

Editorial

Impella combined with veno-arterial extracorporeal membrane oxygenation (VA-ECMO) for advanced hemodynamic supportRaphaël Giraud^{1,2,3,*}, Benjamin Assouline^{1,2,3}, Carlo Banfi^{2,3,4}, Karim Bendjelid^{1,2,3}¹Intensive Care Unit, Geneva University Hospitals, 1205 Geneva, Switzerland²Faculty of Medicine, University of Geneva, 1206 Geneva, Switzerland³Geneva Hemodynamic Research Group, 1206 Geneva, Switzerland⁴Department of Cardio-thoracic Surgery Istituto Clinico Sant'Ambrogio, Gruppo Ospedaliero San Donato, Milan, and Chair of Cardiac Surgery, University of Milan, 20149 Milan, Italy*Correspondence: raphael.giraud@hcuge.ch (Raphaël Giraud)

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Cardiogenic shock (CS) continues to be a challenging state resulting in end-organ hypoperfusion and tissue hypoxia associated with about 40%–50% mortality, despite early revascularization and medical therapeutics in heart failure [1]. Up to now, veno-arterial extracorporeal membrane oxygenation (VA-ECMO) has been broadly used to ensure life support for these refractory CS patients [2]. In these circumstances, VA-ECMO may be used either as a bridge to myocardial function recovery, long-term mechanical circulatory supports or heart transplant [3].

Recently, several observational studies reported that VA-ECMO was related with a significant increase in survival and had notably enhanced outcomes of shocked patients [4]. However, there is a lack of evidence, as no large randomized trial has been able to confirm these results. Moreover, in spite of the advantages of VA-ECMO on organ perfusion, one of the most detrimental effect is the increase in left ventricular (LV) afterload related to the retrograde aortic flow [5] (Fig. 1). Indeed, the augmented LV afterload induces an increase in wall stress and oxygen demand that both impede myocardial microcirculation, produces myocardial ischemia, and finally impairs recovery from CS [6,7]. Increase in LV pressure may also induce LV dilatation, and increase left atrial (LA) pressure resulting in pulmonary edema [8]. Ultimately, VA-ECMO may induce the aortic valve to not open and thus lead to intraventricular thrombosis [9]. Thus, the increased LV afterload is part of as a major limitation in the success of VA-ECMO in CS with severe reduction in LV contractility and correlated with increase in morbidity and mortality [10].

Numerous techniques have been described to unload the left ventricle and reduce LV afterload, to reduce the impact of VA-ECMO on cardiac coronary coupling [11]. One of these strategies to unload the LV consists to insert a microaxial blood pump (Impella, Abiomed Inc, Danvers, MA, USA) through the aortic valve. The blood inlet of the device is placed into the left ventricle under the aortic valve while the outlet and the pump motor are positioned beyond the aortic valve. The device passes through the aortic valve is able to deliver continuous blood flow of up to 3.5 L/min

from the LV into the aorta. Because, Impella reduces LV distension and lower end-diastolic pressure, it appears to be safe in patients on VA-ECMO and may be associated with improved outcomes. This strategy has been named: “ECMELLA” [12].

In this edition of Reviews in Cardiovascular Medicine, Fiorelli *et al.* [13] published a meta-analysis aiming to study efficacy and safety of LV unloading with Impella during ECMO in CS. Studies comparing the use of ECMO with and without Impella (ECMELLA vs. ECMO) were included. Primary endpoint was short-term all-cause mortality. Secondary endpoints included major bleeding, haemolysis, need for renal replacement therapy (RRT) and cerebrovascular accident (CVA). Five studies reunited the inclusion criteria, with an overall population of 972 patients. The ECMELLA cohort showed improved survival compared to the control group (RR (Risk Ratio): 0.86; 95% CI (Confidence Interval): 0.76, 0.96; $p = 0.009$). When including in the analysis only studies with homogeneous comparator groups, LV unloading with Impella remained associated with significant reduction in mortality (RR: 0.85; 95% CI: 0.75, 0.97; $p = 0.01$). Hemolysis (RR: 1.70; 95% CI: 1.35, 2.15; $p < 0.00001$) and RRT (RR: 1.86; 95% CI: 1.07, 3.21; $p = 0.03$) occurred more frequently in the ECMELLA group. No difference was noted between the two groups concerning major bleeding (RR: 1.37; 95% CI: 0.88, 2.13; $p = 0.16$) and CVA (RR: 0.91; 95% CI: 0.61, 1.38; $p = 0.66$). To conclude, this meta-analysis showed that Impella inducing LV unloading during ECMO was related to improved survival, despite increased hemolysis and need for RRT, without additional increase in major bleeding and CVA. In patients presenting with CS, the recent 2021 ESC-Guidelines for the diagnosis and treatment of acute and chronic heart failure recommend the rapid use of short-term mechanical circulatory device (MCS) to increase cardiac output and sustain end-organ perfusion [14].

