the stroke- volume reduction. Therefore, the poorly oxygenated blood due to pulmonary edema and the increased myocardial oxygen demand might further worsen the LV function [7].

***Figure 3.***

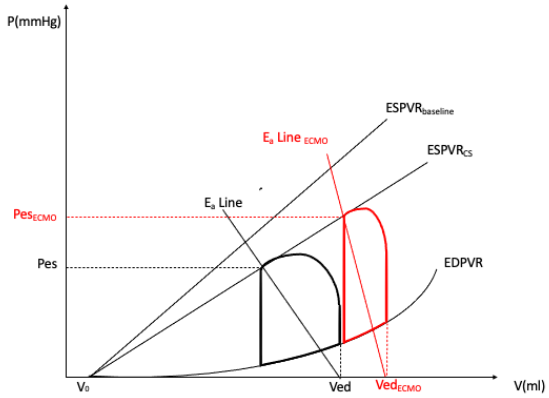


***Figure 3.*** **Pressure Volume Loop changes in Veno arterial Extracorporeal Membrane Oxygenator support during Cardiogenic Shock.** The Pressure Volume Loop moves rightward and becomes narrow. ESPVR, end-systolic pressure–volume relationship; EDPVR, end-diastolic pressure–volume relationship; Pes, end systolic pressure, Ved, end diastolic volume; P, pressure; V, volume, Ees, end-systolic elastance, Ea, arterial elastance

## Venting the Left Ventricle

### Rationale of LV Venting

LV overload caused by peripheral VA-ECMO is a crucial concern for LV recovery. The detrimental effect of retrograde flow in the aorta that might lead to LV dilatation, increased left atrial pressure, and pulmonary edema is prominent. Moreover, it jeopardizes ventricular recovery, particularly in the presence of ischemia-induced myocardial impairment. In case of extreme overload and severe LV dysfunction, the aortic valve may remain closed, even during systole, causing blood stasis in the LV and increasing the risk of thrombus formation [11].

### LV Venting Techniques

When the pharmacologic LV venting, through the modulation of LV contractility and systemic vascular resistance (SVR), is insufficient, mechanical strategies should be utilized to decompress the left ventricle. The first step considered usually was intra-aortic balloon pump (IABP) counterpulsation, which unloads the LV by afterload reduction [12]. Nevertheless, more sophisticated approaches are required in order to overcome significant ventricular overload. These include surgical techniques or percutaneous techniques. A review paper showed an increased use of percutaneous techniques, confirming the growing attention to noninvasive approaches [13]. The percutaneous approach might consist of placing a venting cannula in the pulmonary artery or in the left side through the transaortic or transseptal approach. Furthermore, different percutaneous assist devices, such as Impella or Tandem Heart, may be useful

for avoiding or reducing the LV overload [11]. The most common locations of unloading were the left atrium (31%), followed by the aorta/IABP (27%) and transaortic (27%) [11]. As a matter of fact, the optimal technique and the target patient population who actually will benefit from venting procedures are still under investigation.

**ECPella**

Among percutaneous devices, Impella (Abiomed, Danvers, MA) represents the most extensively validated solution. The Impella is a catheter-mounted microaxial flow pump capable of drawing from 2.5-to- 6.0 L/min of blood from the LV into the aortic root, across the aortic valve. The current use of Impella and VA-ECMO is called “ECPella” and is an efficient technique to unload the LV [6].

**Hemodynamics of ECPella**

As previously discussed, VA-ECMO support in cardiogenic shock leads to a significant afterload increase, which shifts the PVL upward and rightwards. The overall effects consist of higher end-diastolic volume, stroke work rise, and MVO2 increase. This overload condition might be followed by increased left atrial and capillary wedge pressures and pulmonary oedema [14].The hemodynamic effects generated by Impella may be summarized in three main concepts analyzing the single role of this device: (1) increasing cardiac power output, (2) increasing oxygen supply, and (3) decreasing oxygen demand. First of all, the Impella’s outflow, placed in the aortic root, provides an active flow that depends on the pump support setting (P level) and the aorta-LV pressure gradient. The combination between P level setting and pressure gradient, as a consequence of VA-ECMO support and afterload, results in a forward flow that is significantly increased by Impella [15,16]. Second, Impella is able to raise oxygen supply. The flow through the coronary arteries is influenced by the pressure gradient across the artery and vascular resistance. Assuming the venous pressure and the primary artery tract resistance as fixed, the flow depends on the microvascular resistance and aortic pressure. In addition to the increased ascending aortic pressure, the unloading of the LV, reducing end-diastolic pressure and volume, causes reductions of wall tension and micro- vascular resistance, according to Laplace’s Law [7]. These assumptions are supported by different investigations: Sauren et al reported a maximum 47% increase in coronary flow with Impella in animals, [17] and Remmelink et al reported this augmentation in humans [18]. The microvascular effects were studied by Aqel et al using a perfusion imaging technique; this experience showed the improvement of myocardial perfusion with Impella support, explained by the augmentation of the blood flow through the collateral pathways. Finally, the total result of the combination between these factors leads to the myocardial oxygen supply’s increase [19]. Third, the Impella’s inflow drainage reduces ventricular end-diastolic volume and pressure, left atrial and wedge pressures, drawing blood directly from the

ventricle [15]. Sauren et al showed a significant reduction from baseline in mechanical work and end-diastolic pressure- volume with Impella [17] in an acute animal model, further confirmed by Valgimigli et al [18]. As a consequence of reducing mechanical work and decreasing myocardial wall tension, the myocardial oxygen demand is lowered [20,21,22]. Overall, the total balance of myocardial oxygen demand and supply becomes favorable [15,17]. Reesink et al, considering only the kinetic work, demonstrated a 36% improvement with Impella compared with an 18% improvement with IABP [15]. Differently, Sauren et al took into consideration the potential energy component, reporting a 69% improvement with Impella compared with 15% with IABP [17].

**Pressure-Volume Loops of ECPella**

To summarize, the hemodynamic effects of Impella in combination with VA-ECMO may be identified as direct or indirect (see *Figure 4*):

1. Direct: the first direct impact is the loss of isovolumic periods, caused by continuous pumping of blood from the LV to the aorta, independently of the phase of the cardiac cycle. The lack of these components modifies the PVL from its nor- mal trapezoidal shape to a triangular shape. LV results in progressive unloading, shifting the PVL leftward [23].
2. Indirect: all of these changes cause reductions in PVA and MVO2, improving blood oxygenation, systemic pressure, and perfusion, leading to beneficial secondary changes in LV contractility and SVR [24].

***Figure 4.***

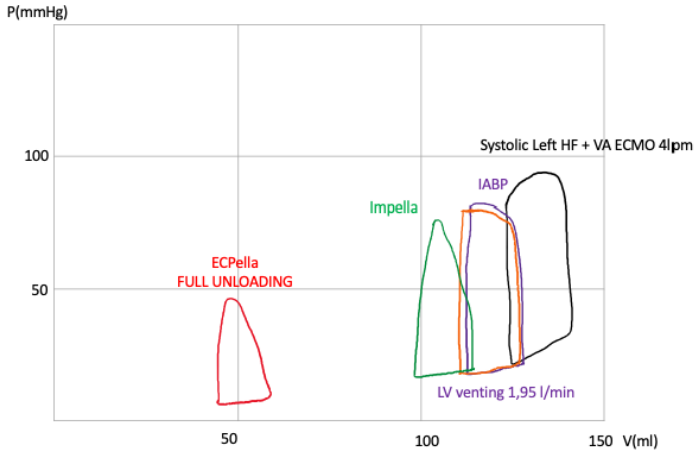


***Figure 4.*** **LV venting techniques and related Pressure Volume** Loops. In case of cardiac failure (shock or arrest), ECPella provides full left ventricle unloading. In ECPella configuration, Pressure Volume Loop moves leftward and becomes triangular.

Furthermore, Impella, as an unloading strategy in combination with VA-ECMO, has relevant effects on the pulmonary and systemic hemodynamics [25]. First, total blood flow increases, and pulmonary artery wedge pressure decreases.

Second, the increase in pulmonary artery capacitance exceeds the reduction in pulmonary vascular resistance; thus, increasing the pulmonary artery time constant, being the product of pulmonary artery capacitance and pulmonary vascular resistance. The increase in pulmonary artery capacitance is particularly relevant, being a measure of pulsatile right ventricle (RV) afterload [26]. Therefore, the global result should be the reduction of RV afterload, increasing right stroke volume and reducing arterial CO2 pressure end-tidal CO2 gradient, caused by the reduction of alveolar dead space ventilation. Importantly, this reduced arterial CO2 pressure- end-tidal CO2 gradient remains abnormal, and indicates residual ventilation-perfusion abnormalities, which, in combination with increased LV output, might induce delivery of poorly oxygenated blood into the systemic circulation, as confirmed by the reduction in right radial arterial oxygen saturation. This phenomenon might be particularly evident in the upper half of the body and depends either on the residual gas exchange abnormalities in the lungs or the anteroretrograde balance of blood flow, generated between LV output and the extra-corporeal life support arterial cannula and warrants continuous monitoring, especially in the early phases until pulmonary edema is resolved and gas exchange is improved [22].

**ECPella Evidences**

After a preliminary case series [27] Pappalardo et al showed that patients supported with the ECPella strategy not only had improved outcomes but also showed a trend toward higher left ventricular ejection fraction after weaning. This experience investigated 34 ECPella support: after propensity score matching, the ECPella group presented significantly lower in-hospital mortality (47% v 80%, $p < 0.001$) and a higher rate of successful bridging to either recovery or further therapy (68% v 28%, $p < 0.001$), as compared with VA-ECMO alone patients [28]. Patel et al showed similar results with 30-day mortality significantly lower in the ECPella cohort (57 v 78%; hazard ratio 0.51[0.28-0.94], log rank p=0.02); moreover, the inotropic score was greater in the VA-ECMO group by day two (11 v 0; $p = 0.001$). Bridge to recovery, although not statistically significant, was numerically almost double in the ECPella cohort (40% v 22%; $p = 0.18$); bridge to left ventricular assist device (LVAD) was more prevalent in the ECPella group as well (33 v 13%; p=0.60). No statistically significant differences in terms of hemolysis, bleeding, renal failure, and stroke were observed [29]. This was further corroborated by the work of Truby et al, which showed that myocardial recovery was higher in patients without left ventricular distention, prompting the need for LV venting [30]. They also identified extracorporeal cardiopulmonary resuscitation as the clinical scenario with higher need for decompression. Interestingly, these figures were independent from the site of arterial cannulation (femoral, central or axillary) and were reported in a group of patients receiving an average ECMO flow of 3.6 L/min [30]. Finally, Schrage et al recently reported the most important evidence on the combined use of Impella and VA-ECMO. In this

international, multicenter cohort study, 255 propensity- matched patients supported with ECPella were compared with 255 patients supported with only VA-ECMO. Left ventricular unloading was associated with lower mortality in patients with cardiogenic shock treated with VA-ECMO, despite higher complication rates [6].

**Clinical Applications**

**Different Models and Different Placement**

The Impella devices are commercially available in different models, characterized by their capacity to guarantee different support [31] (ranging from 2.5-to-6 L/min):

- the Impella 2.5 (maximum flow rate 2.5 L/min): percutaneous insertion with a 12-Fr sheath in the femoral artery
- the Impella CP (3.0-4.0 L/min): percutaneous insertion with a 14-Fr sheath in the femoral artery
- the Impella 5.0 (5.0 L/min): surgical cut-down insertion with a 21-Fr sheath; axillary artery is the preferred site of placement, facilitating ambulation and a longer period of support
- the Impella 5.5 (up to 6.0 L/min): surgical cut-down insertion with a 21-Fr-sheath; axillary artery or directly to the ascending aorta, facilitating long-term use and full LV unloading

The Impella 2.5/CP is FDA-approved to provide circulatory support for up to five days and the Impella 5.0 is approved for up to ten days [32]. The new Impella 5.5 with ceramic bearings is intended for prolonged use, up to 30 days.

**Contraindications**

ECPella has the same contraindications as isolated Impella support: LV thrombus, mechanical aortic valve, and significant aortic regurgitation. In these scenarios, other venting strategies should be pursued. For instance, IABP may be the less-invasive approach compared with a cannula connected to the drainage side of the VA-ECMO circuit, which might be more elaborate. Furthermore, significant arterial disease should be systematically investigated in order to quantify the risk of navigating through an atherosclerotic aorta [33].

**Device Selection, Timing, and Targets**

The adequate Impella device should be chosen according to the amount of required support [34,35,36] and the severity of hemodynamic compromise. In VA-ECMO and concomitant Impella support, the total cardiac output is not simply the sum of the pre-insertion cardiac output and the flow generated by the Impella. Since the LV should be fully or partially unloaded by the Impella device, the native heart contribution subsequentially decreases [18].The Impella's performance should be set in order to provide sufficient LV

unloading and adequate hemodynamic support, avoiding excessive suction. This might be particularly demanding over the first hours of support. In fact, the full venous drainage and the aortic valve closure lead to frequent LV size changes over this first period of time.Although there were clinical reports proving the effectiveness of Impella and IABP combination [37,38], a European expert user group did not recommend the systematic simultaneous use of the Impella device with IABP. First, Impella forward flow might be attenuated by IABP during diastole. Second, this combination might lead to misinterpretation of alarms, potential position issues, and, finally, increased risk of hemolysis and thrombosis [13].The necessity to unload the LV ventricle during VA-ECMO support might be summarized in four main scenarios, each of which has specific features and goals that are described in the following table *(see Table 2)*.

***Table 2.***

| | **Stone heart (after eCPR)[39]** | **Acute Severe Myocardial Dysfunction (AMI[40], Myocarditis [41])** | **Chronic Severe Myocardial Dysfunction [42] (End Stage Chronic HF)** | **Myocardial Dysfunction in Post-Cardiotomy Patients [43]** |
|---|---|---|---|---|
| **Configuration** | peripheral V-A ECMO | peripheral V-A ECMO | peripheral V-A ECMO | central V-A ECMO |
| **Expected duration** | days | days | days to weeks | 2 -15 days |
| **Timing** | Early LV distension | Early LV distension | Early and delayed LV distension | Early LV distension |
| **Device** | *Impella 2.5 or CP** | *Impella 2.5 or CP** | *Impella 5.0*, 5.5* | *Impella 2.5, CP or 5.0,5.5* based on the clinical situation* |
| **Impella Insertion** | 13-Fr or 14-Fr sheath Femoral Artery | 13-Fr or 14-Fr sheath Femoral Artery | Surgical cut-down insertion through 8-10mm Dacron graft anastomosed to the axillary artery | 13-Fr or 14-Fr sheets or surgical cut-down insertion through 8-10mm Dacron graft anastomosed to the axillary artery or directly in the ascending aorta. |
| **Goal** | BTD,De-escalation, Myocardial Recovery | De-escalation, Myocardial Recovery | BTT, BTD or Bridge to LVAD implantation | Myocardial Recovery |

***Table 2.*** **Clinical scenario and detailed ECPella configurations.** AMI: acute myocardial infarction, HF: heart failure, BTT: Bridge to transplant, BTD: Bridge to decision
*In combination with Impella RP in case of RV dysfunction

## Access Site, Impella Placement and Monitoring

The selection and management of the access site should consider the patient's anatomy and the operator's experience. The advisable site for the percutaneous placement is the common femoral artery, while the axillary artery is suitable in the surgical approach. The appropriate access management techniques should guarantee low risk of arterial complications such as local bleeding and access site-related ischemia [44,45]. However, considering the concomitant VA-ECMO support, the risk of complications might be lower, as limb ischemia can be managed by reperfusion via the ECMO circuit [33]. On

the other hand, the ECMO-induced coagulopathy might be responsible for a higher incidence of bleeding complications.
The positioning of the Impella device should prevent migration into the LV and avoid hemolysis, suction episodes, and inadequate hemodynamic support; in particular, for long-term support. The placement can be performed in the catheterization laboratory or operating room, but also at the bedside, which is particularly attractive for patients who are critically unstable on VA-ECMO [19]. The inlet should be placed approximately 3.5 cm (Impella 2.5, CP, and 5.0) or 5.0 cm (Impella 5.5) distal to the aortic valve without being close to the mitral subvalvular apparatus or interfering with the anterior mitral leaflet and papillary muscles. Bedside echocardiography should be available, possibly transthoracic, to evaluate the correct placement, in addition to right ventricular function and volume status [13] (see *Figure 5*). The ECPella monitoring requires a right radial arterial line for oxygenation monitoring, a daily x-ray to assess pulmonary edema, and regular echocardiographic studies, especially in case of an abnormal positioning signal on the console monitor. Echocardiography should be able to check the Impella position, to exclude pericardial effusion, to evaluate cardiac chamber loading, and to examine valvular function.[46] However, decision-making during ECPella support might be extremely demanding and requires direct and reliable hemodynamic information. Therefore, advanced hemodynamic monitoring with a pulmonary artery catheter is strongly recommended [47]. These measurements help to better understand the complex changes in order to adjust device flows, medical therapy and volume management.

***Figure 5.***

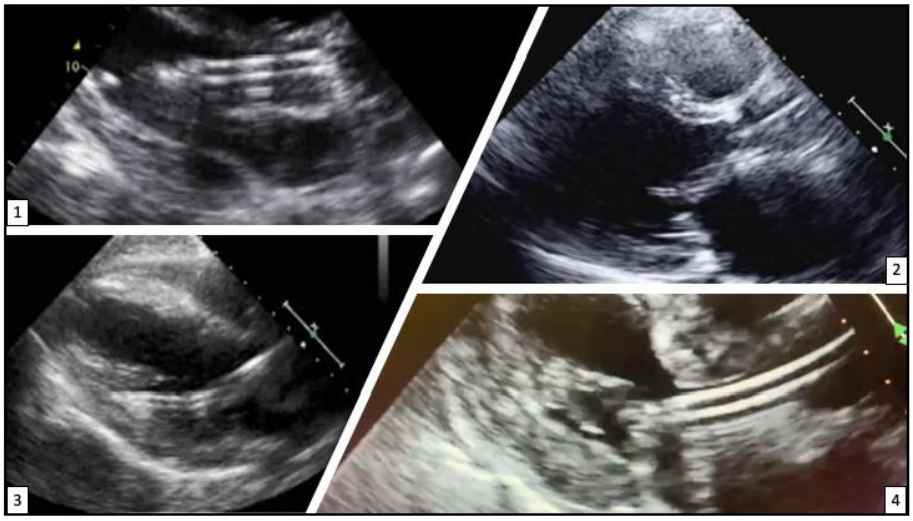


***Figure 5.*** **Impella Positioning.** 1. Normal Impella position in Parasternal Long Axis (3,5 cm from the Aortic valve plane); 2. Impella position in Aorta; 3. Impella position too far in left ventricle; 4. Impella pigtail caught in papillary muscle

**Clinical Remarks**

Firstly, clinical decisions basically should be guided by carefully weighing potential therapeutic benefits and risks in every individual patient, including the intended goal and expected length of the bridging strategy under VA-ECMO. Left ventricular overload at any time during VA-ECMO may develop in up to 70% of patients [48], however, an urgent decompression is undertaken in only roughly 10% of cases, whereas an additional 20% of cases might need an unloading intervention at a later stage [30]. Notably, recent literature suggests improved outcomes when adjunct unloading strategies are employed.6 In routine clinical practice, patients under high- flow VA-ECMO support (>4 L/min) and exhibiting a dilated LV in the virtual absence of native left ventricular contractility, should be considered at a very high risk for significant LV overload. Secondly, the right-left ventricular interaction is of para- mount importance, as sustained right ventricular contractility may actually contribute to mechanical overload, which negatively impacts on the failing left ventricular myocardium [23]. In this setting, despite right ventricular drainage, it still may be able to eject enough blood via the left atrium into the failing LV that is facing an increased afterload as mediated by the retrogradely-directed extracorporeal flow in the aorta toward the LV.

Therefore, paradoxically, preserved right ventricular function is a critical additional risk factor for significantly overloading a failing LV under VA-ECMO support.

Thirdly, Impella automated controller algorithms may detect suction at the device inflow in case of full LV unloading. In fact, the suction alarm may be triggered by constant high aorta-LV differential pressures and low pulsatility on the aortic pressure waveform. Finally, the patients who have worsening lung function supported with VA-ECMO may demonstrate the “Harlequin syndrome” [49]. Impella seems to be the most effective method, allowing earlier and expeditious weaning from VA-ECMO [50]. This would focus not only on LV unloading, but also on the respiratory system, which should be protected from injurious mechanical ventilation.

**Weaning**

Patients treated with ECPella should be supported until hemodynamics are stable with resolution of shock.

The de-escalating process should start by first removing inotropes. Thereafter, VA-ECMO reduction should be pursued. At this time, the focus should be on the right ventricle, as this is the major limitation for de-escalating from biventricular to univentricular support. If biventricular failure is predominant, despite successful hemodynamic optimization, evaluation for heart transplantation or biventricular support is warranted; if left ventricular support only is required, de-escalation to an axillary approach for a prolonged attempt at heart recovery should be pursued. The axillary approach encompasses the use of the Impella 5.0 and/or 5.5 regardless of the residual function of the LV, in light of its dedicated tools for axillary surgery that allow ambulation, better

hemocompatibility, and a longer pump duration [51]. A total percutaneous approach with the Impella implanted in the axillary artery may be envisioned in the future in patients who are of small size and, therefore, require lower flow. This bridge-to-bridge strategy has proven very effective in improving results in patients requiring a durable LVAD, as it is associated with lower complications compared with the direct transition from VA-ECMO to LVAD. Indeed, from the hemodynamic standpoint, this is an 'LVAD test' that challenges the right ventricle and avoid futile implants [52].

**ECPella Advantages**

The ECPella approach has some valuable advantages. ECPella approach results are extremely attractive, since the treatment of cardiogenic shock should be effective within a short time frame after initiation of mechanical circulatory support. In fact, significant reduction of lactates [53] and of the inotropic score [54] should be an important achievement within 24 hours. Impella provides additional flow to the ECMO and overcomes the limitation of ECMO performance driven by the cannula size. According to the size of the cannula usually selected for femoro-femoral cannulation (21-29 Fr venous 15- 19 Fr arterial), the VA-ECMO pump would not provide more than 5 L/ min of flow. An associated LV pump provides an additional flow that has to be viewed in a double perspective. On the one hand, Impella is a 'resuscitative' flow, and on the other hand, the device allows smoother weaning from mechanical circulatory support [55]. Indeed, ECMO removal is a complex issue: patients will recover aortic pulsatility and normal cardiac output, although echocardiography usually shows a low ejection fraction, and this translates into a consistent number of patients who are weaned from ECMO but eventually will die before hospital discharge [56,57].

Furthermore, the ECPella approach guarantees the chance for shorter duration of the extracorporeal support that is associated with more side effects in each patient [58]. However, this approach may prolong the total time when the patient is on a pump. If it is assumed that medical treatment is the target for the management of heart failure after the acute failure, the LV pump might avoid the use of inotropes [59] during weaning and might facilitate the titration of ACE inhibitors and beta blockers under progressive lower levels of Impella support.

**ECPella Shortcomings**

The major ECPella shortcomings are bleeding complications, hemolysis, and ischemic complications.

Recently, Schrage et al showed higher rates of severe bleeding (38.4% v 17.9%) and hemolysis (33.6% v 22.4%) in ECPella support compared with VA-ECMO alone. Furthermore, the association between ECPella use and a higher likelihood of interventions because of access site-related ischemia was consistent. In fact, interventions because of access site- related ischemia occurred in 21.6% of patients treated with ECPella versus 12.3% of patients

treated with VA-ECMO. Furthermore, laparotomies because of abdominal compartment syndrome were seen in 9.4% of patients treated with ECPella, compared with only 3.7% of patients treated with VA-ECMO. However, no differences were found in ischemic strokes or bowel ischemia [6].
On the one hand, the presence of two devices and related arterial access may increase the likelihood of bleeding/ischemic complications [60]. On the other hand, these complications might be explained by the relatively large vascular access required (12/14-French for the Impella 2.5/CP) [61]. Furthermore, Impella leads to a high shear stress on blood elements and is associated with increased hemolysis [62].
Interestingly, Pappalardo et al found a higher rate of need for continuous veno-venous hemofiltration in patients supported with ECPella compared with those with VA-ECMO alone [28]. This was confirmed by Schrage et al in a large multi- center study [6]. Obviously, survivorship bias might, to a certain degree, explain higher need for renal replacement therapy. However, this association should be investigated by further study. Finally, another critical and not negligible issue is represented by the cost of this combined configuration.

**Conclusions**

Up to now, the ECPella strategy has been discussed as a primary configuration. However, it is to be acknowledged that this is far from the 'real world'. Many patients are salvaged by Impella implantation in combination with VA-ECMO because complications related to LV distention have ensued. Furthermore, Impella patients escalate to ECMO because the severity of shock has progressed, mostly due to concomitant right heart failure or inadequate pump selection. This might be overcome by the implementation of new concepts in the management of cardiogenic shock patients: (1) systematic LV venting, (2) assessment of the severity of shock by the inotropic score and mechanical support strategy to avoid toxic catecholamine levels, and (3) right ventricular 'sensitivity' and early application of biventricular support. Further studies are needed to face this demanding medical condition.

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# Chapter 6.

## Atrial septostomy for left ventricular unloading during extracorporeal membrane oxygenation for cardiogenic shock: animal model

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**Abbreviations**
BAS: balloon atrial septostomy
CS: cardiogenic shock
ESPVR: end-systolic pressure-volume relationship
P_ed: left ventricle End Diastolic Pressure
V_ed: left ventricle End Diastolic Volume
P_es: left ventricle End Systolic Pressure
V_es: left ventricle End Systolic Volume
PE: potential energy
PVA: pressure-volume area
SW: stroke work

**Abstract**

**Objectives**

To quantify and understand in detail the unloading effect of percutaneous balloon atrial septostomy (BAS) in acute cardiogenic shock (CS) treated by veno-arterial extracorporeal membranous oxygenation (VA-ECMO).

**Background**

In VA-ECMO treated CS, increased left ventricular (LV) afterload is observed that commonly interferes with myocardial recovery or even promotes further LV deterioration. Several techniques for LV unloading exist, but optimal strategy and actual extent of such procedures have not been fully disclosed till today.

**Methods**

In a porcine model (n=11, 56 (53;58) kg) CS was induced by a coronary artery balloon occlusion (57 (53;64) minutes). Then, step-up VA-ECMO protocol (40-80 ml/kg/min) was run before and after percutaneous BAS was performed. LV pressure/volume loops, and multiple hemoglobin saturation data were evaluated. Wilcoxon rank-sum test was used to assess individual variable differences.

**Results**

Immediately after BAS while on VA-ECMO support, LV work decreased significantly: pressure-volume area (PVA), end-diastolic pressure and stroke volume to ~78%; and end-systolic pressure to ~86%. Superior vena cava and tissue oximetry did not change. During elevating ECMO support (40-80 ml/kg/min) with BAS versus without BAS we observed: i. significantly less mechanical work increase (122% vs. 172%); ii. no end-diastolic volume increase (100% vs. 111%). End-systolic pressure increase (144% without, 134% with BAS) was the strongest determinant of mechanical work increase.

**Conclusions**

In acute cardiogenic shock supported by VA-ECMO, atrial septostomy is an effective tool for LV unloading. When LV work reduction is priority, arterial pressure should carefully be kept low while maintaining organ perfusion.

**Background**

Venoarterial (VA) extracorporeal membrane oxygenation (ECMO) is one of the most frequently applied mechanical circulatory support modes in cardiogenic shock (CS) [1]. However, the benefits may be limited by VA ECMO–related complications and inherent shortcomings. Increased afterload to the left ventricle is one of the most critical side effects. In fact, this phenomenon may lead to left ventricular (LV) dilatation, increases in LV and left atrial end-diastolic pressures, blood stasis or thrombosis, and pulmonary edema [2]. This may compromise myocardial recovery and prolong the resulting lung injury unless the left heart is vented or unloaded. Several surgical (invasive or minimally invasive) or percutaneous techniques are available for clinical use to decompress the left heart. However, evidence and comparisons regarding some of the most common techniques, such as intra-aortic balloon pumps, the TandemHeart (LivaNova), and transaortic suction devices, are limited [2].
Interestingly, the presence of atrial communication, leading to a left-to-right shunt decompressing the left ventricle, may positively influence the hemodynamic balance in the setting of VA ECMO support associated with LV overloading, representing a favorable exit route in the presence of increased left- sided pressure, as in CS or cardiac arrest [2].
Previous case reports [3,4] and small studies [5,6] have documented the feasibility and efficacy of percutaneous balloon atrial septostomy (BAS) in adult and pediatric patients on VA ECMO, but the real impact on LV unloading and performance is still not well understood in detail.
Therefore, we designed an experimental study of CS managed by VA ECMO in which BAS was per- formed to assess the effects of this technique on LV decompression and workload, together with the impact on overall end-organ oxygen delivery.

**Methods**

The study was approved by the Charles University First Faculty of Medicine Institutional Animal Care and Use Expert Committee and was performed in the university laboratory in accordance with Act No. 246/ 1992 Coll., which is harmonized with European Union directives on the protection of animals used for scientific purposes.

**Anesthesia and Instrumentation**

Details on anesthesia and instrumentation have been previously reported [7]. Briefly,11 female swine, weighing 56 kg (53-58 kg), were subject to BAS as an LV unloading technique during VA ECMO under total intravenous anesthesia (propofol, midazolam, and morphine). First, hemodynamic and oximetry monitoring systems were introduced: a superior vena cava catheter (PreSep, Edwards Lifesciences) provided central venous pressure and hemoglobin saturation; a pulmonary artery catheter (CCombo connected to a Vigilance II monitor, Edwards Lifesciences) provided pulmonary artery pressure, wedge pressure, hemoglobin saturation, and continuous cardiac output; and 2 near-

infrared spectroscopic tissue oximetry sensors (INVOS, Somanetics) were attached to the skin of the forehead and right forearm. Then, an LV pressure-volume (PV) catheter was inserted. Second, the VA ECMO circuit was established using a femorofemoral percutaneous approach. Third, CS was induced by percutaneous transluminal coronary angioplasty balloon occlusion of the proximal left anterior descending coronary artery. Subsequently, a step-wise ECMO support protocol before and after BAS was performed. At the end of the protocol, support was withdrawn, resulting in hemodynamic collapse, thus confirming the severity of CS.

**Left Ventricular pressure-volume measurement**

The PV catheter (5.0-F VSL Pigtail, Transonic) was percutaneously inserted under fluoroscopic guidance through a 7-F sheath in the left carotid artery, advanced retrogradely into the left ventricle, and connected to an ADV 500 PV System (Transonic). The conductance catheter acquired LV pressure, LV volume, phase, and magnitude, while LabChart Pro software (ADInstruments) provided calculations of multiple LV parameters: end-diastolic pressure and volume, end-systolic pressure and volume, and pressure-volume area (PVA) (mmHg × mL) and its components, stroke work (SW) and potential energy (PE) [8,9]. Vo (the theoretical volume when no pressure is generated) was arbitrarily assumed to be zero in each animal and was kept constant throughout the protocol.

**VA-ECMO**

The femorofemoral circuit consisted of arterial 15-F (HLS, Maquet), and 21-F venous (Multi- hole, Maquet) cannulas, a centrifugal pump controlled by Biomedicus 550 console (Medtronic), and a membranous oxygenator (Quadrox, Maquet). Arterialized blood was continuously sampled for blood gases and pH using a CDI-500 monitor (Terumo) and kept at a target partial pressure of oxygen (120-150 mmHg) and partial pressure of carbon dioxide (≈ 40 mmHg).

**Cardiogenic shock model**

The proximal left anterior descending coronary artery was occluded by a regular percutaneous coronary compliant balloon (4 × 20 mm) that was kept inflated for 42 to 66 minutes. The aim was to achieve profound CS, defined as cardiac output <40% of baseline. If the animal developed ventricular fibrillation, VA ECMO flow was instituted to maintain a mean arterial pressure (MAP) of about 50 mmHg. At the end of CS induction, if needed, defibrillation was performed (200 J, biphasic, repeated as necessary) to restore sinus rhythm. Circulation was stabilized for at least 15 minutes, and ECMO support was reduced to 20 mL/kg/min or minimum tolerated before CS assessment and protocol initiation.

**Atrial septostomy**

BAS procedures were achieved under fluoroscopic and intracavitary echocardiographic guidance via the femoral vein using a needle transseptal puncture followed by static atrial septum balloon dilation [10] over a guidewire placed in the left atrium. The midportion of the balloon (Z- Med II X, NuMed) was located across the atrial septum and inflated with diluted contrast until disappearance of the balloon waist on fluoroscopy. Blood flow across the atrial communication was checked using intracavitary ultrasound. Finally, septostomy morphology, including dimension, was assessed postmortem (*Figure 1*).

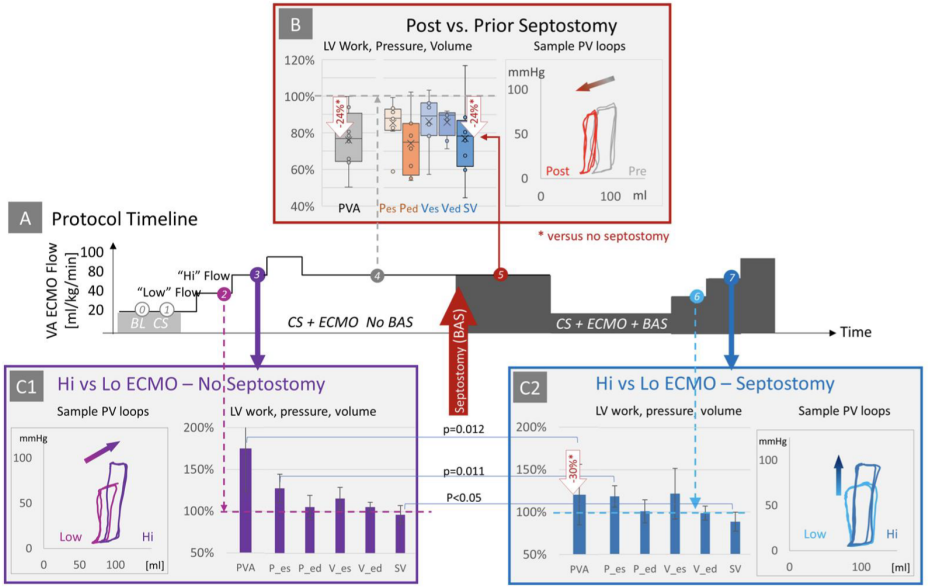
**Experimental protocol and data acquisition**

The experimental protocol is presented in *Central Illustration A*. The ECMO ramp-up test included a stepwise flow increase every 10 minutes in increments of 20 mL/kg/min from a minimum of 20 mL/kg/min up to the target maximum of 100 mL/kg/min (if achievable). Norepinephrine was continuously administered whenever MAP dropped below 50 mmHg and was discontinued once MAP increased to more than 60 mmHg.

All parameters were continuously recorded using LabChart Pro software. Hemodynamic, PV, ECMO, and oximetry parameters were manually extracted from continuous records at preset time points (Central Illustration A). PV data were averaged from 4 cycles during expiration period.

**Statistical analysis**

First, data describing CS supported with VA ECMO flow before septostomy were compared with those immediately after the BAS procedure. Second, CS supported with VA ECMO at minimum and maximum flow without septostomy was compared and then identically after septostomy was performed. Comparisons between pre- and postseptostomy and low and high ECMO flow were performed in terms of absolute and relative changes. Data are presented as median and first and third quartile. Given the small sample size, the Wilcoxon rank sum test was used to assess individual variable differences. P values <0.05 were considered to indicate statistical significance. Statistical analyses were performed using SPSS version 13.0 (SPSS).




**Central Illustration. Effect of balloon atrial septostomy (BAS) in cardiogenic shock supported by V-A ECMO.** A: Protocol Timeline: BL - baseline; CS - cardiogenic shock induction; CS+ECMO No BAS - ECMO ramp-up protocol without septostomy; BAS red arrow - BAS performed; CS+ECMO+BAS - ECMO ramp-up protocol with septostomy. Numbers in circles are data collection timepoints. Panel B: Immediate effect before and after septostomy was performed at constant VA ECMO support. Box plot represents values after septostomy relative to pre-septostomy. After septostomy, mechanical work (PVA) decreased in 7 of 8 animals, on average by 24% (of pre-septostomy value) indicated by white arrow. Stroke volume decreased by 24%. Sample pressure-volume loop illustrates typical change from prior- to post-septostomy (indicated by arrow) in one animal. Panel C1 - No septostomy and Panel C2 –Septostomy: change in LV mechanics parameters due to stepwise increase in VA ECMO support from low to high flow (40-80 ml/kg/min). 100% represents low flow values. With septostomy versus no septostomy, increasing VA ECMO support resulted in significantly less mechanical work increase (121 vs. 175%, p 0.012, i.e. 30% reduction), lower end-systolic pressure and lower stroke volume. PV loops nicely illustrate, that though BAS prevents volume loading, ECMO-elevated end-systolic pressure still causes considerable increase in LV work. PVA – pressure-volume area; P – pressure, V – volume, es – end-systolic, ed – end-diastolic; SV – stroke volume.

## Results

Eleven animals entered the protocol; however, 3 were excluded from further analyses because of serious or fatal complications: unrecoverable ventricular fibrillation, extremely severe CS not allowing low ECMO flows, and hemorrhagic shock. Hence the results from 8 adult swine (56 kg [53-58 kg]) are presented.

***Table 1.***

| Baseline | | | CS Induction | | | CS parameters | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Animal ID | Body weight [kg] | BL CCO* [ml/kg] | Coronary occlusion duration [min] | VF† onset after occlusion [min] | # of Defibrillations | $SO_2$ PAC‡ [%] | NIRS Head§ [%] | CCO* [LPM] | CCO* % BL | MAP‖ [mmHg] | ECMO [ml/min] | NOR¶ [µg/kg/min] |
| 11 | 48 | 104 | 58 | 0 | 2 | 53 | 56 | 1.48 | 30% | 47 | 2,090 | - |
| 10 | 48 | 135 | 63 | 42 | 12 | 61 | 48 | 1.48 | 23% | 56 | 2,400 | 0.09 |
| 8 | 59 | 105 | 53 | 3 | 4 | 81 | 64 | 2.55 | 41% | 53 | 2,130 | - |
| 7 | 55 | 133 | 65 | 4.5 | 5 | 65 | 48 | 2.25 | 31% | 37 | 1,940 | 0.12 |
| 6 | 68 | 113 | 51 | 2.5 | 6 | 51 | 49 | 1.94 | 25% | 41 | 2,400 | 0.20 |
| 4 | 58 | 117 | 66 | 2 | 7 | 43 | 40 | 2.41 | 35% | 30 | 1,060 | 0.57 |
| 2 | 55 | 91 | 42 | 31 | 16 | | 44 | 2.3 | 46% | 64 | 1,114 | Dop# |
| 1 | 56 | 107 | 56 | 14 | 1 | 59 | 67 | 2.4 | 40% | 46 | 1,010 | - |
| *aver* | *55.9* | *113.2* | *56.8* | *11.5* | *6.6* | *59.0* | *52.0* | *2.1* | *34%* | *46.2* | *1,713* | *0.16* |
| *SD* | *6.4* | *14.8* | *8.1* | *16.3* | *4.5* | *11.2* | *8.9* | *0.4* | *8%* | *10.5* | *537* | *0.20* |

***Table 1.*** **Baseline (BL) characteristics, cardiogenic shock (CS) induction and cardiogenic shock parameters.** * CCO = continuous cardiac output; † VF = ventricular fibrillation; ‡ SO2 PAC = oxygen saturation in pulmonary artery catheter; § NIRSHead = near-infrared spectroscopy tissue oximetry in forehead; ‖ MAP = mean arterial pressure; ¶ NOR = norepinephrine immediately after CS induction; # Dop. = dopamine temporary administration

## CS model, induction

After CS induction and stabilization, cardiac output was 33% (28%-40%) of baseline, and the minimum ECMO flow tolerated by the animals was 31 mL/kg/min (20-38 mL/kg/min). Four animals required administration of norepinephrine (0.09-0.60 mg/kg/min) to maintain MAP. Norepinephrine was down-titrated as early as possible and was kept constant during the measurement phases. One animal required temporary administration of dobutamine. *Table 1* provides details on baseline and CS parameters.

## Septostomy

Intracavitary echocardiography demonstrated significant blood flow from the left to the right atrium. Disappearance of interatrial pressure gradient repre-

sented by pulmonary capillary wedge pressure minus central venous pressure 2 mmHg (1.2- 3.5 mmHg) indicated unrestrictive condition. Post mortem evaluation revealed an average septostomy diameter of 8.9 mm (7.9-9.2 mm). For sample results, see *Figure 1B.*

**Septostomy - immediate effect at constant ECMO flow in CS**

After BAS had been performed, significant decreases in all mechanical work parameters were observed (*Central Illustration B*): PVA decreased to 78% (62%-89%), SW to 66% (43%-87%), and PE to 71% (57%-84%); all values are relative to preseptostomy. In post- versus pre-BAS, we did not notice any significant changes in tissue and venous oximetry, central venous pressure (4 mmHg vs 5 mmHg; P = NS), pulmonary artery pressure (29 mmHg vs 31 mmHg; P = NS), and thermodilution cardiac output (2.1 L/min vs 2.2 L/min; P = NS). For details, see *Table 2*. Sample PV loops illustrating the immediate effect of BAS are provided in *Figure 2B.*

***Figure 1.***

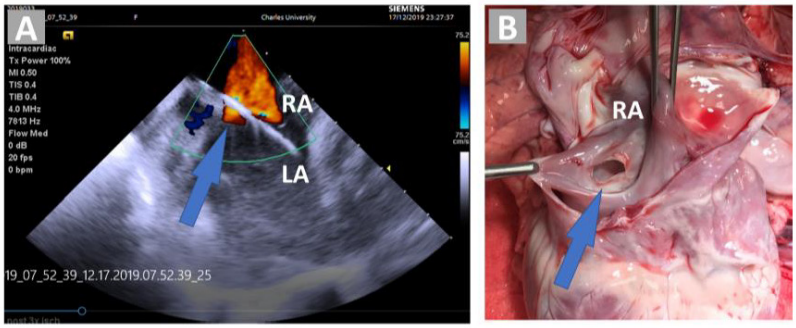



***Figure 1.*** **Septostomy sample evaluation.** Panel A: intracardiac echocardiography. Arrow points to septostomy between left atrium (LA) and right atrium (RA). Panel B: post mortem. Arrow points to septostomy – view from right atrium (RA). See online supplement video for sample echocardiography loop.

**Increasing ECMO flow in CS – without versus with atrial septostomy**

Without septostomy, increased ECMO flow from low to high (typically 40 - 80 mL/kg/min) resulted in a marked increase in LV mechanical work (Central Illustration C): PVA 172% (138%-199%) (P = 0.012, high vs low flow), SW 151% (102%-200%) (P = NS), and PE 186% (168%-229%) (P = 0.012). With BAS, the same change in ECMO flow from low to high resulted in a significantly lower increase in PVA of 122% (104%-131%) (P = 0.026 vs no BAS), a decrease in SW of 95% (86%-102%) (P = 0.020 vs no BAS), and no different PE increase. For details, see *Table 3*. Sample PV loops from 1 typical animal and 1 animal with profound CS are presented in *Figures 2C* and *2D*, respectively.