The Intra-aortic Balloon Pump in Cardiogenic Shock II (IABP-SHOCK-II) trial revealed no difference in 30-day, likewise in long-term mortality between intra-aortic balloon pump (IABP) and optimal medical treatment (OMT) in pa-



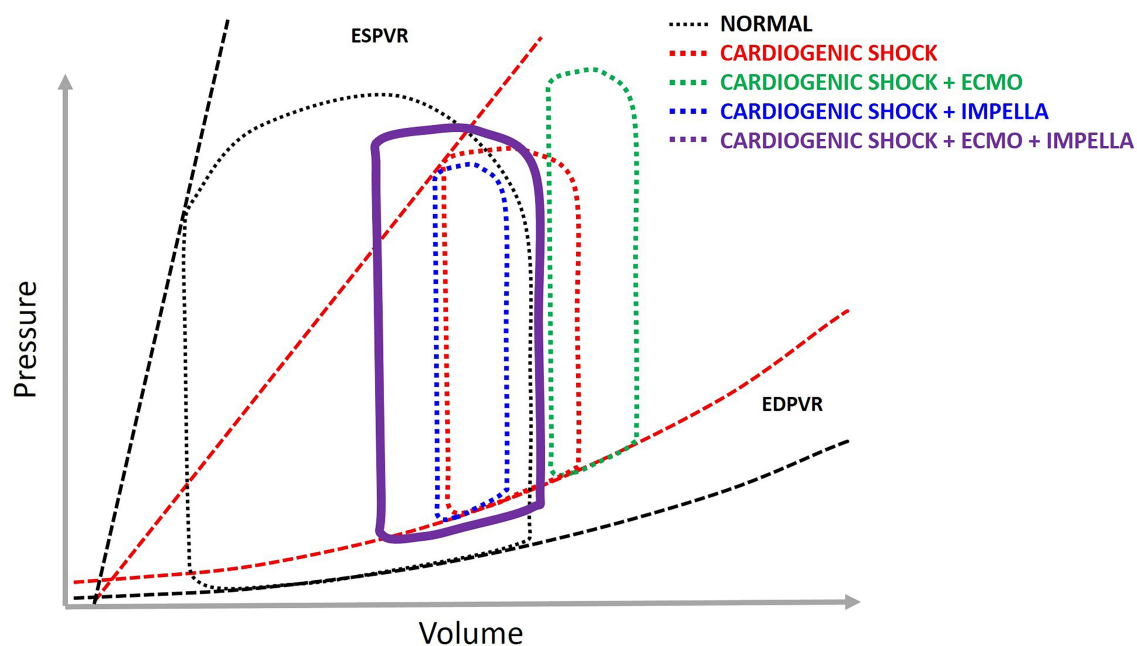


Fig. 1. Left ventricular (LV) pressure-volume loops showing differential hemodynamics states (black loop indicating physiological patterns), of cardiogenic shock associated to short-term circulatory support with microaxial-flow pump (Impella®), extracorporeal membrane oxygenation (ECMO) or combination of both. In cardiogenic shock related to myocardial infarction, both end-systolic and end-diastolic pressure-volume relationship (red dotted lines) are impaired, along with stroke volume (red dotted loop). Impella® (blue dotted loop) sends blood flow from the ventricle to the aorta and decreases LV pressure, LV size and LV wall tension. Veno-arterial ECMO provides counterflow support into the systemic circulation, leading to an increase in LV pressure, LV size and LV wall tension (Green dotted loop). Combining Impella® with VA-ECMO (purple loop) allows an increase in cardiac output associated to a simultaneous decrease in LV size, LV pressure, and LV wall tension. ESPVR, End-Systolic Pressure-Volume Relationship; EDPVR, End-diastolic Pressure-Volume Relationship.

tients with CS resulting from acute myocardial infarction (MI) [15,16]. As a consequence of the findings, IABP is no more routinely recommended in patients with CS related to MI [14] although it remains useful in some patients with partial native LV contractility and ejection [17–19]. Percutaneous mechanical circulatory support device including the Impella micro-axial pump is increasingly utilized in CS following acute-MI (CS-AMI), even though narrow evidence for its effectiveness. In a recent retrospective study of patients with CS-AMI comparing 237 patients treated with an Impella matched to 237 patients from the IABP-SHOCK II trial, the use of an Impella device was not associated with lower 30-day mortality compared with matched patients from the IABP-SHOCK II trial treated with an IABP or medical therapy [20]. Thus, the use of an Impella as a stand-alone MCS in these patients seems to be ineffective.

In this context, VA-ECMO has become the most chosen short-term assist device for hemodynamic support in CS patients [2]. Even if randomized controlled trials (RCT) comparing VA-ECMO with IABP or medical treatment are missing, a meta-analysis from observational studies exhibited promising outcomes in patients with CS treated with VA-ECMO compared to controls [4]. However, according