***Table 2.***

| | | Pre | BAS | Post | BAS | Pre/ Post | Absolute Post-Pre | | Relative Post/Pre | | Correlation w PVA rel. |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | unit | avg | SD | avg | SD | p | avg | SD | avg | SD | |
| PVA* | mmHg.ml | 4,827 | ±2639 | 3,460 | ±1997 | 0.006 | 1,367 | ±991 | 76% | ±16% | n.a. |
| SW† | mmHg.ml | 1,980 | ±2117 | 1,412 | ±1964 | 0.006 | -567 | ±409 | 66% | ±34% | 0.9192 |
| PE‡ | mmHg.ml | 2,848 | ±1436 | 2,012 | ±1011 | 0.010 | -836 | ±677 | 74% | ±19% | -0.0487 |
| P es§ | mmHg | 74 | ±13 | 63 | ±14 | 0.005 | -11.0 | ±7.3 | 85% | ±11% | 0.7088 |
| P ed‖ | mmHg | 13 | ±4 | 10 | ±2 | 0.011 | -3.9 | ±3.0 | 74% | ±16% | -0.8306 |
| V es¶ | ml | 81 | ±45 | 71 | ±48 | 0.049 | -9.4 | ±10.5 | 83% | ±16% | -0.3850 |
| V ed# | ml | 130 | ±65 | 108 | ±53 | 0.023 | -22.3 | ±20.3 | 85% | ±9% | 0.4756 |
| SV** | ml | 49 | ±37 | 36 | ±33 | 0.056 | -13 | ±15 | 76% | ±22% | 0.9035 |
| C.O.†† | ml/min | 3,443 | ±2,281 | 2,768 | ±2,381 | 0.042 | -728 | ±775 | 79% | ±19% | 0.9337 |
| $SO_{2\ PAC}$§§ | % | 77 | ±16 | 78 | ±14 | 0.535 | 1 | ±4.3 | 102% | ±7% | 0.7612 |
| $SO_{2\ SVC}$ | % | 79 | ±13 | 79 | ±13 | 0.502 | 0.5 | ±1.9 | 101% | ±2% | -0.4602 |
| $NIRS_{Head}$ | % | 62 | ±9 | 61 | ±9 | 0.334 | -0.7 | ±1.6 | 99% | ±2% | 0.4057 |
| $NIRS_{R}$ | % | 66 | ±10 | 69 | ±10 | 0.180 | 2.9 | ±5.1 | 105% | ±9% | 0.0198 |

***Table 2.*** **Immediate effects of septostomy in cardiogenic shock treated by V-A ECMO.** The values are taken before (Pre) and after (Post) balloon atrial septostomy (BAS) at constant peripheral VA ECMO flow.

* PVA = pressure volume area; † SW = stroke work; ‡PE = potential energy; §P es = end-systolic pressure; ‖P ed = end-diastolic pressure; ¶ V es = end-systolic volume; # V ed = end-diastolic volume; ** SV = stroke volume; ## C.O. = LV cardiac output; §§ SO2 PAC= oxygen saturation pulmonary artery catheter, SO2 SVC = oxygen saturation superior vena cava; NIRS = near-infrared spectroscopy tissue oximetry. Head = forehead, R = right fore-arm. Correlation of each parameter change (post/pre BAS) with PVA change (post/pre BAS).

*Table 3.*

| | | V-A ECMO, NO BAS | | | | | | | V-A ECMO + BAS | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| V-A ECMO Flow | | Low | | High | | p | Hi/Low | | Low | | High | | p | Hi/Low | |
| PVA* | mmHg.ml | 3,759 | ±2193 | 5,795 | ±2931 | 0.005 | 175 | ±53% | 3,637 | ±1740 | 4,127 | ±2105 | 0.175 | 121 | ±36% |
| SW† | mmHg.ml | 1,845 | ±1947 | 2,325 | ±2153 | 0.155 | 145 | ±62% | 2,068 | ±1642 | 1,857 | ±1515 | 0.194 | 87 | ±27% |
| PE‡ | mmHg.ml | 1,914 | ±1484 | 3,470 | ±2667 | 0.014 | 212 | ±87% | 1,569 | ±1317 | 2,270 | ±1448 | 0.018 | 217 | ±147% |
| P es§ | mmHg | 59 | ±14.1 | 88 | ±9.6 | 0.000 | 155 | ±34% | 56 | ±11.7 | 75 | ±15.6 | 0.003 | 137 | ±11.5% |
| P ed‖ | mmHg | 15 | ±4 | 16 | ±7 | 0.372 | 111 | ±28% | 10 | ±2.6 | 10 | ±4 | 0.696 | 102 | ±2.6% |
| V es¶ | ml | 67 | ±54 | 83 | ±64.3 | 0.015 | 131 | ±26% | 55 | ±45.6 | 64 | ±44.3 | 0.011 | 143 | ±6.5% |
| V ed# | ml | 114 | ±60.7 | 126 | ±68.8 | 0.053 | 111 | ±11% | 103 | ±46.6 | 98 | ±46.5 | 0.433 | 97 | ±11.9% |
| SV** | ml | 50 | ±40 | 47 | ±41 | 0.582 | 92 | ±22% | 51 | ±35.6 | 39 | ±28 | 0.028 | 77 | ±17% |
| C.O.†† | l/min | 3.76 | ±2.96 | 3.27 | ±2.88 | 0.333 | 90 | ±28% | 3.56 | ±2.46 | 2.7 | ±2 | 0.032 | 79 | ±20% |
| MAP | mmHg | 51 | ±12.2 | 77 | ±8 | 0.003 | 160 | ±49% | 45 | ±10 | 69 | ±12.5 | 0.000 | 158 | ±5.4% |
| $SvO_2$ PAC | % | 62 | ±16 | 80 | ±12 | 0.003 | | | 72 | ±12 | 87 | ±6 | 0.001 | | |
| $SvO_2$SVC | % | 70 | ±16 | 84 | ±8 | 0.056 | | | 72 | ±9 | 84 | ±8 | 0.003 | | |
| NIRS $_{Head}$ | % | 52 | ±9 | 65 | ±4.6 | 0.005 | | | 55 | ±8.9 | 65 | ±9.6 | 0.000 | | |
| NIRS $_{R}$ | % | 56 | ±9 | 66 | ±6.7 | 0.001 | | | 61 | ±8.8 | 72 | ±9.8 | 0.000 | | |

***Table 3.* Effects of increasing V-A ECMO flow (Low = 40 ml/kg/min, High = 80 ml/kg/min) without and with balloon atrial septostomy (BAS) on left ventricular mechanics, systemic hemodynamics and oximetry.*** PVA = pressure volume area; † SW = stroke work; ‡PE = potential energy; §P es = end-systolic pressure; ‖P ed = end-diastolic pressure; ¶ V es = end-systolic volume; # V ed = end-diastolic volume; ** SV = stroke volume; ## C.O. = cardiac output; §§ SO2 PAC= oxygen saturation pulmonary artery catheter, SO2 SVC = oxygen saturation superior vena cava; NIRS = near-infrared spectroscopy tissue oximetry. Head = forehead, R = right forearm. p-value reflects comparison of respective parameter at High vs. Low ECMO flow

***Figure 2.***

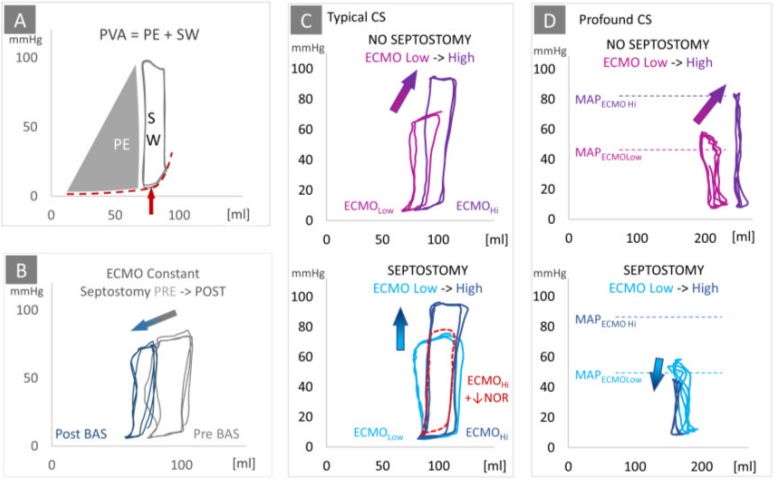



***Figure 2:* Sample PV loops illustrating LV mechanics in CS supported by variable VA ECMO flow with and without atrial septostomy.** Panel A: PV loop from animal #1 illustrating the key compoments of PVA: SW – area inside PV loop, PE - gray triangle. Red dashed line represents diastolic compliance, that is markedly non-linear in the last portion. Panel B: Comparison of PV loops minutes before and after septostomy at constant VA ECMO flow. Both pressure and volume unloading and SV reduction after BAS can be clearly identified. Panel C: Representative loops form CS animal demonstrating the change of PV loop morphology under low and high V-A ECMO support (40 to 80 ml/kg/min, indicated by arrow). Top looops – before septostomy, bottom after septostmy. BAS prevents volume loading, but not pressure increase. Red dotted loop shows the effect of reducing noradrenaline infusion after elevating ECMO support. Panel D: identical to Panel C but profound CS is presented. Narrow PV loops at high ECMO support indicate non-ejecting LV unable to compete with ECMO. PVA – pressure-volume area, SW – stroke work, PE - potential energy; MAPECMO – mean arterial pressure at given V-A ECMO support (low or high). ↓NOR – noradrenaline infusion reduced by 50%.

**Discussion**

The most extensive available experience with BAS during VA ECMO comes from a retrospective investigation of 64 pediatric and adult patients. This technique was rapidly able to resolve pulmonary edema within 24 hours [11]. Our results in an acute ischemic heart failure model support the idea that BAS is a powerful unloading tool. The key finding is that besides volume unloading, a very important component of LV work reduction by BAS is end- systolic pressure decrease.

**Hemodynamic effects of atrial septostomy in peripheral VA-ECMO**

Under near maximal VA ECMO support, atrial septostomy resulted in rapid reduction of LV work (PVA) by 22%. This is less than with the Impella (~35%) and more than with a pulmonary artery drainage cannula (~10%), as we observed in a preceding study with a similar hemodynamic setup [7]. Thus, BAS belongs among the most powerful nonsurgical LV unloading methods. Further investigation should be performed to quantitatively compare the effect of septostomy and biatrial drainage-left atrial VA ECMO [12,13].

The expected effect of BAS is LV preload reduction. Indeed, LV end-diastolic volume decreased in all subjects (by ~10%), but in 2 cases this did not translate into significant work reduction (*Central Illustration B*). Also, the correlation between the decrease in LV end-diastolic volume and PVA was rather weak (0.472), indicating that other parameters of LV work reduction play an important role. Among all LV parameters, the strongest correlation with PVA decrease was found for stroke volume (0.904), which also expressed a larger relative change pre- versus post-BAS (~22% decrease) and contributed to reduced cardiac output and hence reduced total minute volume (ie, cardiac output + ECMO flow). With reduced minute volume, blood pressure should decrease and/or total peripheral resistance should increase. We observed a reduction in end-systolic pressure of about 15%. Thus, besides volume unloading, pressure reduction is a very important component of LV unloading and recovery strategy. Despite reduced MAP and cardiac output, oxygen delivery did not seem to deteriorate, as reflected by unchanged tissue oximetry and superior vena cava saturation (*Table 2*). Although no oxime- try parameter is an ideal marker of oxygen delivery and/or tissue perfusion during VA ECMO support, the combination of several venous and tissue results, which are all in accord, offers reasonable insight. Following BAS, we did not notice any signs of right ventricular overload. We hypothesize that VA ECMO may have provided some unloading to the right ventricle.

**Atrial septostomy - unloading effect in increasing VA-ECMO flow**

To better understand the effects of BAS in a more complex setup and in the longer term, we compared the effects of stepwise increasing peripheral VA ECMO flow with versus without BAS.

**VA ECMO without LV unloading**

When ECMO flow was increased from 40 to 80 mL/kg/min, total myocardial work (PVA) almost doubled (172%), while end-diastolic volume increased moderately by 11% (P = 0.05) (*Table 3*). This corresponds to other findings from acutely failing hearts that dilate consider- ably less compared with chronic heart failure [14,15]. Again, a much stronger determinant of LV work increase was end-systolic pressure, which grew by 44%, 4 times more than the end-diastolic volume change. Such pressure increase also indicates that some contractile reserve exists even in failing hearts. It may be recruited by high VA ECMO flow via LV dilatation (the Frank-Starling mechanism) and/or by increasing diastolic arterial pressure (hence improving coronary perfusion). Both mechanisms increase the force of contraction and thus help maintain stroke volume and cardiac output despite increased afterload, both at the cost of increased oxygen demand. Surprisingly, an LV end-systolic pressure increase was seen even in our most profound CS case, in which a considerably dilated left ventricle was unable to eject against growing afterload generated by VA ECMO. But even with virtually zero pulse pressure, LV mechanical work increased to 170% (*Figure 2D*). This observation would remain completely obscured if LV pressure and volumes were not monitored, and thus the left ventricle might be wrongly considered as resting.

In VA-ECMO with atrial septostomy, step-up ECMO flow resulted in significantly less PVA increase than without BAS (122% vs 172%). Virtually no preload increase was observed, indicating efficient left atrial unloading, which may even have been proportional to ECMO flow. In contrast, end-systolic pressure (afterload) still grew considerably (~134%), representing again a major determinant of LV work increase. Greater LV afterload with limited LV preload likely explain stroke volume reduction (by ~23%), which was a key mechanism opposing PVA increase.

To reduce PVA, in some animals with MAP well over 60 mmHg, we down-titrated norepinephrine support after the experimental step was completed. This way we were still able to maintain tissue perfusion, as reflected by unchanged tissue and central venous oximetry and even achieve absolute reduction in mechanical work at full ECMO support (see red loop in *Figure 2C*).

**Clinical implications**

Septostomy is an efficient method to reduce preload and afterload. It is percutaneous, affordable, and widely available, and it does not introduce artificial bodies or challenge the aortic valve, so it may be considered among the top-level unloading strategies. To stay efficient, several core principles must be respected.

*Hemodynamic optimization*. In VA ECMO, every effort should be taken to reduce myocardial work load before considering additional mechanical intervention, as noted by Camboni and Schmid [16]. Also, heart rate must be

kept low because of its paramount effect on myocardial oxygen consumption and delivery.
Volume unloading is a common target in peripheral VA ECMO venting, but it was not the strongest determinant of work reduction in BAS, as explained earlier. Additionally, end-diastolic volume can sometimes be a misleading target: the diastolic PV relationship is nonlinear, often with steep portion, specifically in acute CS (*Figure 2A*, red arrow). Even a small change in LV end-diastolic volume might correspond to a dramatic change in LV end-diastolic pressure, conveying a high risk for pulmonary edema. Such a situation was observed in half of our cases. Clinically it can easily be identified by pulmonary wedge pressure monitoring.

*"Permissive hypotension".* In the setting of acute CS treated with peripheral VA ECMO, the major determinant of LV mechanical work increase may be end-systolic pressure (rather than volume increase), as demonstrated in this study. When aiming for the lowest LV work to support myocardial recovery, "pressure unloading" should be targeted together with volume unloading. Septostomy provides both effects. Although some data indicate that higher MAP is associated with survival [17], other investigators recommend resting the heart as much as is reasonable [18,19] and moderate to rather low MAP [20,21]. Our venous and tissue oximetry results indicate that even MAP of about 50 mmHg may provide sufficient oxygen delivery (*Table 3*). Thus, we favor "permissive hypotension," with MAP of roughly 60 mmHg, pro- vided that coronary revascularization and perfusion are sufficient and organ perfusion is preserved, again mandating continuous monitoring.
Vasopressors are often used to control MAP during CS. Even moderate doses have dramatic effects on peripheral resistance, tissue perfusion, and myocardial work (hence oxygen demands and myocardial recovery). With any increase in ECMO support, MAP most likely increases as well, and thus down-titration of vasopressors should be considered. Maintaining vasopressors may oppose a significant portion of unloading effect and/or contribute to a nonejecting left ventricle.

*Monitoring.* In CS, hemodynamic and metabolic status may evolve dramatically and frequently. Conclusions drawn from systemic pressure and incidental LV volume assessment may be overtly inaccurate. Proper evaluation of myocardial work, recovery, and hemodynamic consequences requires frequent or continuous, accurate monitoring of ventricular chamber pressures, volumes, flow, systemic pressures, multiple oximetry parameters, metabolic markers, and organ functionality. Pulmonary artery catheterization is strongly advocated [22,23], but pulmonary artery saturation must be interpreted with caution; because of both VA ECMO support and shunt flow, it does not represent mixed venous blood and hence systemic perfusion. Multiple tissue oximetry monitoring is an attractive alternative [24]. Optimally, a decision support system analyzing and interpreting in real time multiple

interdependent, frequently changing parameters would be extremely valuable. Recent hemodynamic models, such as Aplysia (Aplysia Medical) or Harvi (PVLoops) seem promising and ultimately the only practically applicable approach to managing such complex situations at the bedside [21,25].

*BAS Limitations.* By reducing LV work and stroke volume, septostomy may contribute to a nonejecting left ventricle, with potential development of intracavitary or aortic root blood stasis and, hence, high risk for thrombus formation with devastating consequences. Adequate anticoagulation and careful hemodynamic monitoring are mandatory. Pulse pressure values approaching or <10 mmHg should draw immediate attention. Echocardiography is indispensable, as it can rapidly confirm significant reduction of aortic valve opening during systole and differentiate between hypovolemia and severe dilatation with low contractility. Smokelike sign in the left ventricle, associated with severely reduced aortic valve opening or its protracted closure, should prompt effective actions to counteract such a complication. Available remedies include downtitrating VA ECMO support, “permissive hypotension,” carefully titrated inotropes, intra-aortic balloon pumps, and, ultimately, alternative LV venting methods.
Another concern is poor control over atrial communication size, which can further evolve over time. Premature closure has not been reported. In adults, persistent atrial septal defect is often asymptomatic or may cease. In one pediatric cohort, persisting shunt was documented in about 75% of survivors with mild to moderate signs of right-sided overload [5]. If indicated, the defect can be closed percutaneously by transcatheter devices (such as Amplatzer). In cases in which other cardiac surgery is performed, the defect is closed during these procedures. Episodes of heart failure recurrence or worsening after ECMO weaning due to septostomy have not, to our knowledge, been reported.

**Study Limitations**
*The CS model.* Despite the use of homogeneous population and strict adherence to the protocol, the resulting degree of CS was less uniform than planned, probably because of the variability in coronary anatomy, time to hemodynamic stabilization, myocardial electric stability, and capillary permeability (leaking). Also, CS severity might have changed over several hours of the study. Thus, we report the data as ratios (before and after the intervention) rather than absolute differences.

*Septostomy model.* Unfortunately, we were unable to accurately quantify blood flow through the atrial septostomy, nor we did measure shunt fraction. On the basis of thermodilution and PV cardiac output measurement, we estimated a shunt fraction of 1.25. After BAS, the interatrial pressure gradient was 2 mmHg, indicating unobstructive condition.

*O2 consumption.* On the basis of classic work by Suga [26], we assumed a linear relationship between PVA and oxygen consumption. Variable contractility and variable calcium cycling efficacy in failing myocardium, which might offset the PVA/oxygen relationship [27], were not considered in our interpretation.

*PV measurements.* Although impedance-based PV measurement represents the gold standard in CS studies, by design, the method is prone to volume drifts (due to varying impedance), specifically over long periods of time. Frequent recalibration would improve the accuracy, but this is technically challenging, as all usual cardiac output measurement methods may easily be adversely affected by VA ECMO and BAS. Contrast-enhanced computed tomography seems an ultimate tool to accurately quantitate hemodynamic status during VA ECMO [28].

**Conclusions**

In acute CS supported by peripheral VA ECMO, atrial septostomy provides immediate and significant work reduction (approximately 22%) by reducing both preload (end-diastolic volume) and afterload (end- systolic pressure). Vasopressors and inotropes, which are commonly used in these situations, may increase LV work substantially, even in relatively low doses. If LV work reduction is a priority, pharmacology support should be carefully kept as low as possible.

## PERSPECTIVES

**WHAT IS KNOWN?** A failing left ventricle sup- ported by VA ECMO often mandates unloading. Atrial septostomy is among a handful of possible interventions. However, its mechanism and quantification have yet not been fully understood.

**WHAT IS NEW?** BAS can significantly reduce LV work by about 22% by reducing preload, afterload, and stroke volume. Thus, septostomy belongs among the most powerful unloading strategies. When elevating VA ECMO support, the major determinant of LV work increase is end-systolic pressure (afterload). Thus, besides unloading, careful blood pressure control should be an essential component in CS management with VA ECMO assistance.

**WHAT IS NEXT?** In CS, LV preload, afterload, unloading efficacy, and oxygen supply and demand may evolve readily over minutes. VA ECMO management on the basis of incidental evaluation of systemic arterial pressure and LV volume (or pulmonary wedge pressure) may be overtly incomplete or inaccurate. Decision support systems analyzing and interpreting multiple interdependent, real-time hemodynamic, perfusion, and oximetry data on the basis of recent computational models (Aplysia, Harvi) seem promising and ultimately the only practically applicable approach to bedside management of complex situations such as CS.

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# Chapter 7.

## Influence of left ventricular unloading on pediatric veno-arterial extracorporeal life support outcomes

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**Abbreviations**
AS: Atrial septostomy
E-CPR: extracorporeal-cardiopulmonary resuscitation
CHD: Congenital Heart Disease
IABP: Intra-aortic Balloon Pump
LV: Left Ventricle
V-A ECLS: Veno-arterial extracorporeal life support

**Abstract**

**Background**

The effectiveness of veno-arterial extracorporeal life support (V-A ECLS) in treating neonatal and pediatric patients with complex congenital cardiac disease (CHD) and requiring cardio-circulatory assistance is well known. Nevertheless, the influence of left ventricle (LV) distension and its countermeasure, namely LV unloading, on survival and clinical outcomes in neonates and children treated with of V-A ECLS needs still to be addressed. Therefore, the aim of the current study is to determine the effects of LV unloading on in-hospital survival and complications in neonates and children treated with of V-A ECLS.

**Methods**

The clinical outcomes of 90 CHD pediatric patients under 16 years of age supported with V-A ECLS for post-cardiotomy cardiogenic shock (CS) in a tertiary center were retrospectively reviewed, particularly in relationship with the presence or absence of an active LV unloading strategy.

**Results**

The patient cohort included 90 patients (age range 19,6±339,8 months, 64,4% males), 42 of whom were vented with different techniques (38 with atrial septostomy or left atria cannula, 2 with cannula from LV apex, 1 with intra-aortic balloon pump and 1 with pigtail across aortic valve). Unloading strategy significantly increased the in-hospital survival (OR= 2.74 CI 1.06-7.08; p= 0,037). On the contrary, extracorporeal cardio-pulmonary resuscitation decreased the related survival (OR= 0.323, CI 1.09-0.96; p= 0,041). The most common complications were infections (28.8%), neurological injury (26%) and bleeding (25.6%). However, these did not differently occur in venting and no-venting groups.