to the depression of the myocardial function and/or coexistent mitral regurgitation, VA-ECMO may increase LV afterload with an increase in LV end-diastolic pressure leading to pulmonary edema. In these cases, a way to unload the LV could be performed by adding the Impella device [21]. Moreover, in an animal model of acute myocardial infarction in swine, the authors showed that LV unloading using Impella, during coronary occlusion, increases the microcirculatory blood flow and decreases the infarct size [22].

Like Fiorelli *et al.*, other meta-analyses including retrospective observational studies had reported that VA-ECMO combined with LV unloading showed an increase in short-term survival rate in contrast with VA-ECMO only [13,23–25]. However, this combined device therapy requiring two arterial access sites and increasing both the shear stress on blood components may be at higher risk to induce vascular complications (hemorrhage and stroke) [12]. For the first time, the present meta-analysis reported neither increase in terms of major bleeding nor CVA. Despite the inclusion in this meta-analysis of the multicenter cohort study from Schrage *et al.* including patients with CS treated with VA-ECMO in whom 255 with left ventricular unloading were compared with 255 patients with-

out LV-unloading, showing that vascular complications occurred more frequently in patients with LV-unloading, no additional risk of major bleeding or cerebrovascular events are described in the present meta-analysis. However, increased hemolysis and need for renal replacement therapy were noted.

Even if ECMELLA seems to be a promising combination for CS patients, especially in terms of mortality, some questions remain unanswered: whether to unload all patients with cardiogenic shock placed on VA-ECMO or which patients could benefit the most from it, and finally, for how long this LV-unloading are supposed to be left in place. For all these unresolved questions, randomized studies are needed. In the meantime, as clinicians using applied physiology, we may consider that during CS related to acute myocardial infarction, VA-ECMO is beneficial to support end-organ perfusion but harmful to the ischemic heart, whatever the timing and the result of revascularization [22]. In this regard, in the present setting ECMELLA is a way to support end-organ perfusion without giving up the heart.

Author contributions

Conceptualization—RG and KB; writing—original draft preparation—RG and KB; writing—review and editing—RG, BA, CB and KB; figures—RG, BA and KB; supervision—CB and KB; All authors have read and agreed to the published version of the manuscript.

Ethics approval and consent to participate

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Conflict of interest

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