**Conclusion**

In pediatric CHD patients supported with V-A ECLS for post-cardiotomy CS, the LV unloading strategy was associated with increased survival.

## Introduction

The effectiveness of veno-arterial extracorporeal life support (V-A ECLS) in supporting neonatal and pediatric patients with post-cardiotomy shock following correction of complex congenital cardiac disease (CHD) is well established [1]. Although V-A ECLS is able to unload the right ventricle, the effect of retrograde flow in the aorta towards the left ventricle (LV) is one of the most important concerns in this setting. Indeed, mainly in the presence of severe myocardial dysfunction, the V-A ECLS-related LV afterload increase may not be overcome by the LV [2]. This may lead to LV dilatation, increased left atrial pressure and pulmonary oedema. Additionally, LV overload increases wall stress and myocardial oxygen consumption, jeopardizing ventricular recovery. In case of severe overload, the aortic valve may remain constantly closed causing blood stasis and thrombi formation in the LV [3]. Left heart overload in pediatric patients managed on V-A ECLS may be mainly addressed by atrial septostomy (AS) [4], although alternative techniques may be also applied[5]. Most of the reported experience of LV decompression in pediatric V-A ECLS patients consist of case reports and small case series [ 6,7].

The few largest published studies were able to demonstrate that adequate LV decompression can only prevent the above-mentioned related complications [8,9]. Given the limitations of these studies, however, LV unloading in pediatric patients has never been specifically addressed and associated with improved ECLS in-hospital survival [9,10].

We aimed to determine the effects of LV unloading on in-hospital survival and complications in neonates and children treated with of V-A ECLS in a referral center for pediatric cardiac surgery.

## Methods

Between December 2010 and January 2020, a total of 115 patients received V-A ECLS support in our pediatric intensive care unit. Patients with complex anatomy were excluded. A complex anatomy was defined as the presence of mixing physiology at the atrial or ventricular level with a documented shunt between right and left circulation or when this shunt could not be excluded. Therefore, this could not allow to judge the effect of LV venting,The analyzed patients were less than 16 years of age, the mean age was 17.3±31.54 months. The 64.4% were males. The indication for V-A ECLS was the evidence of low cardiac output syndrome, cardiogenic shock, or extracorporeal-cardiopulmonary resuscitation (E-CPR). We retrospectively reviewed the major clinical outcomes, including survival and complications, in relationship with the occurrence of an active LV unloading strategy.

### *Techniques of left ventricular venting*

Decompression procedures were performed in the operative room immediately after V-A ECLS initiation. The LV unloading strategy was set at the discretion of the local Heart Team (including the intensivist, the cardio-surgeon, and the anesthesiologist) each time such a procedure was considered necessary. The

main criteria for this decision-making process were the hemodynamic status and/or degree of LV distension/disfunction, defined with an echocardiographic evaluation (moderate to severe reduction of LV ejection fraction, namely less than 45%, LV dilatation with/without “smoke-like” effect, increased LV filling pressure). A venting strategy was used in patients whenever there was evidence of poor decompression of the left side of the heart. If left-sided structures were distended, a low-moderate dose of epinephrine infusion (<0.1 mcg/kg/min) was started to improve the contractility and LV ejection. LV decompression was achieved in different locations in our center: 1) Left atrium: either with a direct insertion of a venting cannula through the superior pulmonary vein or through atrial septostomy 2) left ventricle: either with a cannula draining blood from the LV apex or pigtail catheter across aortic valve 3) Aorta: intra-aortic balloon pump (IABP). The decision among the available unloading techniques was based on three main criteria: clinical scenario, patient anatomical features, surgical expertise. The unloading effect was carefully monitored during the following ICU stay through serial clinical, echocardiographic, and instrumental (X-ray) evaluations.

*Atrial Septostomy and atrial cannula vent*
An atrial septal fenestration (2.5 – 3.5 mm according to the patient’s weight) was surgically performed in the overwhelming majority of the patients, leading to a left-right communication. Differently and less frequently, according to the clinical scenario and the appliable cannula size, we also placed a curved venous cannula (Edwards Lifescience TF010-090, Pacifico cannula 8-10 Fr) in the left atrium as a drainage cannula through the superior pulmonary vein.

*Left ventricular apex venting and pigtail across aortic valve*
These techniques can draw directly from the LV. The LV venting cannula needed to be carefully implemented from the LV apex in the operation room. Whereas, a guide wire was first used to cross the aortic valve, allowing the 6 F pig tail catheter to be advanced over it into the LV in a small size neonate, weighing less then 3 kilograms. Patients were carefully observed with electrocardiographic and hemodynamic monitoring.

*Intra-aortic balloon pump implantation*
The IABP implementation in a pediatric patient should carefully evaluate and perform. The choice of the insertion site and balloon length, according to the related guidelines, are crucial to avoid complications, such as cerebrovascular accidents, renal and mesenteric ischemia. We used to implant IABP only in pediatric patients weighting above 40 kg. Therefore, the contra-lateral femoral artery of the V-A ECLS cannulation site was used for balloon placement (Seldinger method). If feasible (no major resistance at IABP passage through the small skin incision), a sheathless technique was used to reduce the incidence of leg ischemia. The tip of the balloon was placed 1 cm distal to the junction with the left subclavian artery, as assessed by echocardiographic assessment and by a mobile chest x-ray system at the bedside. Either of the

electrocardiogram or the aortic blood pressure curve was used as a trigger; for the electrocardiogram, the descending section of the R wave (representing closing of the aortic valve) was used to calibrate the counter-pulsation interval, with an IABP ratio of 1:1.

*Primary and secondary endpoints*

In-hospital patient survival was the primary endpoint investigated to assess the effect of LV unloading. Furthermore, the secondary endpoints included the mortality on ECLS and after weaning, as well as all the occurred complications, including liver and kidney end organ damage (defined as creatinine and bilirubin peaks). Data on adverse events included: cerebral injury (stroke, transitory ischemic attack, intracranial hemorrhage and seizures by electroencephalogram), acute kidney injury requiring continuous renal replacement therapy, hemolysis (defined as increased free hemoglobin level above 50 mg/dl ), peripheral vascular damage, infections (defined as positive bacterial, fungal or viral culture or polymerase chain reaction test), coagulation disorders (either thrombosis or hemorrhage) and ECLS failure (pump or oxygenator failure, or both).

*Statistical analysis*

Unless otherwise specified, data are presented as mean (minimum-maximum) or frequency (%). Paired vented / no vented V-A ECLS data were compared using two tails significance T-Test for independent continuous samples or two tails significance chi-square for categorical variables. The association between the main outcomes and dependent predictors were tested through a binary logistic regression model. Furthermore, based on the binary logistic regression model and depending on the emerged significant variables, the patients were assigned to different groups. Survival assessment included Kaplan Meier analysis with Log Rank test for differences between groups, producing a hazard ratio with 95% confidence interval. All the statistical tests were done using computerized packages (SPSS 22.0, IBM, Chicago, IL and a MedCalc, Ostend, Belgium).

**Results**

Among 115 pediatric patients supported with V-A ECLS in our pediatric intensive care unit, 25 were excluded according to their complex anatomy. A total of 90 patients were analyzed. All supports were placed in post-cardiotomy setting. Among them, 26.7% accounted for Dextro-Transposition of the great arteries (d-TGA), 14.4% for pulmonary artery disorders, while 12.2% were represented by other valve disease. The distribution of CHD is presented in detailed in *Table 1*. In 42 patients the LV was vented, while the remaining 48 were supported with V-A ECLS alone.

*Demographic and clinical features*

The two groups didn't present any significant differences in terms of age, weight, risk adjustment for congenital heart surgery method 1 and main

baseline features such as kidney or liver function. Patients who received venting strategy had a higher occurrence of either systemic or pulmonary hypertension (systemic hypertension: no venting 18.3% vs venting 45.2%, p=0.021; pulmonary hypertension: no venting 16.3% vs venting 23.8%, p=0.013). E-CPR occurrence didn't differ between two groups (no venting 26.7.% vs venting 23.8%, p=0.759). All demographic and clinical features are shown in *table 2*.

***Table 1.***

| Baseline congenital heart disease | N (Percentage) |
|---|---|
| LA aneurysm and Superior Cava Vein in Coronary sinus | 1 (1.1 %) |
| Anomalous pulmonary venous return | 4 (4.4%) |
| Atrioventricular canal (AVC) | 5 (5.6%) |
| AVC | 4 |
| AVC and hypoplastic Aortic Arch | 1 |
| Combined disorder | 6 (6.7%) |
| Coronary artery abnormalities | 6 (6.7%) |
| Double outlet right ventricle | 3 (3.3%) |
| Aortic arch interruption | 1 (1.1 %) |
| Outflow tract obstruction | 1 (1.1 %) |
| Patent ductus arteriosus | 2 (2.2 %) |
| Pulmonary artery disorders | 13 (14.4%) |
| Pulmonary atresia and Ventricular septal defect | 1 |
| Pulmonary atresia, Ventricular septal defect and MAPCAS | 8 |
| Pulmonary and aortic stenosis | 2 |
| Pulmonary sling | 2 |
| Shone Syndrome | 2 (2.2%) |
| Dextro-Transposition of the Great Arteries (d-TGA) | 24 (26.7%) |
| d-TGA | 12 |
| d-TGA and Atrial or Ventricular septal defect | 10 |
| d-TGA and Ebstein | 1 |
| d-TGA + pulmonary stenosis | 1 |
| Tetralogy of Fallot (TOF) | 2 (2.2%) |
| TOF | 1 |
| Tetralogy of Fallot and Pulmonary atresia | 1 |
| Truncus arteriosus | 2 (2.2%) |
| Truncus arteriosus | 1 |
| Truncus arteriosus and aortic stenosis | 1 |
| Valve disease, other than pulmonary valve | 11 (12.2%) |
| Others | 7 (7.8%) |

***Table 1.* Distribution of congenital heart disease.** Legend: MAPCAS, Major Aortopulmonary Collateral Arteries, LA, left atrium.

***Table 2.***

| | No Venting (N=48) | Venting (N=42) | p-value |
|---|---|---|---|
| **Demographic** | | | |
| Age, days | 693.9±1167.7 | 476.6±835.0 | .316 |
| Male | 69.4% | 59.5% | .326 |
| Weight, kg | 9.4±9.5 | 8.0±6.8 | .427 |
| Height, cm | 74.3±28.9 | 72.7±24,5 | .773 |
| BSA | 0.4±0,3 | 0.4±0,2 | .540 |
| **Comorbidities** | | | |
| Previous CVA | 4.3% | 7.1% | .555 |
| Hypertension | Mild: 16.3%<br>Moderate: 2,0% | Mild: 38.1%<br>Moderate: 7,1% | .021 |
| Pulmonary Hypertension | Mild: 4.1%<br>Moderate: 12.2% | Mild: 21.4%<br>Moderate: 2.4% | .013 |
| Cyanotic | 53.1% | 45.2% | .457 |
| **Surgery** | | | |
| Open chest | 83.7% | 90,5% | .339 |
| RACHS I | 3.2±0.9 | 3.2±0.5 | .691 |
| AoR | 2,0% | 2.4% | .912 |
| MVR | 4.1% | 4.8% | .875 |
| CABG | 2.0% | 0% | .875 |
| **Arteriopathy** | | | |
| Inferior Arms | 2.0% | 0% | .875 |
| Thoracic Aorta | 10.2% | 4.8% | .331 |
| **Clinical features** | | | |
| EF, % | 41.2±15.8 | 37.1±18.4 | .266 |
| Creatinine, mg/dl | 0.5±0.4 | 0.5±0,4 | .647 |
| Bilirubin, mg/dl | 2.8±3.8 | 1.9±3.1 | .275 |
| Lowest Hb, g/dl | 9.3±1.4 | 9.2±1.2 | .786 |

***Table 2.*** **Demographic and clinical features.** Legend: AoR, aortic regurgitation; BSA, body surface area; CABG, coronary artery bypass graft; CVA, cerebral vascular accident; EF, ejection fraction; Hb, Hemoglobin; MVR, mitral valve regurgitation; RACHS-1, risk adjustment for congenital heart surgery method 1.

**Veno-arterial extracorporeal life support features**

Different venting techniques were used as LV unloading strategy in our patients. The majority received venting from the left atrium (N= 38, 90.5%), either with a venting cannula (N=8) or through atrial septostomy (N=30). Three patients were directly vented in the LV (N=3, 7,15%), two children through a draining cannula from the LV apex (N=2), whereas one neonate with a pigtail catheter across aortic valve (N=1). Finally, according to the body size, one intra-aortic balloon pump (IABP) (N=1, 2.35%) was placed as a venting strategy.

Technically, V-A ECLS duration was not different between vented and not vented supports. Peripheral cannulation was adopted more frequently in the no-venting group (no-venting 18.4.% vs venting 4.8%, p=0.047). Regarding the peripheral setting, the favorite arterial cannulation sites in peripheral mode were carotid artery and femoral artery, respectively, whereas femoral and jugular veins were the most common sites for the venous cannula. Finally, all central V-A ECLS were placed using the Aorta and the right atrium as implantation sites. Bivalirudin was the chosen anticoagulation strategy in the 54.2% of no vented ECLS and 47.6% of vented V-A ECLS (p=0.535). *Table 3* describes the V-A ECLS features.

**Primary and secondary outcomes**

The The primary and secondary outcomes are shown in *Table 4*. All major complications occurring on V-A ECLS such as stroke, acute kidney injury and bleeding did not show any significant difference between groups. Regarding in-hospital mortality patients who were vented on V-A ECLS showed a significant higher survival at discharge (no venting 51% vs venting 73.8 %, p=0.026). Although deaths on V-A ECLS did not differ between the two groups, with higher post-weaning death rate in no-venting V-A ECLS patients (no-venting 22.4% vs venting 7.1%, p=0.398).

***Table 3.***

| | No venting (N=48) | Venting (N=42) | p-value |
|---|---|---|---|
| **V-A ECLS features** | | | |
| E-CPR | 26.7% | 23.8% | .759 |
| ECLS, hours | 134.5±87.4 | 142.4±86.6 | .696 |
| Peripheral cannulation | 18.4% | 4,8% | .047 |
| Arterial Cannula | Aorta: 81.6%<br>Femoral Artery: 6.1%<br>Carotid Artery: 12.2% | Aorta: 95.2%<br>Femoral Artery: 2.4%<br>Carotid Artery: 2.4% | .132 |
| Cannulation Mode | Direct: 100%<br>Distal reperfusion: 6.1% | Direct: 95.2%<br>Distal reperfusion: 2.4%<br>Vasc prosthesis: 2.4% | .388 |
| Venous Cannula | Atria-PV: 81.6%<br>Femoral Vein: 8.2%<br>Jugular Vein: 10.2% | Atria-PV: 95.2%<br>Femoral Vein: 2.4%<br>Jugular Vein: 2.4% | .139 |
| Bivalirudin | 54.2% | 47.6% | .535 |
| **Vent location/strategy** | | | |
| LA/ AS or LA cannula | | 38 (90.5%)<br>AS (30)<br>LA cannula (8) | NA |
| LV/ LV cannula | | 2 (4.8%) | |
| Aorta/IABP | | 1 (2.35%) | |
| LV/Pigtail across AV | | 1 (2.35%) | |

***Table 3.*** **V-A ECLS features.** Legend: AS, atrial septostomy; AV, aortic valve; IABP, intra-aortic balloon pump; LA, left atrium; LV, left ventricle; Vasc, vascular; PV, pulmonary vein.

### *Predictors of survival*

The main predictors of the in-hospital survival were the use of venting strategy and absence of E-CPR. Venting strategy significantly increased the survival at the discharge by almost three times (OR= 2.74, CI 1.06-7.08; p= 0.037). On the contrary, E-CPR was associated with decreased survival (OR= 0.323, CI 1.09-0.96; p= 0.041). These results were adjusted for risk adjustment for congenital heart surgery method 1class, peripheral cannulation, age and the presence of pulmonary hypertension, as presented in *Table 5*.

***Table 4.***

| | No venting (N=48) | Venting (N=42) | p-value |
|---|---|---|---|
| **Primary outcomes** | | | |
| Deaths on ECLS | 26.5% | 19.0% | .398 |
| Deaths after weaning | 22.4% | 7.1% | .044 |
| In-hospital Survival | 51.0% | 73.8% | .026 |
| **Secondary outcomes** | | | |
| Infections | 34.6 % | 22.2% | .443 |
| Cerebral Injury | 21.7% | 31.0% | .144 |
| CRRT | 20.4% | 22% | .902 |
| Hemolysis | 17.1% | 11.8% | .855 |
| Thrombosis | 14.6% | 14.3% | NS |
| Bleeding | 22.9 % | 28.6% | .397 |
| DIC | 0% | 4.8% | NS |
| Bleeding, ml | 809.5±1383.4 | 1000.0±1303.0 | .512 |
| Vascular damage | 2.1% | 7.1% | .245 |
| ECLS failure | 14.4% | 11.9% | .646 |
| **Organ Damage** | | | |
| Peak creatinine, mg/dl | 0.8±0.7 | 0.9±0,5 | .540 |
| Peak Bilirubin, mg/dl | 5.5±5.8 | 5.4±10.2 | .925 |

***Table 4.*** **Primary and secondary outcomes.** Legend: DIC, disseminate intravascular coagulopathy; CRRT, continuous renal replacement therapy; ECLS, extracorporeal life support

Based on the regression model result, the patients were divided in four groups (E-CPR + no venting, N=12; E-CPR + venting, N=10; no E-CPR + no venting, N=36; and no E-CPR + venting, N=32). The survival function (*figure 1*) demonstrated a significant (p=0.012) between patients with E-CPR and no venting and patients without E-CPR and receiving venting (hazard ratio 3.6, 95% confidence interval 1.18 – 11.0)

***Table 5.***

| | Regression Coefficient | p-value | OR | 95% CI | |
|---|---|---|---|---|---|
| | | | | Lowe | Upper |
| **LV Venting** | 1.008 | .037 | 2.741 | 1.061 | 7.079 |
| **RACHS-1 class** | -.016 | .960 | .985 | .534 | 1.816 |
| **Peripheral Cannulation** | -.411 | .615 | .663 | .133 | 3.290 |
| **E-CPR** | -1.129 | .041 | .323 | .109 | .957 |
| **Age** | .000 | .166 | 1.000 | 1.000 | 1.001 |
| **PH** | -.443 | .263 | .642 | .295 | 1.395 |

***Table 5.*** **Logistic regression rodel predicting in-hospital survival.** Legend: OR, odds ratio; CI, confidence interval; LV, left ventricle; RACHS-1, risk adjustment for congenital heart surgery method 1; E-CPR, extracorporeal cardiopulmonary resuscitation; hypertension

***Figure 1.***

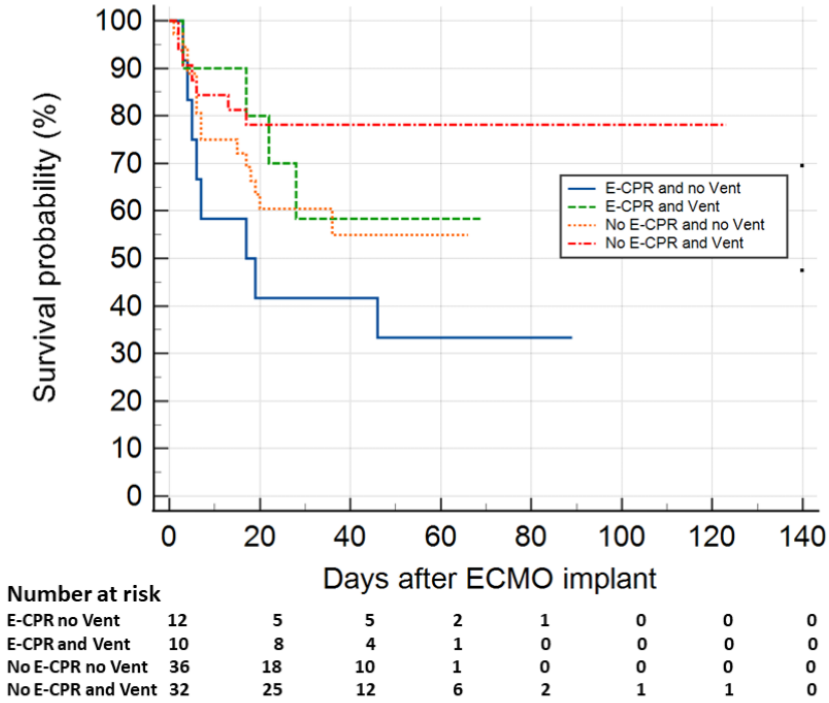



***Figure 1.*** **Survival in pediatric patients support with V-A ECLS, based on the presence/ absence of E-CPR and LV unloading strategy.** The function showed a significant higher survival (p=0.012) in patients without E-CPR and receiving venting compared to those undergone to E-CPR and who not had LV unloading (hazard ratio 3.6, 95% confidence interval 1.18 – 11.0). E-CPR, extracorporeal-cardiopulmonary resuscitation; ECLS, extracorporeal life support; Vent, venting.

**Discussion**

To the best of authors' knowledge, this study represented one of the largest investigations on pediatric CHD populations supported with V-A ECLS in post-cardiotomy setting, in association with different LV venting techniques. Furthermore, the complex anatomies which characterized patients referred to our national referral center for pediatric cardio-surgery gave us the opportunity to investigate the role of these strategies specifically and adequately in a unique setting.

First of all, in this population of CHD patients supported with V-A ECLS, we found a rate of major complications comparable to other experiences [13].

Our findings demonstrate high rates of acquired infection and bleeding during pediatric V-A ECLS. Our observed rates are consistent with a recent metanalysis on post cardiotomy ECLS in pediatric patients. In fact, Lorusso et al showed a rate of infections ranging from 3.1% to 50%, while bleeding is very variable, peaking at 69%[13].

Neurologic injuries were also very common in our children supported with ECLS. Chow et al in a study of 90 patients only 15 children survived without neurologic sequelae [14]. On the contrary, in the ELSO Registry, only 14% had a neurologic complication [15]. In our population, 13.3% accounted for neonates weighting less than 3 kg and 24.4% for E-CPR, which are considered well known risk factors for neurologic injury [14]. As a consequence, this may lead to our high rate of neurological complications.

Furthermore, one out five patients required CRRT. This confirmed that acute kidney injury frequently occurred in pediatric patients on ECLS in post-cardiotomy setting, ranging from 9% to 78% in the literature [13]. All ECLS complications own a negative impact on the survival [16].

Although the rate of complications did not differ in venting and no-venting groups, the in-hospital survival was significantly higher in vented patients. The primary aim of this study was to determine the effects of LV unloading on in-hospital survival and secondly on the complications.

Only very few studies have previously evaluated the association of LV unloading with major outcomes in children or neonates supported by V-A ECLS. Choudhury et al, in their retrospective review of the Extracorporeal Life Support Organization registry, revealed an association between left heart decompression and higher odds of survival in children with myocarditis and dilated cardiomyopathy on extracorporeal membrane oxygenation [17]. On the contrary, Eastaugh et al did not find a difference in mortality in a single-center experience evaluating the impact of percutaneous left heart decompression in pediatric on V-A ECLS [8].

However, this study included a highly heterogenic population, since this consisted of children with CHD mixed with structurally normal hearts. Zampi et al identified the impact of earlier LV unloading on clinically important outcomes, such as ECLS and mechanical ventilation durations, but it failed to reveal an impact on in-hospital survival [18].

Despite the lack of consensus in the literature, our study interestingly showed a

strong association between LV venting and in-hospital survival rate in pediatric patients supported with V-A ECLS. LV venting is able to guarantee short-term benefits, directly related to the hemodynamic effects, and also middle-long term advantages, mostly linked with myocardial remodeling prevention.
The potential benefits of LV venting have been recently addressed and described in computational model [19], as well as preclinical [20] and clinical setting [21,22]. When the LV is unloaded, LV mechanical power expenditure is reduced, which minimizes myocardial oxygen consumption and reduces the hemodynamic forces leading to ventricular remodeling [23]. As a direct consequence, unloading reduces infarct size and preserves mitochondrial function after ischemia– reperfusion injury [24]. Therefore, venting the LV on V-A ECLS may mitigate the acute negative effects generated of the increased LV afterload generated by retrograde flow Subsequently, the advantages related to LV unloading are more related to the prevention of myocardial remodeling, ventricle dilation and severe residual dysfunction. In fact, stretching of cardiomyocytes induces alterations in multiple intra and extra-myocyte pathways in parallel, including sarcomere changes, cytoskeletal proteins, and mitochondria [23].
Also, the inflammation initiated by the tissue injury plays an important role, activating matrix metalloproteases primed to receive the increased hemodynamic load force [23]. Furthermore, the pressure overload acts synergistically with tissue injury to cause LV remodeling in a mouse model as demonstrated by Weinheimer et al [25].
In our population, the mortality on V-A ECLS was not significantly different in patients who were vented. In acute phase, under cardio-circulatory shock conditions of severe end-organ hypoperfusion, the clinical effect of LV unloading might be less appreciable. However, the myocardial protection promoted by the LV unloading seems to be crucial in the sub-acute phase, namely after weaning, with a consistently lower mortality in vented V-A ECLS supports during the post-ECLS hospital course.
Among all the available LV venting techniques [5], the overwhelming majority of our pediatric patients were vented in the left atrium, by AS or by placing a venting cannula through the septum.
Eastaugh et al also reported left heart unloading in 42 patients supported with V-A ECLS, via AS or left atrial venting across the atrial septum [8]. All techniques were percutaneous and equally effective. In another monocentric study, Hacking et all showed left heart decompression in children on central V-A ECLS. They reported 39 cases successfully managed with left atrial venting and only 5 with AS [9].
Our findings confirmed the safety and effectiveness of AS as LV as previously suggested by the abovementioned experiences [8,9].
This is in contrast with the recent results of IMPACT registry. Deshpande et al collected 233 patients underwent percutaneous AS. This procedure was associated with significant morbidity, including procedural complications [26]. On one hand, this registry recorded data from 55 independent centers whom

local expertise might significantly vary. On the other hand, the percutaneous approach might lead to a high rate of procedural complications compared to surgical septostomy used in our CHD cohort.
Furthermore, we encountered 3 cases of left atrium cannula thrombosis which required urgent removal, as shown in *Figure 2*. The cannula was promptly removed and replaced. This concern and other shortcomings regarding left atrium cannula in children, particularly in neonates, were previously reported [8]. In addition, the low frequency of hemodynamically significant residual atrial shunt8 may lead to consider AS as our first current choice in pediatric, mainly post cardiotomy, ECLS.
The impact of LV venting on in-hospital survival was significant in our study. The probability of survival at discharge were almost three times higher in patients undergoing LV venting, despite risk adjustment for congenital heart surgery method 1 class, peripheral cannulation, age, pulmonary hypertension and E-CPR. The latter was negatively associated with in hospital survival, as already confirmed in the literature [27].
This result on LV unloading is in accordance with the most recent evidences described in adult-related investigations. Russo et al, in a meta-analysis of 17 observational studies, found an association between LV unloading and decreased mortality in adults with cardiogenic shock treated with V-A ECLS [28] .

***Figure 2.***

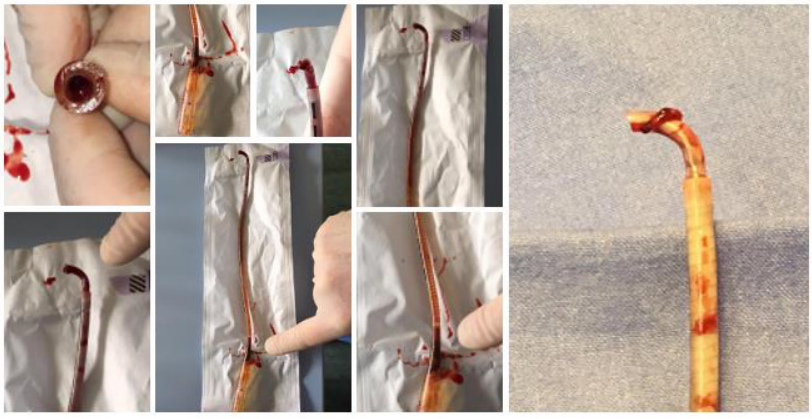


***Figure 2.*** **Clots found in the left atrium cannula.** The presence of significant thrombi occurred in three cases in this series of patients. This required urgent removal, since the clots obstructed the cannula blood flow. Thereafter, the cannula was promptly removed, and the remaining atrial septum hole left as vent strategy.

However, the adult population is characterized by several confounding factors [29]. As a result, most of the proofs regarding the LV unloading impact in adults have required matched populations [21,30]. Therefore, the impact on the survival found in our pediatric population may underline the real effect of

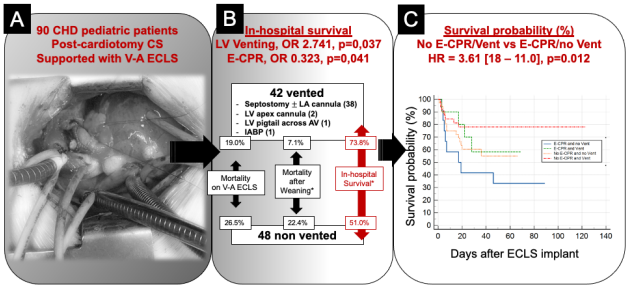
LV unloading in a homogeneous patient group without significant confounding factors, like comorbidities.
The pediatric population affected by a primary cardiac disease and common absence of further comorbidities, might represent a more appropriate condition to investigate the impact of LV venting on the overall survival.
Moreover, the pediatric CHD patients represent a selected cohort which might have additional benefits from LV unloading compared to other populations.
Additional studies are however warranted to further investigate and confirm our findings of the advantage of LV venting on V-A ECLS related in-hospital survival in pediatric patients.

**Limitations**

The current study should be considered in the context of some limitations.
First, this is not randomized controlled trial examining the use of LV unloading during V-A ECLS in pediatric population. Data are merely derived from an observational retrospective dataset and, therefore, influenced by biases related to this study design.
There was scanty data to investigate survival in relation to the specific CHD or cardiac surgery, LV unloading strategy (i.e., left atrium venting vs. LV apex venting vs. IABP vs. pigtail across the aortic valve) with adequate statistical power.
Furthermore, specific etiology of cardiogenic shock were not available for the study analysis. All these factors might temper the found relationship between left ventricular unloading during V-A ECLS and survival.

**Conclusions**

In pediatric patients supported with V-A ECLS for cardiogenic shock or cardiac arrest, the implementation of a concomitant LV unloading strategy was associated and predicted higher in-hospital survival.
LV unloading should be strongly considered for selected CHD pediatric patients in post-cardiotomy setting. Further investigations are urgently needed to better clarify this apparently significant advantage.




**Impact of left ventricular (LV) unloading on the in-hospital survival in pediatric veno-arterial extracorporeal life support (V-A ECLS) following congenital heart disease surgery.** Panel A. In a tertiary pediatric cardiac surgery center, ninety pediatric patients affected by different congenital heart disease were supported with V-A ECLS for post-cardiotomy cardiogenic shock were retrospectively reviewed. Panel B. Forty-two patients were vented with different techniques (38 with atrial septostomy or left atria cannula, 2 with cannula from LV apex, 1 with intra-aortic balloon pump and 1 with pigtail across aortic valve). According to a lower mortality during and after V-A ECLS, the vented patients showed a significant higher in-hospital survival. The LV unloading led to approximately three times higher in-hospital survival. On the contrary, E-CPR negatively impacted with the survival. Panel C. The Kaplan Mayer showed a significant better survival in patients who were not submitted to E-CPR and received LV unloading (red continued line) compared with those without any venting strategy and who did not have E-CPR (blue dashed line). CHD, congenital heart disease; CS, cardiogenic shock; E-CPR, extracorporeal cardiopulmonary resuscitation; HR, hazard ratio; LA, left atrium; LV, left ventricular; OR, odds ratio; V-A ECLS, veno-arterial extracorporeal life support.

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# Chapter 8.

## ECMO and left ventricular unloading: what is the evidence?

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## Introduction

Although mechanical circulatory support (MCS) has been used to support patients with cardiogenic shock (CS) for many years, recent advances in device technology, together with the lackluster performance of isolated pharmacological therapy, have increased its utilization in this setting.[13] Veno-arterial extracorporeal membrane oxygenation (V-A ECMO) has been increasingly implemented, particularly in patients with postcardiotomy CS or cardiac arrest, because V-A ECMO has several advantages over other MCS modalities. Advantages of V-A ECMO include rapid deployment, biventricular support, gas exchange provisions, peripheral and percutaneous approaches for insertion, the ability to be provide support for days or weeks, relatively inexpensive disposables for the equipment, and widespread availability with well established programs at most major centers.[4] However, despite the established benefits of V-A ECMO, several shortcomings of this technology persist and remain a matter of thorough debate.

One persistent shortcoming of V-A ECMO is that increased left ventricular (LV) afterload is induced by retrograde flow, particularly when V-A ECMO is inserted peripherally.[5,6] This retrograde extracorporeal membrane oxygenation (ECMO) flow toward the aortic valve can reduce or impede LV ejection, which then leads to blood stasis and left chamber distension.[48] LV afterload always increases during peripheral V-A ECMO but does not lead to overt LV distension or evident left chamber or aortic root blood stasis in most patients.[7,8] However, reduced or absent forward blood flow across the aortic valve might occur also due to a mismatch between LV afterload, LV preload, and LV contractility. Some degree of preload is necessary with ECMO support to maintain aortic valve opening. A completely empty ventricle might not eject with normal afterload or adequate contractility, a situation which might be generated by excessive LV drainage. This potential disadvantage of uncontrolled LV unloading underlines the relevance of close monitoring to adequately determine the need, and pros as well as cons of LV decompression during V-A ECMO. The impelling need and benefits of LV venting in a severely dysfunctional heart that does not generate an effective ejection or that is markedly dilated are fairly well established.[9] However, even in the absence of severe LV failure, there is increasing evidence that LV unloading during V-A ECMO is beneficial. Uniform protocols for LV unloading using dedicated devices and procedures failed to provide conclusive evidence, and the ideal timing and modalities for LV unloading remain undefined.[7,8]

Specific questions to evaluate were as follows: (1) Is LV unloading during V-A ECMO beneficial, even in the absence of overt LV distension, to reduce or avoid further myocardial damage? (2) Is LV unloading instrumental, even in the absence of overt LV distension, for enhanced or quicker LV recovery? (3) Does LV unloading during V-A ECMO affect ECMO weaning, survival, or the ability to bridge the patient to more advanced therapies? (4) Do complications related to LV unloading techniques affect patient outcomes? (5) Which LV unloading strategies are available and are well managed with the local expertise at each center? To address these questions, the pros and cons of LV unloading during V-A ECMO are discussed and recent publications and ongoing research are highlighted, with a specific focus on postcardiotomy

V-A ECMO. In addition, our standard practice and future directions for LV unloading during V-A ECMO in patients suffering CS are addressed.

***Figure 1a.***

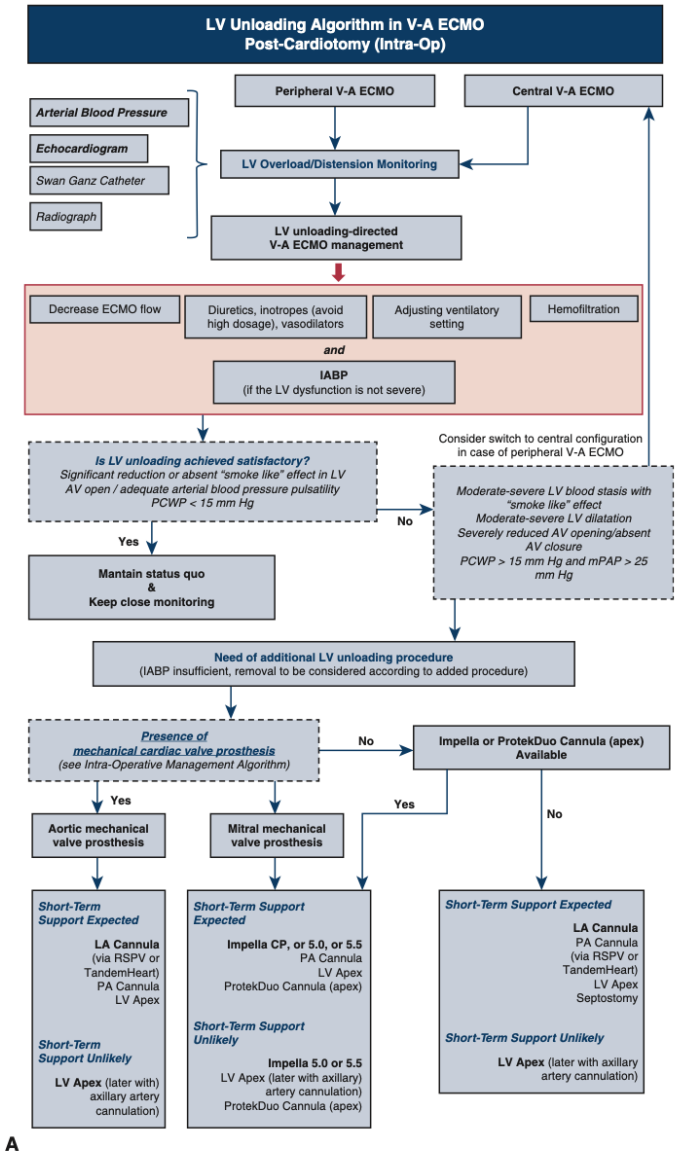


***Figure 1. A.*** **Algorithm for management of LV unloading to accompany intra-operative ECMO insertion post-cardiotomy.** Red boxes indicate measures that should be considered in all patients supported by V-A ECMO to unload the LV and avoid LV distension and aortic valve dysfunction.AV, aortic valve; ECMO, extracorporeal membrane oxygenation; IABP, intra-aortic balloon pump; LA: left atrium; LV, left ventricle; LVAD, left ventricular assist device; mPAP, mean pulmonary arterial pressure; PA, pulmonary artery; PCWP, post-capillary wedge pressure; RSPV, right superior pulmonary vein; V-A, veno-arterial.

***Figure 1b.***

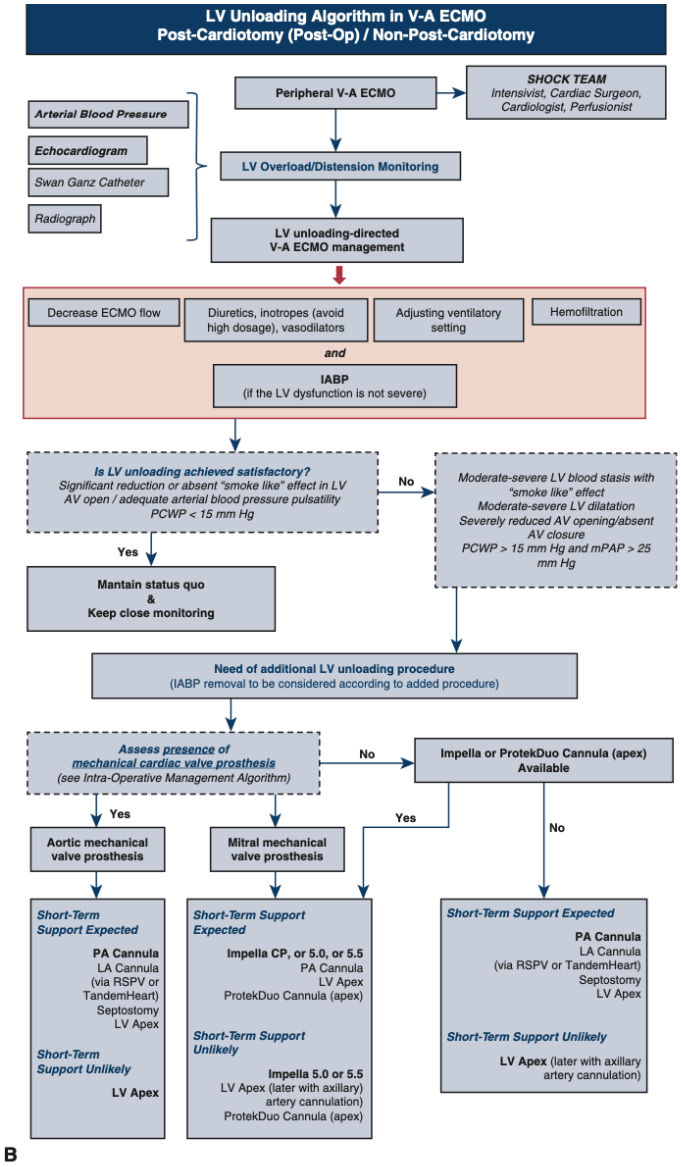


***Figure 1. B.*** **Algorithm for management of LV unloading when ECMO is inserted postoperatively or in a non-post-cardiotomy setting.** Red boxes indicate measures that should be considered in all patients supported by V-A ECMO to unload the LV and avoid LV distension and aortic valve dysfunction.AV, aortic valve; ECMO, extracorporeal membrane oxygenation; IABP, intra-aortic balloon pump; LA: left atrium; LV, left ventricle; LVAD, left ventricular assist device; mPAP, mean pulmonary arterial pressure; PA, pulmonary artery; PCWP, post-capillary wedge pressure; RSPV, right superior pulmonary vein; V-A, veno-arterial.

**Modalities for LV unloading**

There are several ways to achieve LV unloading during V-A ECMO including noninvasive maneuvers and invasive non-catheter, catheter-based, and device-dependent modalities. Each approach allows for either direct (active) or indirect (passive) unloading. The available modalities differ in terms of access, extent of LV decompression, complexity, cost, and potential complications (*Table 1*) [8,10,11].

Thus far, limited comparisons of LV unloading techniques have been published, and more compelling evidence is necessary to determine the superiority or inferiority of any of the various techniques [12-14]. Until such evidence is available, the advantages and disadvantages of each modality should be considered during the decision-making process with attention to potential therapeutic actions after ECMO weaning, patient management, and the presence of mechanical cardiac valves on the left side of the heart (*Figure 1*) [7,8].

**Noninvasive Modalities**

Several noninvasive maneuvers can be immediately applied during all ECMO application procedures as tolerated to reduce LV afterload. Noninvasive methods for reducing LV afterload include avoiding high ECMO flow, increasing positive end expiratory pressure (PEEP) slightly, limited vasodilation, and limited administration of inotropic drugs. These prompt actions may prevent or limit the negative effects of increased LV afterload even when an aggressive LV venting procedure has been implemented before to ECMO insertion because of intraoperative implant, failure to wean from cardiopulmonary bypass, or the presence of an intra-aortic balloon pump (IABP) or an Impella device (Abiomed, Danvers, MA, USA) [11]. Noninvasive maneuvers to decrease LV afterload have potential shortcomings, however, and are not tolerated by or effective in all patients. Limiting ECMO flow may increase the volume flowing into the pulmonary artery bed and, in combination with protective, limited ventilatory settings, can result in hypo-oxygenated blood reaching the left ventricle and aortic arch, generating differential hypoxemia or Harlequin syndrome [4,5]. The use of diuretics, hemofiltration, or vasodilators to reduce the LV preload or afterload is rarely effective in the presence of severe CS requiring a high level of ECMO flow. Inotropes have often been suggested to enhance the residual cardiac contractility and promote LV ejection, while also allowing for effective aortic valve opening. However, negative effects of inotropes in patients with an ongoing or recent myocardial injury has been repeatedly demonstrated, suggesting that such agents should be used judiciously, particularly in the presence of ischemia-induced myocardial damage [7,8,11].

**Invasive Modalities**

Invasive catheter-based and device-dependent procedures can achieve effective LV decompression without relying on the residual LV contractile

resources. The location of catheter placement determines whether decompression is direct (active) or indirect (passive) and the efficacy of the chosen approach (*Table 1*) [10,12,13]. IABP placement is the easiest device-based approach because percutaneous access allows easy and fast insertion and removal. The IABP has repeatedly shown benefits when used in combination with V-A ECMO [15,16,17]. However, the IABP has a limited effects as compared with alternative direct and indirect LV unloading approaches, and improved early survival as a result of IABP placement has not been demonstrated [4].

Furthermore, the site of blood stasis resulting from LV afterload should be carefully assessed because the location of stasis and additional variables (such as the presence of a mechanical valve prosthesis) will dictate the most appropriate strategy to achieve LV decompression [7,8]. Not all forms of LV unloading reduce blood stasis at the aortic root, which is often caused by protracted aortic valve closure or severely reduced valve opening. Additionally, stasis may be exacerbated by several LV unloading procedures including indirect modalities or direct LV unloading without trans-aortic or aortic access. If there are no contraindications, aortic systems, such as an IABP, or trans-aortic systems, such as the Impella CP, 5.0, or 5.5, or the PulseCath i-VAC (PulseCath BV, Arnhem, Gelderland, The Netherlands), can be utilized to reduce the risk of complications as compared with trans-apical LV unloading. Impella devices have been increasingly utilized when invasive, direct LV unloading with device-based approach is desired. The Impella devices are axial pumps that can be inserted using a percutaneous, transfemoral approach (Impella 2.5 or Impella CP) or surgical access (Impella 5.0 or Impella 5.5), but the presence of a mechanical aortic valve prosthesis is a contraindication for their use.

**Safety/Complications**

The use of any of the LV unloading strategy must always be entertained with caution and appropriate knowledge of the functionality of the available procedures and devices, as well as the complications associated with each [7,8]. Adverse events related to the application of LV unloading techniques and the potential for maladaptive changes in the pulmonary vasculature and cardiac valve, structural disease, bleeding, thrombosis, and pathophysiological and hemodynamic changes are of paramount importance (*Table 1*). Complications of LV decompression modalities include protracted aortic valve closure, hemolysis, leg ischemia, bleeding, cardiac chamber perforation, renal replacement therapy, and infection. *(Table 1a* and *1b*). Complications of unloading occur concurrently with the risks imparted by V-A ECMO support.

***Table 1a.***

| Procedure | Mechanisms of LV Unloading | Efficacy of LV Unloading[a] | Approach | Cost and Complexity of Application[a] | Advantages | Disadvantages/Complications |
|---|---|---|---|---|---|---|
| | **Noninvasive Maneuvers** | | | | | |
| Reduced ECMO flow | Enhanced LV ejection/unloading (indirect) | ✓ - ✓✓ | | ✓ | - Immediate action<br>- Noninvasive procedure | - Reduced peripheral/organ perfusion |
| Modified ventilator settings (increased PEEP) | Increased right-sided drainage (indirect) | ✓ - ✓✓ | | ✓ | - Immediate action<br>- Noninvasive procedure | - Increased RV afterload<br>- Increased barotrauma |
| Diuretics | Reduced cardiac loading (indirect) | ✓ - ✓✓ | | | - Noninvasive procedure<br>- Reduced extravascular volume<br>- Improved lung gas exchange | - Reduced intravascular volume<br>-Time needed to be effective<br>-Preserved and responsive renal function required<br>- Worsening of renal function |
| Hemofiltration | Reduced cardiac loading (indirect) | ✓✓ | | ✓✓ | - Limited invasiveness<br>- Usually already in place for concomitant renal failure<br>- Limited personnel required for management | - Infection<br>- Dependent on patient's hemodynamics<br>- Bleeding<br>- Excessive volume reduction<br>- reducing ECMO system loading |

| | | | | | | |
|---|---|---|---|---|---|---|
| Inotropes | Enhanced LV ejection (indirect) | ✓✓ | | ✓ | - Immediate action<br>- Noninvasive procedure | -Increased myocardial O2 consumption<br>- Ischemia induction<br>- Myocardial stunning<br>- Vasoconstriction (if part of the properties of the agent)<br>- Heart rhythm/heart rate disturbances |
| Systemic vasodilation | Enhanced LV ejection (indirect) | ✓ - ✓✓ | | ✓ | - Noninvasive procedure | - Reduced perfusion pressure<br>-Increased peripheral volume sequestration |

***Table 1a.*** **Left ventricular unloading during veno-arterial extracorporeal membrane oxygenation: modalities, advantages and potential complications.**

LV: left ventricular; ECMO: extracorporeal membrane oxygenation; VAD: ventricular assist device; ASD: atrial septal defect; VSD: ventricular septal defect; RV: right ventricular; PA: pulmonary artery; VAV: veno-arterial-venous; PEEP: positive end expiratory pressure.

a Grade from least to most powerful (✓ to ✓✓✓✓✓)

Modified from Lorusso R. European Journal of Heart Failure 2017; 413–415, doi:10.1002/ejhf.6

***Table 1b.***

| Procedure/Device | Mechanisms of LV Unloading | Efficacy of LV Unloading[a] | Approach | Cost and Complexity of Application[a] | Advantages | Disadvantages/Complications |
|---|---|---|---|---|---|---|
| | **Extracardiac Procedures** | | | | | |
| **IABP** | Reduced LV afterload (enhanced systolic ejection) and reduced LV end-diastolic pressure (enhanced left atrium and pulmonary veins unloading) (indirect) | ✓ | Percutaneous, femoral (or surgical in case of specific adverse conditions, line severe peripheral vascular disease requiring an axillary or trans-aortic implant) | | - Prolonged use<br>- Partial LV support once ECMO removed<br>- Percutaneous implant<br>- Not expensive<br>- No major complications<br>- Not personnel dependent<br>- User friendly | - Limb ischemia<br>- Vascular access bleeding<br>- Emboli<br>- If malpositioned (low), it may occlude bowel or renal arteries |
| | **Trans-Aortic Procedures** | | | | | |
| **Percutaneous left-assist devices (Impella 2.5, CP, 5.0 amd 5.5)** | LV blood suction (direct) | ✓✓✓✓✓ | | ✓✓✓✓✓ | - No stasis in the left cardiac chambers and aortic root<br>- LV support once ECMO removed | - Hemolysis<br>- Vascular access bleeding<br>- Required personnel<br>- Cost/ Expensive<br>- When used in VSD, it may reverse intra-septal shunting (from left-to-right, to right-to-left)<br>- Contraindicated with a mechanical aortic valve |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | Percutaneous, femoral | | **Impella 2.5 and CP** | |
| | | | | | - Quick percutaneous placement | - Less effective LV support<br>- Higher risk of potential dislodgment |
| | | | Surgical, trans-subclavian, or axillary, or aortic | | **Impella 5.0 and 5.5** | |
| | | | | | - Prolonged LV support (> 2 weeks)<br>- Axillary/ Subclavian artery access allowing patient mobilization | - Lower risk of hemolysis as compared to Impella CP or 2.5<br>- Higher risk of vascular access-related bleeding |
| **Trans-aortic catheter** | LV blood suction (direct) | ✓✓✓✓✓ | Percutaneous, femoral | ✓✓✓✓ | - No stasis in the left cardiac chambers and aortic root | When used in patients with a VSD, it may reverse intra-septal shunting (from left-to-right, to right-to-left)<br>Air embolism |
| **Trans-apical Dual-Lumen Cannula (ProtekDuo)** | LV unloading (direct) | ✓✓✓✓ | Surgical (left mini-thoracotomy) Cannula through the cardiac apex up to the ascending aorta | ✓✓✓✓ | - Not very expensive<br>- Controllable Flow<br>- Usable for short or prolonged support<br>- With or without oxygenator<br>- No stasis in the left cardiac | - Limited published experiences (only one case report)<br>- Bleeding<br>- Myocardial infarction<br>- Emboli<br>- Infection<br>- Contraindicated with a mechanical aortic valve<br>- Limited expertise |

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| | | | | | chamber and aortic root | |
| **Trans-aortic pump (PulseCath i-VAC)** | LV blood ejection (direct) | ✓✓✓ | Percutaneous, femoral | ✓✓✓ | - No stasis in the left cardiac chambers and aortic root | - Potential limb ischemia<br>- Vascular access bleeding<br>- Limited expertise |
| | **Left Ventricular Apex Procedures** | | | | | |
| **Trans-apical or trans-mitral valve catheter** | LV unloading (direct) | ✓✓✓✓✓ | Surgical (left mini-thoracotomy) Catheter in the LV | ✓✓✓✓ | - Not expensive<br>- Controllable<br>- Can provide long-lasting support (apex/subclavian artery configuration – VAD-like mode) | - Surgical procedure required<br>- Bleeding<br>- Myocardial infarction<br>- Emboli<br>- Aortic valve closure and aortic root stasis and thrombosis<br>- Infection<br>- Air embolism |
| | **Transeptal or Bi-Atrial Procedures** | | | | | |
| **Percutaneous septostomy usually with ballooning or stenting** | Left-to-right atrial shunt<br>Increased right atrial drainage (indirect) | ✓✓✓ | Percutaneous, femoral (venous access) | ✓✓✓ (for all procedures) | Not expensive<br>Can avoid need for indwelling device | - Expertise required<br>- Residual ASD (in some cases to be closed after ECMO weaning)<br>- Not controllable/non-maneuverable shunt |
| | **Left Atrium Procedures** | | | | | |
| **Transeptal or interatrial groove, or left atrial roof, or right superior pulmonary vein catheter or cannula attached to the** | Left atrium unloading<br>LV unloading and unloading of the pulmonary veins (indirect) | ✓✓✓✓ | Surgical (either via sternotomy or right mini-thoracotomy) | ✓✓✓✓ | - Easily performed in the operating room | - Surgical or septostomy-guided procedure<br>- Systemic emboli<br>- LV perforation<br>- Bleeding<br>- Extreme LV unloading with minimal or absent forward LV ejection (risk for |

| | | | | | | |
|---|---|---|---|---|---|---|
| **ECMO venous return** | | | | | | intraventricular or aortic root stasis and thrombosis) |
| **TandemHeart** | Left atrium unloading<br>LV unloading and unloading of the pulmonary veins (indirect) | ✓✓✓✓ | Percutaneous, femoral (venous access) or Surgical (only arterial access) | ✓✓✓✓✓ | - Percutaneous approach | - Septostomy-guided procedure<br>- Bleeding<br>- Extreme LV unloading with minimal or absent forward LV ejection (risk for intraventricular or aortic root stasis and thrombosis) |
| | **Pulmonary Artery Procedures** | | | | | |
| **Pulmonary artery cannula surgically or percutaneously placed** | Increased right-side blood drainage<br>Unloading of pulmonary veins and left cardiac chambers (indirect) | ✓✓ | Percutaneous (right internal jugular vein) or surgical, sternotomy (direct or through a vascular prosthesis) | ✓✓✓ | - Effective reduction of pulmonary vein flow (immediate solution of pulmonary edema)<br>- Use as perfusion port (for RV dedicated support or to solve north/south (Harlequin) syndrome in VAV ECMO configuration) | - Risk of perforating the RV or PA<br>- Impact of main blood drainage on the PA-related drainage and risk of low flow with thrombosis of the cannula<br>- Extreme LV unloading with minimal or absent forward LV ejection (risk for intraventricular or aortic root stasis and thrombosis)<br>- Increased ECMO flow with increased LV afterload |
| | **Increased Systemic Venous Blood Drainage (additional cannulas)** | | | | | |
| **Systemic vein (femoral, jugular, subclavian) or right atrium** | Increased right-side blood drainage<br>Unloading of pulmonary veins and left cardiac chambers (indirect) | ✓✓ | Percutaneous (venous access) or sternotomy (central access) | ✓✓✓ | - Easily Applicable<br>- No specialty expertise required | - Bleeding from the new cannulation site<br>- Extreme LV unloading with minimal or absent forward LV ejection (risk for |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | | | | intraventricular or aortic root stasis and thrombosis)<br>- Increased ECMO flow with increased LV afterload |

***Table 1b.*** **Left ventricular unloading during veno-arterial extracorporeal membrane oxygenation: modalities, advantages and potential complications.**

LV: left ventricular; ECMO: extracorporeal membrane oxygenation; VAD: ventricular assist device; ASD: atrial septal defect; VSD: ventricular septal defect; RV: right ventricular; PA: pulmonary artery; VAV: veno-arterial-venous; PEEP: positive end expiratory pressure.

a Grade from least to most powerful (✓ to ✓✓✓✓✓)

Modified from Lorusso R. European Journal of Heart Failure 2017; 413–415, doi:10.1002/ejhf.69

**Current Controversies**

**Is unloading the LV during V-A ECMO necessary?**

There is significant debate as to whether unloading the LV during V-A ECMO is necessary, especially using invasive modalities. Camboni and Schmid reported use of a LV venting procedure in only 2% of their patients supported with V-A ECMO and instead preferred to regulate LV afterload using noninvasive methods [18]. In contrast, Truby and colleagues reported that 22% of their patients supported with V-A ECMO had subclinical LV distension and 7% had clinical LV distention requiring decompression immediately after ECMO initiation. In total, 16% of the patients in their case series experienced LV distension requiring decompression during V-A ECMO support [19]. Importantly, Weber and colleagues showed that 4% of patients who underwent femoral V-A ECMO developed intracardiac or extracardiac thrombi despite receiving adequate anticoagulation, a condition representing the worst scenario linked with protracted LV distension and blood stasis [20]. Although some of the patients with thrombi underwent surgical procedures to remove the clots, none ultimately survived [20]. A “smoke-like effect” indicating blood stasis in the LV, LA or at the aortic root and pulmonary congestion secondary to protracted aortic valve closure are not infrequent observations in patients supported with V-A ECMO [5,7,8,21]. Moreover, an aggressive anticoagulation regimen, which is sometimes suggested when blood stasis occurs during ECMO, is a pro-hemorrhagic intervention and often predisposes the patient to cerebral hemorrhage or uncontrollable generalized bleeding episodes. We believe the potential for these complications makes LV decompression advisable.

**Evidence of the benefits of LV unloading**

*Table 2* includes several relevant publications, including limited single-center analyses, multi-center studies, and extensive meta-analyses, that specifically addressed the occurrence of LV distension-related events and the effects of LV unloading in patients supported by V-A ECMO. From these studies, the need for and the benefits of LV unloading, particularly if applied early, appear concrete and relevant. Most studies identified advantages of LV decompression during V-A ECMO with increased rates of weaning from ECMO, early survival, and bridging to more advanced therapies [15,16,17,19,22-26]. It is worth mentioning, however, that no randomized trials of LV unloading have been published, and patients selected for LV unloading and studied in retrospective analyses were likely at high risk. Furthermore, several different modalities were used for LV unloading in the available studies. Modalities were often mixed within each study and included IABP, Impella, direct LV cannulation, and left atrial (LA) venting. Each approach has unique benefits and shortcomings.

**Timing of LV unloading**

*Figure 2* details available diagnostic tools for monitoring LV function during V-A ECMO and recommended algorithms to determine the urgency and preferences of LV unloading measures. Accurate monitoring and earlier LV unloading translates into an increased likelihood of myocardial recovery, faster myocardial recovery and a better early survival [16,24,26-28]. Indeed, Chen and colleagues demonstrated that the concomitant implementation of IABP and ECMO was associated with more favorable survival outcomes than adjunctive support with an unloading system after EMCO insertion. Their study was performed primarily in the ICU in patients affected by post-cardiotomy CS [16]. Na and associates confirmed that favorable outcomes, namely a lower early mortality rate and a higher likelihood of successful bridging to more advanced MCS, occurred more frequently in patients who underwent immediate, prophylactic LV venting as compared with patients who were treated with a therapeutic strategy to treat overt LV distension [24].

***Figure 2.***

| Monitoring Method | Factor | Grade of severity | | | Intervention |
|---|---|---|---|---|---|
| **Arterial line** | Arterial Blood Pressure Pulsatility | Mild Reduction of Pulsatility (15-10 mm Hg) | Moderate Reduction of Pulsatility (8-10 mm Hg). | Severly Reduction of Pulsatility (< 8 mm Hg) or Pulseless | Noninvasive LV Unloading Maneuvers *(to be always applied)* |
| **Central venous Line** | $Scvo_2$ | 75-55% | 55-45% | < 45% | |
| | CVP | 8-12 mm Hg | 12-16 mm Hg | > 20 mm Hg | Noninvasive LV Unloading Maneuvers + IABP |
| **Echocardiogram** | AV Opening | Reduced or Opening every 2 bpm | Severly Reduced or Opening every 3-4 bpm | Protracted Closure | |
| | LV distension | Mild | Moderate | Severe | Invasive Catheter/Cannula/Device-Based LV Unloading Maneuvers |
| | LA distension | Mild | Moderate | Severe | |
| | "Smoke-like" effect[1] | Mild-Moderate | Moderate | Severe | |
| | IVC dilatation[2] | 1.5 to 2.5 cm | > 2.5 cm | > 2.5 cm | |
| | IVC collapse[3] | < 50% | < 50% | No change | |
| **Swan Ganz Catheter** | PCWP | 15-20 mm Hg | 20-25 mm Hg | > 25 mm Hg | |
| **Chest Radiograph** | Congestion[4] | Alveolar edema | Interstitial edema | Redistribution | |

***Figure 2.*** **Monitoring and determining the urgency of LV unloading in patients undergoing VA ECMO** (modified from Meani P and colleaugues). ScvO2: central venous blood oxygen saturation; CVP: central venous pressure, AV: aortic valve; bpm: beats per minute; LV: left ventricle; LA: left atria, IVC: inferior vena cava; PCWP: post capillary wedge pressure.1Classification according to D. Fatkin et al. Quantification of blood echogenicity: evaluation of a semiquantitative method of grading spontaneous echo contrast. Ultras Med Biol 1995;21:1191-8.2 IVC diameter during inspiration (Hallemat et al. Crit Dec Emerg Med 2013;27:14-12). 3 IVC collapse during expiration (Hallemat et al.Crit Dec Emerg Med 2013;27:14-12). 4 Classified according to C.E. Ravin. Radiographic analysis of pulmonary vascular distribution: a review. Bull NY Acad Med 1983; 59: 728-743.

Al-Fares and colleagues conducted an extensive meta-analysis that included almost 8000 patients and showed that an unloading procedure within 12 hours after the start of ECMO was significantly associated with better weaning and early survival as compared with LV unloading procedures initiated more than

12 hours after the initiation of ECMO support. Interestingly, there were benefits of LV unloading using an with IABP, regardless of timing, and the difference outcomes was driven mainly by the timing of Impella implementation [26]. Finally, Schrage and colleagues recently demonstrated that implantation of the Impella device within 2 hours of ECMO application was associated with a lower mortality risk, regardless of the patient demographics (i.e. older vs. younger, pre-cardiac arrest or not) [28]. This reduction in mortality risk was no longer observed when combination of devices was applied more than 2 hours after ECMO application, however, highlighting the influence of early venting as opposed to late venting or no venting [28].

In summary, the current evidence, although still limited, supports that LV unloading using noninvasive measures should be immediately instituted when managing V-A ECMO, and LV afterload and function should be continuously monitored. A more aggressive strategy, with a highly effective, direct or device-based unloading modality, might also be needed and should be instituted either at the time of ECMO insertion or within 2-12 hours of the initiation of ECMO support.

*Table 2.*

| Author | Study Design | Patients | LV Unloading Modality | Outcomes | LV Unloading Technique-Related Complications | Limitations of the Study |
|---|---|---|---|---|---|---|
| **Weymann**[22] | Single-center | 12 | Central cannulation<br>Right superior pulmonary vein | No control group | NR | Central V-A ECMO (right atrium-aorta) in all patients<br>IABP used in 25%<br>Recovery in only 3 patients of 12 patients |
| **Truby**[19] | Single-center | 121 | Impella, septostomy | No difference in survival | NR | Classification of LV distension (no LV distension, sub-clinical LV distension, clinical LV distension) incomplete<br>Data available on 121 patients of 224 patients |
| **Pappalardo**[23] | Two Centers; Propensity-Matched | 153<br>(2:1 propensity match analysis, 42 without and 21 with Impella) | Impella | Lower in-hospital mortality (47% vs. 80%)<br>Higher bridging rate to recovery or upgraded therapy (68% vs. 28%) | Hemolysis (76% vs. 33%)<br>CVVH (48% vs. 19%) | Limited patient cohort<br>Not clear indication for LV unloading |
| **Brechot**[15] | Single-center | 259 (40.1% with LV unloading)<br>(126 patients with propensity macth for each group) | IABP | Lower risk for pulmonary edema<br>More days off mechanical ventilation | NR | No<br>No wedge pressure measurement |

| | | | | | | |
|---|---|---|---|---|---|---|
| **Chen**[16] | Single-center | 60 | IABP | Better survival-to-discharge in patients with concomitant V-A ECMO+IABP versus delayed IABP after ECMO implant | NR | Limited patient cohort<br>Only post-cardiotomy shock patients<br>Limb ischemia in 22% not described if distal perfusion- or IABP -related |
| **Na**[24] | Single-center | 50[a] (half prophylactic and half therapeutic) | Transeptal atrial cannula | Lower mortality rate and higher rate for bridging in the prophylactic group | NA | Only 50 patients of 335 patients in this study |
| **Meani**[17] | Single-Center | 10[b] (single-center) | IABP | Aortic valve opening in 80% of the treated patients with protracted aortic valve closure during peripheral V-A ECMO | None | Limited patient cohort<br>Selection bias possible<br>Hemodynamic effects by LV unloading not evaluated |
| **Russo**[25] | Systematic Review, Meta-Analysis | 3997 (17 observational studies)(42% with LV unloading) | -IABP (91.7%)<br>-Percutaneous Devices (5.5%)<br>-Pulmonary Vein or Transeptal Cannulation 2.8%) | Lower mortality (54% vs. 65%) | Hemolysis | No RCT<br>No evaluation about impact of LV unloading timing<br>Underpowered analysis about complications<br>Lack of uniform definition about LV distension and stasis among the studies |

| | | | | | | |
|---|---|---|---|---|---|---|
| **Al-Fares**[26] | Systematic Review, Meta-Analysis | 7955 (62 observational studies) (3458 with LV unloading) | All modalities | Improved weaning and improved early survival with early LV unloading (<12 hrs), improved short-term survival<br>More favorable outcome especially in primary graft failure after HTx or ischemic cardiomyopathy | More time on V-A ECMO and mechanical ventilation<br>Hemolysis | No evaluation about impact of LV unloading timing<br>Likely underreporting of adverse events<br>No head-to-head comparison of different venting strategies |
| **Kowalewski**[27] | Systematic Review, Meta-Analysis | 7581 (44.1% with LV unloading) | All modalities | 35% higher chance of V-A ECMO weaning<br>12% risk-reduction for in-hospital mortality | No difference between Unloading and No Unloading | Lack of RCTs<br>No information about timing of V-A ECMO and LV unloading institution<br>Lack of information about LV unloading escalation (e.g. from IABP to Impella, or others)<br>Incomplete information about V-A ECMO weaning strategy |
| **Schrage**[28] | Multi-Center, Retrospective, Propensity-Matched | 686 (337 patients with LV unloading) (255 patients matched for each group) | Impella | Lower 30-day mortality (HR 0.79%, CI 063-0.98) | Increased severe bleeding, access-site related ischemia, abdominal compartment syndrome, and renal replacement therapy | No detailed description of LV distension in all patients<br>Incomplete hemodynamic description |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | | | | Incomplete information about V-A ECMO weaning strategy |

***Table 2.*** **Summary of recent publications specifically addressing the use of left ventricular unloading during veno-arterial extracorporeal membrane oxygenation**

[a] Of 355 patients studied [b] Of 182 patients studied.

NR: not reported; NA: not applicable; LV: left ventricular; IABP: intra-aortic balloon counterpulsation; CVVH: continuous veno-venous hemofiltration; V-A ECMO: veno-arterial extracorporeal membrane oxygenation;; HTx: heart transplant; RCT: randomized controlled trial; HR: hazard ratio; CI: confidence interval.

**LV unloading and post-cardiotomy extracorporeal life support**

LV unloading during V-A ECMO is of particular importance in post-cardiotomy patients. Post-cardiotomy CS is often characterized by several factors associated with poor outcomes, such as prolonged myocardial ischemic time and edema, complications of the procedure requiring cardiotomy, cardiopulmonary bypass-related inflammatory reactions, preoperative heart dysfunction, and an increased tendency to bleed. Therefore, the potential shortcomings of post-cardiotomy ECMO may further exacerbate cardiac compromise and the inability to cope with the increased afterload, particularly in patients with retrograde flow from peripheral V-A ECMO. The decision between taking a central or peripheral approach for V-A ECMO has been recently addressed in 2 meta-analysis [29,30]. Although the central approach is well-suited for effective right and left ventricular unloading, both meta-analyses demonstrated fewer bleeding complications and lower in-hospital mortality with the peripheral configuration. Thus, peripheral V-A ECMO is currently recommended, and LV unloading may be of the utmost importance to facilitate good outcomes [31]. Furthermore, post-cardiotomy ECMO might be required under conditions that carry an increased risk of thrombosis due to blood stasis, such as in patients with mechanical prostheses. Nonaggressive procedures that promote LV ejection and IABP use from the start of ECMO are always recommended, particularly in the presence of a mechanical valve prosthesis (*Figures 1a* and *1b*). When a more aggressive LV unloading approach is needed, the use of techniques with a reduced risk of bleeding is also recommended, such as preferring a left atrial or trans-aortic approach based on the presence or absence of a mechanical prosthesis. Furthermore, the use of techniques that can simultaneously accomplish LV unloading and support, such as implantation of an IABP or Impella, is preferable in post-cardiotomy to promote weaning from the device. (*Figure 1a*).

**Recommendations for LV unloading: a stepwise approach**

Our policy is that LV unloading should be immediately established after V-A ECMO insertion to prevent LV distension and related complications. We believe that noninvasive maneuvers to enhance LV ejection together with an early implantation of an IABP, should be routinely performed at the start of ECMO (*Figures 1a* and *1b*). The lowest ECMO flow that provides metabolic/hemodynamic support (as indicated by decreasing lactates), light inotrope support, slightly increased positive end-expiratory pressure, and light vasodilation, if afforded by the patient's hemodynamics, should be always immediately instituted. The extent of LV unloading should be continuously and indirectly or directly monitored even with this strategy in place (*Figure 2*). In patients with persistence of LV distension and blood stasis, more aggressive LV unloading should be pursued using either a direct device-based or direct catheter/cannula-based strategy. The Impella devices have been the focus of several clinical investigations, and outcomes appear favorable when used in combination with V-A ECMO [4,23]. The type of aggressive strategy will

depend on the setting (e.g. intra-operative, post-cardiotomy, or in a non-post-cardiotomy patient; central or peripheral ECMO,), the cardiac function of the patient (degree of residual contractility), ECMO requirements (high or low flow), and the chances of myocardial recovery (*Figure 1*). We recommend this approach until conclusive and convincing evidence defining the standard of care is available, as there are clearly advantages of an aggressive approach to LV unloading concurrent with the initiation of ECMO support.

**Ongoing clinical and pre-clinical studies and future perspectives**

Despite several reviews, meta-analyses, and multi-center experiences providing clinical data as well as modeling and bench-simulation studies [7,8,12,13,21,25,26], conclusive evidence on the safety and efficacy of LV unloading is still lacking. Clinical and pre-clinical investigations are ongoing. Two randomized clinical trials are currently investigating the effects of implementing LV unloading procedures from the start of ECMO support as compared with ECMO support without LV unloading in patients with acute CS. One trial is using the Impella CP for ventricular unloading (ClinicalTrials.gov Identifier: NCT03431467), and the other is using the Impella 5.0 (ClinicalTrials.gov Identifier: NCT04084015). The results will hopefully provide compelling information regarding the potential benefits of such an approach relative to V-A ECMO in isolation.

***Figure 3.***

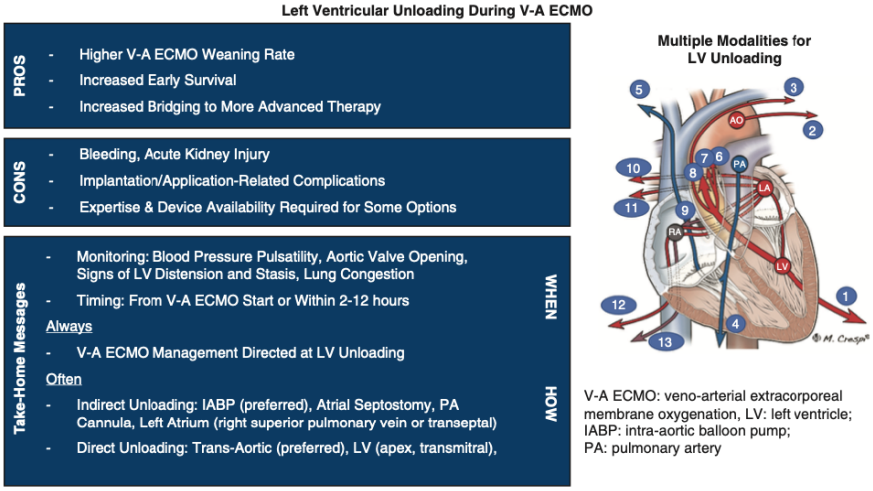


***Figure 3.*** **Modalities for left ventricular (LV) unloading** (modified from Kowaleski M. Malvindi PG, Zilienski K, Martucci G, Slomka A, Suwalski P, Lorusso R, Meani P, Arcadipane A, Pilato M, Raffa GM. Left ventricular unloading with veno-arterial extracorporeal membrane oxygenation for cardiogenic shock. Systematic review and meta-analysis. J Clin Med, 2020). 1. Single-lumen cannula vent; 2. Intra-aortic balloon pump; 3. Single-lumen catheter; 4. Single-lumen pulmonary artery cannula (either percutaneous through femoral vein or surgically implanted directly in the pulmonary artery); 5. Single or double-lumen cannula 6. PulseCath iVAC pump (intraventricular suction and aorta ascendens ejection); 7. Double-lumen cannula (ProtekDuo through the ventricular apex; intraventricular suction and aorta ascendens ejection); 8. Trans-aortic axial pump (Impella CP, 5.0, or 5.5; intraventricular suction and aorta ascendens ejection, through the femoral or axillary or aorta artery); 9. Septostomy; 10. Left atrial catheter (through the right superior pulmonary vein); 11. Trans-mitral LV catheter (through the right superior pulmonary vein); 12. Left atrial catheter/cannula (through the inter-atrial septum and the femoral vein); 13. Left atrial and right atrial catheter/cannula (TandemHeart; through the inter-atrial septum and the femoral vein).

## Conclusions

There is increasing evidence that LV unloading during V-A ECMO, particularly if applied early, might be associated with a higher rate of weaning and improved early survival (*Figure 3*). However, there is still reluctance to apply LV unloading before LV distension develops because of the potential for complications, the cost, and because some advanced devices that can be used for LV unloading are not ubiquitously available. For the time being, LV unloading with noninvasive approaches should be immediately considered for all patients supported with V-A ECMO, and aggressive, catheter- or device-based LV unloading modalities should be considered early after the initiation of ECMO support in a patient-tailored way. It is imperative that healthcare providers who care for V-A ECMO patients know the mechanisms, extent of support, and advantages and disadvantages of LV unloading modalities. Additionally, they should be confident in their ability to perform the necessary

procedures and manage LV unloading including monitoring and timing of application. Further research is needed to provide compelling and conclusive evidence defining the timing, best protocol, balance additional risks and benefits, while keeping up with technological advances, when considering LV unloading during V-A ECMO support.

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# Chapter 9.

## General discussion

**Abbreviations**
AV aortic valve
CS, cardiogenic shock
EDP, end diastolic pressure
EDV, end-diastolic volume
IABP, intra-aortic balloon pump
LV, left ventricular
PE potential energy
PVA pressure-volume area
SW, stroke work
V-A ECLS, veno-arterial extracorporeal life support

**LV venting: shifting from a local habit to a common need**

The findings reported in ***chapter 2*** discussed the approaches to vent the LV during V-A ECLS, with a selection of 45 papers published between 1993 and 2016. We found that 60% of the selected papers evaluated were case reports or case series, demonstrating that the evidence available on this subject remained very limited. Additionally, we highlighted the heterogeneity of LV overload treatment which distinguished the past decades, showing that the most common locations of unloading were highly variable and only the 27% accounted for trans-aortic techniques (i.e., Impella and Trans-aortic venting cannula). Likewise, the rate of unloading inconstantly ranged from 2% [1] to 68% [2]. Therefore, our review firstly pointed out the need of further investigations, such as shared standard protocol and basic research. Since 2017, several papers, including large observational studies [3] and revisions have been published [4,5,6]. Among them, the simulation studies have made it possible to better understand the related physiology [7,8]. Clinically, the rate of venting on veno-arterial extracorporeal life support (V-A ECLS) sharply raised, as well as the use of trans-aortic techniques, such as Impella. In fact, Schrage et al retrospectively analyzed 106 V-A ECLS patients and declared Impella as “the standard of care” for LV unloading in their institution since 2015 [9]. Furthermore, an international multicentric study collecting 686 patients with cardiogenic shock referred to 16 tertiary care centers showed that the rate of unloading on V-A ECLS support was 49%, with all patient being vented with Impella [10].As a result of this growing scientific interest, evidence regarding the need of LV venting and the available strategies is now more consistent than it used to be in the past. Nevertheless, randomized controlled trials are urgently needed to overcome the lack of solid data.

**The Controversial role of IABP**

The role of intra-aortic balloon pump (IABP) as a venting solution is still extremely controversial. However, IABP remains widely used in association with V-A ECLS. Cheng et al. did not find any significant changes in survival outcomes in the combination IABP and V-A ECLS versus V-A ECLS alone [11]. On the contrary, Aso et al retrospectively analyzed a national inpatient database and demonstrated an improved mortality and successful weaning from V-A ECLS when IABP was added [12]. In ***chapter 3***, we showed that IABP was able to restore aortic valve (AV) opening and to recover systemic arterial blood pressure pulsatility in 80% of patients supported with V-A ECLS and experienced AV closure. Based on the use of aortic valve dysfunction as an early marker of LV overload [13], which is treated in the next paragraphs, IABP insertion is usually capable of overcoming this adverse event. Our data suggested to adopt IABP in case of early LV overload stages, such as AV opening impairment and absence of arterial blood pressure pulsatility. According to our findings, IABP implantation in peripheral V-A ECLS was independently associated with a lower frequency of pulmonary oedema and more days off mechanical ventilation under ECLS. Moreover, Brechot et al also found a trend towards lower mortality (odds ratio 0.54, 95% confidence

interval 0.29-1.01; p=0.06) in patients vented with IABP [14].Therefore, IABP should be considered as an effective unloading tool for mild or early LV overload [5]. However, the persistent LV overloading signs should drive the decision-making towards more effective LV unloading techniques.

**Comparison among the most promising LV venting techniques**

These studies are the first to provide a comprehensive description of the hemodynamic changes as a result of different unloading modalities in the setting of V-A ECLS. All investigated LV unloading strategies were associated with significant absolute and relative variations in LV hemodynamics and workload. Although the hemodynamic impact highly varied among these techniques, the chosen strategy should not consider only the capacity to unload to LV, but also other clinical features, such as weaning plan. ***Chapter 4*** and ***chapter 6*** demonstrated that Impella has the most pronounced unloading. *Table 1* and *figure 1* listed and depicted the compared LV hemodynamic and workload parameters.

***Table 1.***

| | Reduction associated with | | |
|---|---|---|---|
| | Pulmonary Artery Drainage (19F) | Atrial Septostomy (8.9 mm) | Trans-aortic mixro-axial pump (Impella 2.5) |
| **SW** | 31% | 34% | 55% |
| **PE** | -1% | 19% | 15% |
| **PVA** | 10% | 22% | 35% |
| **EDV** | 3% | 10% | 14% |
| **EDP** | -4% | 27% | 41% |

***Table 1.*** **Impact of different LV venting techniques on the LV hemodynamics and workload.** Legend: SW, stroke work; PE, potential energy; PVA, pressure volume area; EDV, end-diastolic volume; EDP, end-diastolic pressure.

By a significant end-diastolic pressure drop, the trans-aortic pump was highly effective on SW reduction and therefore on the consequence pressure-volume area (PVA). On the contrary, potential energy was less lowered by Impella in our animal model. However, the short time data capture, expected in our protocol, might not have allowed us to detect more significant impact on this parameter. Atrial septostomy based on a medium size hole, 8.9 mm, was less effective in decreasing the PVA, since its impact on stroke work (SW) resulted significantly lower, as shown by both end-diastolic volume (EDV) and pressure (EDP). However, the effect on potential energy (PE) differed only slightly and it was affected by the same limitation discussed above, namely the short time data capture we have adopted. The pulmonary artery cannula, 19 French, is defined as indirect LV venting. This was confirmed in our cardiogenic shock (CS) model, which showed a significant low impact in all workload parameters. Moreover, the slight increases in PE and EDP observed in our animal experiment might be the consequence of an indirect unloading, as well as the absence of variations in the very early phase.

***Figure 1.***

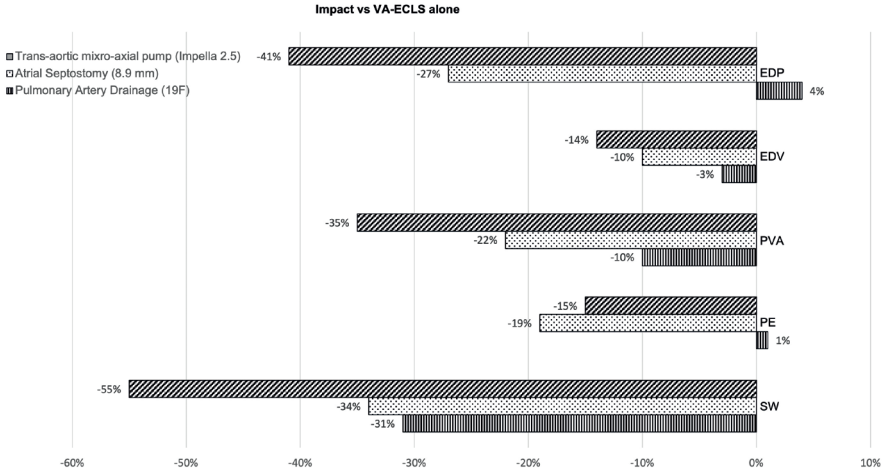


***Figure 1.*** **Impact of different LV venting techniques on the LV hemodynamics and workload.** Legend: EDP, end-diastolic pressure; EDV, end-diastolic volume; LV, left ventricle; PE, potential energy; SW, stroke work; PVA, pressure volume area; V-A ECLS, venoarterial extracorporeal life support

Our findings on preload reduction, defined as EDP and EDV, may be comparable with a recent meta-analysis [15] and the related simulation study [16]. In the metanalysis, Meuwese et al also found a higher degree of unloading in studies using micro-axial blood pump and atrial septostomy compared with IABP [17] and LV venting [18]. The authors declared their results were compatible with a simulation study, which used a dedicated hemodynamic software [19].In this simulation study, Donker et al clearly showed that IABP only marginally decreased cardiac loading comparared to Impella, which enhanced LV unloading [16]. In our CS shock model, Impella was able to reduce EDP, as a marker of preload, by 41%, the same value predicted by the simulator [16]. Accordingly, Meuwese et al observed a pooled relative preload reduction of 34% in micro-axial blood pump studies [15]. On the contrary, analysis on atrial septostomy showed a pooled relative reduction in left atria pressure, as a preload marker, ranging from 27% and 67% [15], whereas Meuwese simulated a reduction of 53% and 73% for atrial septal defect areas of 0.5 and 1.5 cm2, respectively [16]. The EDP reduction was only 27% in our animal model. On one hand, the difference might be explained by the fact that we used EDP as a preload marker, which could be less influenced by the atrial septal communication. On the other hand, our short protocol made it possible to notice only very early variations, which might not be properly detectable in the beside chamber. Finally, no available hemodynamic data regarding pulmonary artery drainage is currently available. Therefore, although the capacity to unload the LV was limited compared to the other techniques, its dynamic potential makes this approach extremely promising n case of biventricular failure or post-cardiotomy cardiogenic shock [20,21].

**Impella: the most effective LV unloading technique**

***Chapter 4*** demonstrated the significant role of Impella as LV unloading technique with a comprehensive in-vivo hemodynamic data, which further illuminate the use of this strategy. At the same time, ***Chapter 5*** provided a solid pathophysiological understanding behind the Impella and V-A ECLS association. Our CS model showed that Impella had a significant impact on LV hemodynamic and workload. Experimental data showed a clear supremacy in providing effective LV unloading compared to the other investigated techniques. For instance, compared to atrial septostomy, the micro-axial pump provided 21% of additional SW reduction and 13% of extra PVA drop, as well as 14% in EDP. In general, our findings are consistent with the findings on the impact on the pulmonary and circulatory physiology emerging from other animal [22,23] and human case series studies [24]. In our animal series, we observed a decreasing trend in all preload parameters, such as EDV, EDP, and (slightly) post capillary wedge pressure. Nevertheless, the impact on the overall pulmonary circulation, in particular mean pulmonary artery pressure, was minimal in our CS model. On one hand, Yourshaw et demonstrated how the maximum Impella effect on post capillary wedge pressure was recorded 12 hours later from the device implantation [25]. Therefore, since our protocol was only focused on the very early hemodynamic changes, the late response was not detectable. On the other hand, a prolonged study protocol allows to detect a slow hemodynamic adaptation after Impella implementation, which should underline the importance of acting early. Recently, Schrage et al, in a sub-analysis of their population vented with Impella, reported a persistent association with a lower mortality risk only in early LV unloading (when the Impella was implanted <2 hours) group [9]. Since the capacity to reverse advanced LV distension, as well as severe pulmonary oedema may last several hours, as indicated by our findings, the prevention of such critical conditions and timing of unloading plays a crucial role. This hemodynamics changes strongly influence the LV workload. By continuously pumping blood from the LV to the aorta, the trans-aortic microaxial pump reduces LV overload. As a consequence, PV loop shifts gradually leftwards and attains a triangular shape [26]. This leads to a direct impact on SW, which sharply drops by more than 50%, as shown in our swine experiments. However, the absence of an early significant effect on the preload parameters might explain the related lower reduction in PE. Therefore, we can speculate that the very early reduction in MVO2 is mainly influenced by SW drop rather than decreases in LV preload and myocardial fibers stretch. The latter variations might occur later, further improving the myocardial oxygen consumption balance and the overall unloading effectiveness.

**LV unloading: myth or miracle?**

In the field of Intensive Care Medicine, improved survival has resulted from several factors such as early diagnosis, treatments, and pre-existing conditions [27].

With respect to LV unloading on V-A ECLS, several studies failed [14,28], and the major positive results have been observed with derived from matched

populations [9,29]. Nevertheless, data from large-scale meta-analysis are promising. For instance, Al Fares et al found Improved short- term survival, weaning and improved early survival with early LV unloading [30]. Similarly, Kowalewski et al showed a 35% higher chance of ECLS weaning and 12% risk-reduction for in-hospital mortality in 7,581 patients, 44% of whom were vented with different techniques [31]. The study discussed in ***chapter 7*** provides the unique opportunity to test the impact of LV unloading in a CS pediatric population mainly in post cardiotomy setting. The encouraging results we found in pediatric population have been confirmed in some other studies. Although the population was small, Lin et al even reported a survival of 100% in vented patients [32]. Earlier timing of LA decompression appeared to be associated with a high probability of weaning from ECLS and reasonable LV functional recovery in children investigated by Kotani et al [33]. In our study, the population consisted in all congenital heart disease patients, who were not affected by any pre-existing comorbidities. Notably, LV venting significantly increased the survival at the discharge, by almost three times, despite all the confounding factors, including E-CPR. This surprisingly high impact of LV unloading on survival might highlight the cardiac pediatric patient as a suitable model for investigating the effects of LV unloading on major outcomes. Moreover, the importance of a prompt LV venting might even more crucial in pediatric patients. Indeed, further investigations and randomized controlled trials are needed to shed further light on this issue.

**Need of common definition and strategy**

*LV overload definition*

The current literature provides no unique definition of LV overload in patients supported with V-A ECLS.As previously discussed in **chapter 1**, the differences in definitions may account for the high variability of LV overload rate.

Among 184 peripheral V-A ECLS, discussed in **chapter 3**, we found that only 5.4% required IABP placement because of a protracted closure of the aortic valve. Since the rate of LV unloading ranges is extremely variable, we can suppose that the decision-making used in the experiences with lower rates should be based more on detailed criteria [34] than on preventive strategies [35]. Nevertheless, the identification of a common definition remains a pressing task for the scientific community and related organizations [36]. In **chapter 3** a multiparameter definition of LV overload was introduced. This definition is based on the evaluation of clinical (such as the arterial line pulse pressure, central venous line pressure and oxygen saturation, as well as pressures obtained from the pulmonary artery catheter), instrumental (X-ray) and mainly echocardiographic parameters (*table 2*). Based on the urgent need of a multidisciplinary approach in the cardiothoracic intensive care field [37], the optimal strategy should be discussed and developed by a dedicated Heart team.

This definition identifies the central role of the echocardiography. The echocardiographic evaluation should provide, firstly, an anatomical overview of the heart. In this regard, the AV function is one the most important parameters,

as reported in other experiences. For instance, Donker et al described the central role of echocardiogram in ECLS evaluation and underlined the importance of AV in the weaning decision-making [38]. In fact, the loss of LV ejection and the subsequent aortic valve standstill can lead to aortic root and LV cavity thrombosis [39]. Moreover, discrete echocardiographic parameters should be collected. The velocity time integral at the LV out-flow tract is certainly the most representative quantitative parameter. The VTI above 10 cm was one of the echocardiographic parameters associated with weaning success in 51 patients supported with V-A ECLS [40].

***Table 2.***

| Method | Factor | Grade of severity | | |
|---|---|---|---|---|
| **Arterial line** | | | | |
| | Arterial Pulsatility | Mild weakness | Moderate weakness | Almost Pulseless |
| **Central venous Line** | | | | |
| | $ScvO_2$ | 75-55% | 55-45% | <45% |
| | CVP (mmHg) | 8-12 | 12-16 | > 20 |
| **Echocardiogram** | | | | |
| | AV | Opening every 2 bpm | Opening every 3-4 bpm | Closure |
| | LV distension | Mild | Moderate | Severe |
| | LA distension | Mild | Moderate | Severe |
| | "Smoke like" effect | Mild | Moderate | Severe |
| | IVC dilatation[1] (cm) | 1.5 to 2.5 | >2.5 | >2.5 |
| | IVC collapse[2] | <50% | <50% | No change |
| **Swan Ganz Catheter** | | | | |
| | PCWP(mmHg) | 13-18 | 18-25 | > 25 |
| **Chest X-ray** | | | | |
| | Congestion[3] | Alveolar edema | Interstitial edema | Redistribution |

***Table 2.*** **Definition of left ventricle overload.**
Legend: ScvO2, Central venous Blood oxygen saturation; CVP, central venous pressure, AV, aortic valve; bpm, beats per minute; LV, left ventricle; LA, left atria, PCWP, post capillary wedge pressure.
1 IVC diameter in inspiration (Hallemat (2013) Crit Dec Emerg Med 27(10): 14-2)
2 IVC collapse in expiration (Hallemat (2013) Crit Dec Emerg Med 27(10): 14-2)
3 classification according to Ravin CE Radiographic analysis of pulmonary vascular distribution: a review. Bull N Y Acad Med. 1983 Oct;59(8):728-43.

Nevertheless, our definition shows some shortcomings. Central venous pressure and oxygen saturation cannot be evaluated during full V-A ECLS support, since the venous cannula is placed at the right atrium. These

parameters should be considered as marker of advanced fluid-overload and disjunction before ECLS support and may drive to an early and aggressive unloading strategy [41].

**LV venting algorithm**

The proposed LV overload definition allows to grade the severity of LV overload, which may guide the subsequent unloading strategy. In ***chapter 8***, a stepwise approach for LV venting was presented. The protocol is depicted in *figure 1A/1B*. First, the early detection of LV overload is crucial and may urgently lead to all non-invasive maneuvers to enhance LV ejection [1] together with an early implantation of IABP. The latter should be adopted as an indirect unloading strategy, which can only manage early or mild LV overload stage. Relatedly, Russo et al in a large meta-analysis found a significant lower mortality in vented V-A ECLS. Notably, 91.7% of patients were vented with IABP [42]. Second, we recognized a central role of Impella in case of failure or persistence of LV distension/stasis. Based on our animal data (***chapter 4***), which confirmed a solid pathophysiological background (***chapter 5***), and the most recent evidence [8,9], transaortic micro-axial pump should be considered, nowadays, the first choice for LV unloading. However, the higher risk of complications associated with Impella9 leads to centralize cardiac care of patients. Finally, in case of any contraindications for Impella placement, such as mechanical aortic valve prothesis or not-suitable vascular access (i.e., pediatric population), the choice should take into consideration the local expertise as well. Among these alternatives, the pulmonary artery cannula owns a high dynamic potential, especially useful in case of post-cardiotomy CS or right ventricular failure [20]. At the same time, atrial septostomy seems to be very effective in pediatric population, as confirmed by our results in ***chapter 7***. Moreover, in our pediatric population, we encountered cases of left atria cannula thrombosis, which were urgently removed. As a result, atrial septostomy should be favored over placing a drainage cannula through into the atrium, particularly in neonates and children.

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# Chapter 10.

## Impact

**Abbreviations**
CA, cardiac arrest
CS, Cardiogenic shock
IABP, Intra-aortic Balloon Pump
LV, Left Ventricle
V-A ECLS, veno-arterial extracorporeal life support

Cardiogenic shock (CS) and cardiac arrest (CA) are among the most lethal manifestation of acute cardiovascular disease, with high in-hospital mortality rates.
CA in North American and Europe approximates 50 to 100 cases per 100,000 [1] and the 30-day survival rate of out-of-hospital cardiac arrest patients who received cardiopulmonary resuscitation is only 10.7% worldwide [2]. Likewise, intensive care unit admission with CS has doubled from 4% to 8% over the past 15 years [3] and it is associated with a high mortality rate ranging from 30% to 40% [4-7].
Extracorporeal life support is increasingly used either in adults or children with acutely impaired cardiac function refractory to conventional medical management, mainly in profound cardiogenic shock and refractory cardiac arrest. In the United States, veno-arterial extracorporeal life support (V-A ECLS) use has raised from 1.613 per million in the year 2001 to 3.597 per million in 2011[8], and from 5.4 per million in the year 2000 to 44.3 per million in 2009 [9]. Despite this therapeutic advancement, mortality from CS and CA remain high [10-12]. Therefore, the efforts in improving the ECLS shortcomings have been increasing over the past decades. One of the most important concerns in V-A ECLS is the increased left ventricular (LV) pressure attributable to retrograde aortic perfusion. This could slow myocardial recovery or damage the myocardium and negatively affect survival [13]. This thesis provides a comprehensive treatise of LV unloading during V-A ECLS support, moving from a picture of the available strategies and the need of standardize the indications and treatments, through solid physiological data based on pre-clinical studies and ending to a clinical experience in a unique setting.

**Scientific impact**
Our work provided two main scientific improvements. First, our findings were based on a meticulous scientific methodology which firstly recognized the urgent need of experimental data supporting the use of these techniques in the daily clinical practice. This led to provide a detailed insight of the LV hemodynamics and workload investigated in a swine CS model, as shown in ***chapter 4*** and ***chapter 6***. Additionally, a comprehensive scientific treatise on the Impella use was reported in ***chapter 5***.
Second, this thesis was certainly one of the first attempt to align all the available indications and approaches. In ***chapter 2***, we firstly recognized the need of a common definition of LV overload. In addition, a multiparametric approach was proposed and, nowadays, it has been one of the few clear indications available in the literature.

**Clinical impact**
***Chapter 2*** proposed, for the first time, a detailed literature review on this topic. We analyzed in depth the available literature and systematically treated each technique with its advantages and disadvantages. Furthermore, our conclusions strongly remarked a lack of knowledge. On one hand,

approximately 60% of the selected papers evaluated in this study accounted for case reports or case series. On the other hand, grounded data regarding the hemodynamic and physiological changes related to each method were absent. The scientific interest on LV unloading has been sharply raised over the following five years.

One of the controversies, mentioned in our review, was the role of intra-aortic balloon pump (IABP) as an effective unloading technique. In ***chapter 3***, despite the limited number of patients, IABP implant will restore aortic valve opening in patients supported with V-A ECLS. Although the aortic valve dysfunction is considered only one of the LV overloading signs, the positive IABP impact confirmed its effectiveness in at least reversing this adverse event. This was a promising insight which drove the role IABP as a tool mainly when early signs of LV overload occurred. In ***chapter 4*** and ***chapter 6*** were the first studies which directly compared the effects of 3 different modalities of LV unloading during peripheral V-A ECLS. In this large animal model with profound cardiogenic shock (CS) supported with V-A ECLS, the Impella, pulmonary artery cannula and Atrial septostomy provided effective LV unloading maintaining adequate end-organ perfusion. Nevertheless, the grade of unloading significantly differed as demonstrated in our CS animal model. Besides the unique experimental data and the consequence better understanding of this phenomenon, these studies firstly provided solid proofs which may guide clinicians in their decision-making process. First, Impella was the most effective unloading technique in our experimental studies. Then, its effectiveness was further confirmed in large multicenter experiences and its use became widespread [14,15]. Second, although the role of pulmonary artery cannula as a dynamic and biventricular support was established [16], little was known regarding the effective impact on LV. Our experiment clarified and enhanced its effect as undirect LV unloading. Third, the use of atrial septostomy was supported by solid preclinical data which confirmed its effectiveness. With specific reference to the latter technique, ***chapter 7*** confirmed its benefits in a unique population of congenital heart disease patients supported V-A ECLS. To best authors' knowledge, this was the first and largest experience which demonstrated the impact of LV unloading on in-hospital survival in such population. Finally, ***chapter 8*** advanced a comprehensive algorithm as a diagnostic and therapeutic tool for properly unloading the LV during V-A ECLS. To summarize, this thesis investigated in depth the mechanisms and the hemodynamic impact of the most promising LV techniques. At the same time, we provided important insight which may support the clinicians in the decision-making process and patient selection. Finally, we opened a new research perspective regarding patients who might benefit LV unloading the most.

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# Chapter 11.

## Summary

V-A ECLS, in both peripheral or central configurations, may represent the final choice for patients in severe CS or refractory CA. Currently, despite ECLS, survival in such advanced and severe conditions remains poor. The efficacy of V-A ECLS is therefore variable, since the outcome can be influenced by numerous factors, such as its shortcomings. Among them, the effect of retrograde flow in the aorta towards the left ventricle is one of the most important concern. This unwanted effect may impact LV performance and jeopardize its recovery.

***Chapter 1.*** This chapter presents a general extensive introduction on ECLS and provides the scientific background. The LV hemodynamics and workload is fully treated, guiding the readers towards a better understanding, not only the unloading “dilemma”, but also the current work aims.

***Chapter 2.*** A comprehensive overview investigating the different LV venting techniques and results currently available is reported. A systematic literature search, including 207 articles published between 1993 and 2016, reveals a significant gap of knowledge and very heterogeneous indications. On one hand, despite the all the controversies, IABP is widely adopted as unloading tool. On the other hand, percutaneous approaches and sophisticated unloading devices seem to become increasingly used options.

***Chapter 3.*** Protracted aortic valve closure is identified as an early marker of increased afterload which may complicate peripheral V-A ECLS. Among 184 adult patients who were treated with peripheral V-A ECLS at Medical University Center Maastricht Hospital between 2007 and 2018, only 10 patients showed protracted aortic valve closure and inefficient LV unloading. Although in a limited number of patients, IABP is able to overcome such a hemodynamic impairment in 8 out of 10 cases, unfortunately, without improving the weaning rate and survival. Additionally, a novel definition of LV overloading is advanced, recognizing a central role the echocardiography.

***Chapter 4.*** A dedicated CS model includes 12 swine supported with V-A ECLS and randomizes to Impella or pulmonary artery drainage. A full evaluation of LV unloading and end- organ perfusion is performed through the pulmonary artery catheter and LV pressure/ volume analysis. The results clearly shows that the transaortic suction device and pulmonary artery drainage provides effective LV unloading during V-A ECLS and maintains adequate end-organ perfusion. Impella is able to achieve a more consistent pressure-volume area reduction, by almost 34.7%, compared to 9.7% with PA cannula. Consequently, Impella provides a greater LV unloading effect and reduces more effectively the total LV stroke work.

***Chapter 5.*** Based on the promising results obtained in our previous CS model, this chapter provides an extensive treatise on the addition of Impella

to V-A ECLS. This strategy, besides the presented pre-clinical data, has been consistently supported by retrospective propensity-matched studies, case series, and meta-analyses. The pathophysiologic background is related to the mitigation of the LV distension and pressure overload as a direct effect of the retrograde flow into the aorta. A deep report of these mechanisms is proposed in addition to an introduction of some clues regarding the best clinical practice and device management.

***Chapter 6.*** This chapter allows to quantify and understand in depth the unloading effect of percutaneous balloon atrial septostomy in profound CS supported with V-A ECLS. CS is induced by a coronary artery balloon occlusion in eleven swine. Immediately after balloon atrial septostomy while on V-A ECLS, left ventricular work drops by about 22%, as a consequence of reduced preload, afterload and stroke volume. Furthermore, our experimental data identifies the end-systolic pressure increase as the strongest determinant of mechanical work increase. Therefore, besides unloading, careful blood pressure control plays a key role in cardiogenic shock management with V- A ECLS.

***Chapter 7.*** Pediatric patients affected by congenital heart disease represent a very interesting study population. On one hand, scanty data are currently available in this cohort of study. On the other end, the common absence of further comorbidities, might better test the impact of LV venting on the major outcomes. The clinical outcomes of 90 pediatric patients affected by different congenital heart disease and supported with V-A ECLS, mainly in post cardiotomy setting, were retrospectively reviewed. The presence of active LV unloading strategy, mostly through surgical atrial septostomy, increased by almost three times the in-hospital survival. On the contrary, cardio-pulmonary resuscitation decreased the related survival.

***Chapter 8.*** This chapter has the primary aim to summarize the most recent evidence on LV unloading. Our experimental findings in association with the available clinical experience are condensed and this piece of work represents nowadays our strategy in patients supported with V-A ECLS. The LV overload definition is, therefore, reproposed and significantly improved. The role of counter pulsation is better clarified, supported by the discovered effectiveness in reversing early signs of overload. Furthermore, the choice of more advanced and aggressive LV unloading strategy is, finally, based on solid experimental findings. The overall result represents our current policy on LV unloading during V-A ECLS which is summarized in a detailed algorithm.

# Chapter 12.

## Samenvatting

V-A ECLS, in zowel perifere als centrale configuraties, kan de uiteindelijke keuze zijn voor patiënten met ernstige CS of refractaire CA. Momenteel, ondanks ECLS, blijft de overleving in dergelijke geavanceerde en ernstige omstandigheden slecht. De werkzaamheid van V-A ECLS is daarom variabel, omdat de uitkomst kan worden beïnvloed door tal van factoren, zoals de tekortkomingen. Onder hen is het effect van retrograde stroming in de aorta naar de linker hartkamer een van de belangrijkste zorgen. Dit ongewenste effect kan de LV-prestaties beïnvloeden en het herstel ervan in gevaar brengen.

***Hoofdstuk 1.*** Dit hoofdstuk geeft een algemene uitgebreide inleiding over ECLS en geeft de wetenschappelijke achtergrond. De LV-hemodynamica en werkbelasting worden volledig behandeld, waardoor de lezers naar een beter begrip worden geleid, niet alleen het lossende “dilemma”, maar ook de huidige werkdoelen.

***Hoofdstuk 2.*** Er wordt een uitgebreid overzicht gegeven van de verschillende LV-ventilatietechnieken en resultaten die momenteel beschikbaar zijn. Een systematisch literatuuronderzoek, inclusief 207 artikelen gepubliceerd tussen 1993 en 2016, onthult een aanzienlijke kennislacune en zeer heterogene indicaties. Aan de ene kant, ondanks alle controverses, wordt IABP algemeen gebruikt als losinstrument. Aan de andere kant lijken percutane benaderingen en geavanceerde losinrichtingen steeds meer gebruikte opties te worden.

***Hoofdstuk 3.*** Langdurige sluiting van de aortaklep wordt geïdentificeerd als een vroege marker van verhoogde afterload die perifere V-A ECLS kan compliceren. Van de 184 volwassen patiënten die tussen 2007 en 2018 werden behandeld met perifere V-A ECLS in het Medisch Universitair Centrum Maastricht Ziekenhuis, vertoonden slechts 10 patiënten langdurige sluiting van de aortaklep en inefficiënte LV-ontlading. Hoewel IABP bij een beperkt aantal patiënten een dergelijke hemodynamische stoornis in 8 van de 10 gevallen kan overwinnen, helaas zonder verbetering van de speensnelheid en overleving. Bovendien is er een nieuwe definitie van LV-overbelasting ontwikkeld, waarbij de centrale rol van echocardiografie wordt erkend.

***Hoofdstuk 4.*** Een specifiek CS-model omvat 12 varkens ondersteund met V-A ECLS en randomiseert naar Impella of pulmonale arteriedrainage. Een volledige evaluatie van LV-ontlading en eindorgaanperfusie wordt uitgevoerd via de longslagaderkatheter en LV-druk/volume-analyse. De resultaten laten duidelijk zien dat het transaortische afzuigapparaat en de drainage van de longslagader zorgen voor een effectieve LV-ontlading tijdens V-A ECLS en een adequate perfusie van het eindorgaan in stand houden. Impella is in staat om een meer consistente vermindering van het drukvolumegebied te bereiken, met bijna 34,7%, vergeleken met 9,7% met PA-canule. Bijgevolg zorgt Impella voor een groter LV-ontlaadeffect en vermindert het effectiever de totale LV-slagarbeid.

***Hoofdstuk 5.*** Gebaseerd op de veelbelovende resultaten die zijn verkregen in ons vorige CS-model, biedt dit hoofdstuk een uitgebreide verhandeling over de toevoeging van Impella aan V-A ECLS. Deze strategie is, naast de gepresenteerde preklinische gegevens, consequent ondersteund door retrospectieve propensity-matched studies, case series en meta-analyses. De pathofysiologische achtergrond houdt verband met de vermindering van de LV-uitzetting en drukoverbelasting als een direct effect van de retrograde stroom in de aorta. Een diepgaand rapport van deze mechanismen wordt voorgesteld naast een introductie van enkele aanwijzingen met betrekking tot de beste klinische praktijk en apparaatbeheer.

***Hoofdstuk 6.*** Dit hoofdstuk maakt het mogelijk om het ontlaadeffect van percutane ballonatriale septostomie in diepe CS ondersteund met V-A ECLS te kwantificeren en diepgaand te begrijpen. CS wordt geïnduceerd door een occlusie van een kransslagaderballon bij elf varkens. Onmiddellijk na ballonatriale septostomie terwijl op V-A ECLS, daalt het linkerventrikelwerk met ongeveer 22% als gevolg van verminderde preload, afterload en slagvolume. Bovendien identificeren onze experimentele gegevens de toename van de eindsystolische druk als de sterkste determinant van mechanische werktoename. Daarom speelt zorgvuldige bloeddrukcontrole, naast het lossen, een sleutelrol bij cardiogene shockmanagement met V-A ECLS.

***Hoofdstuk 7.*** Pediatrische patiënten met aangeboren hartafwijkingen vormen een zeer interessante onderzoekspopulatie. Enerzijds zijn er momenteel schaarse gegevens beschikbaar in dit cohort van onderzoek. Aan de andere kant zou de algemene afwezigheid van verdere comorbiditeiten de impact van LV-ventilatie op de belangrijkste uitkomsten beter kunnen testen. De klinische resultaten van 90 pediatrische patiënten met verschillende aangeboren hartaandoeningen en ondersteund met V-A ECLS, voornamelijk in de postcardiotomiesetting, werden retrospectief beoordeeld. De aanwezigheid van een actieve LV-ontlaadstrategie, meestal via chirurgische atriale septostomie, verhoogde met bijna drie keer de overleving in het ziekenhuis. Integendeel, cardiopulmonale reanimatie verminderde de gerelateerde overleving.

***Hoofdstuk 8.*** Dit hoofdstuk heeft als voornaamste doel om de meest recente gegevens over LV-lossing samen te vatten. Onze experimentele bevindingen in combinatie met de beschikbare klinische ervaring zijn samengevat en dit werk vertegenwoordigt tegenwoordig onze strategie.

# Chapter 13.

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# Chapter 14.

## About the author

Paolo was born on May 14th, 1987, in Merate (Lecco, Italy). He spent his childhood in Lomagna, a lovely town in the heart of Brianza, a green area at the foot of the Alps. He graduated at Milano Bicocca Medical School in 2012 and became specialist in cardiology in 2018, attending the Cardiovascular Department of Niguarda Hospital (Milan, Italy). Scientifically, he was involved on hypertension research, mainly based on arterial physiology, under the guide of *prof. Cristina Giannattasio* at Department of Medicine and Surgery, University of Milano-Bicocca (Milan, Italy). His experience in Maastricht started in 2011 when he was involved in De Maastricht Studie, under the supervision of *prof. Coen Stehouwer* and *dr Ronald Henry.* He focused his study on diabetic cardiomyopathy and cooperated in the analysis of the echocardiographic data until 2016. Nevertheless, the meeting with his mentor prof. Roberto Lorusso and the growing interest on intensive care ultimately drove the next steps of his career. In 2017, Paolo moved to the Netherlands and worked in the Cardiology (under the supervision of *prof. Brunner La Rocca*) and ICU department (under supervision of *prof. R. Lorusso*) of the Medical University Center Maastricht. During his stay in Maastricht, he started his PhD guided by *prof. R.Lorusso* and focused on “LV unloading in VA ECMO support” and received the EUROELSO Basic Science Research Grant which supported part of his PhD on animal experiment. In this regard, Paolo actively cooperated with the research group of Charles University of Prague, in particular *prof. Jan Belolhavek* and gained experience in cardiogenic shock model porcine models, thanks to his valuable teacher *dr. Mikulas Micek*. In 2018, he shortly attended the Cardio-Thoracic ICU of Scott and Baylor University in Dallas (USA) hosted by *dr Detlef Wencker.* Back to Italy in September 2018, he started working as a cardiologist in the Coronary Care Unit at the Cardiovascular Department of Niguarda Hospital (Milan, Italy) and then in the Cardio-thoracic-vascular Intensive Care Unit at Policlinico San Donato (San Donato Milanese, Milan, Italy).

Based on interest in intensive care medicine and physiology, he started his training in Anaesthesiology and Intensive Care at Department of Anesthesia, Critical Care and Emergency, Fondazione IRCCS Ca’ Granda Ospedale Maggiore Policlinico (Milan, Italy) in November 2021.

# Chapter 15.

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