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Venting strategies for extracorporeal membrane oxygenation patients: More questions than answers but A plea for more clinical trials on the topic !

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Venoarterial extracorporeal membrane oxygenation (ECMO) has taken an increasingly important role in the management of refractory cardiogenic shock (CS) regardless of the aetiology with a grade IIaC according to the latest European guidelines.¹ However, several trials have recently addressed its interest in acute myocardial infarction-associated CS with the absence of 30-day survival benefit and high rate of associated complications.² These disappointing results could be due to (i) the absence of consensual indication (CS severity, the best escalation and implantation timing), (ii) the absence of validated protocols for ECMO management and (iii) associated treatments, (iv) its associated complications (bleeding, thrombosis and vascular complications), or (v) simply the haemodynamics under ECMO support. All these considerations account for a wide heterogeneity in practices and probably in results.

Acute, major and continuous increased afterload to the left ventricle is one of its most critical side effects, obviously deleterious from a pathophysiological point of view. This phenomenon increases in parallel with ECMO flow and is majored by acquired or preexisting aortic insufficiency. It may lead to an increase in left ventricular (LV) and left atrial (LA) pressures and volume, LV dilatation. and may compromise cardiac recovery. It is associated with potentially severe complications such as pulmonary oedema, ventricular arrhythmias. intracavitary thrombus and systemic embolisms. which hinders patients' prognosis.³

To prevent or correct LV overload, several approaches are proposed from ECMO flow reduction, restrictive fluid management, increased inotropic support, to left heart decompression (LHD). Several surgical or percutaneous LHD techniques are available and could be separate in active and passive LV venting depending on pump's action and subsequent LV unloading. Active venting may be obtained from different anatomical sites: pulmonary artery, left atrium, left ventricle, and aorta. This could be performed through different approaches: (i) drainage through an additional venous line incorporated into the ECMO circuit, (ii) continuous or pulsatile pump devices inserted across the aortic valve and ejecting into the aorta: or (iii) indirect negative pressure afterload reduction by intra-aortic balloon pumping (IABP). On the contrary, the passive venting utilizes the pressure gradient between the left and right atrium to reduce LV preload and distension mainly via percutaneous access.³

Experts usually agree that LHD should be considered if aortic flow is non-pulsatile. in case of progressive signs of LA or LV distension. elevated pulmonary artery and/or capillary pressures, pulmonary congestion, persistent closure of the aortic valve, or blood stasis with a risk of cardiac or aortic root thrombosis. However, many other aspects have to be kept in mind to reach the best decision including: individual patient characteristics (previous cardiac surgery. vascular access. bleeding risk and presence of LV thrombus) and overall prognosis. But also available techniques, team expertise and medico-economic status.³ Reliable results in the field remain scarce and the latest International Society for Heart and Lung Transplantation/Heart Failure Society of America guidelines suggest to consider LV venting/unloading in case of ECMO initiation (level 11, class C) without differentiating pharmacological/ mechanical approaches, type of device. or timing of initiation.⁴

Interesting retrospective observational data have reported haemodynamic improvement and survival benefits with the IABP or the Impella® devices, but association of multiples devices complicates the management and monitoring of patients and is associated with an increase in complications and costs.^{5,6} Above the device used, the timing for LHD appears crucial since early LV unloading with Impella® or LA venting was associated with reduction in 30-day mortality despite higher complication rates in retrospective series.^{7 8} Indeed, the mortality risk gradually decreases (hazard ratio 0.64, 95% confidence interval 0.46-0.88) following a time-dependent relationship after 2 h between ECMO implantation and initiation of active LV unloading (Impella® in CS patients).⁸

Park et al.⁹ recently published the results of the EVOLVE-ECMO trial, the first randomized trial addressing the crucial question of timing of LV unloading during ECMO support in CS patients. This is then an important trial for this reason, and because of the well-known difficulties to lead this kind of trials. They randomized 60 patients in two centers to early (at ECMO insertion) versus conventional (signs of refractory pulmonary oedema) LA venting. They showed that early LV unloading did not, improve their primary endpoint of ECMO weaning rate (70.0% vs. 76.7%, $P=0.386$), nor survival at discharge (53.3% vs. 50.0%, $P=0.796$) despite rapid improvement in pulmonary congestion score at 48 h. These results suggest that the pathophysiological interest is obtained as expected, but failed to show an improvement of clinical outcomes.

Nevertheless, several limitations should be discussed. First, the authors use the term of 'early venting' with an average delay between ECMO initiation and LA venting of 2.4 h for the early group and 48.4h for the conventional group but only patients who already have clear criteria for overload were included (significant pulmonary oedema on chest radiography and/or

plentiful, frothy, and blood-tinged secretions from the endotracheal tube; and intermittent opening or complete closure of the aortic valve). So, results will only be applicable for curative LHD strategy and not for preventive use. We could then hypothesize this strategy takes place too late. Second, the small size of their population prevents any firm conclusions as stated by authors themselves: 60 patients were planned but 56 were included and only 52 underwent a LHD (29 and 23 in the early and conventional LV unloading groups, respectively). In spite of a relatively long inclusion period. Third, LHD was exclusively obtained via an active LA venting thanks to a cannula inserted through the interatrial septum and connected in 'Y' to the venous line of the ECMO. It is certainly a strength for the comparability of the groups but is questionable regarding the complexity of the system combining an atrial septostomy with the addition of a 21-24 Fr LA cannula left in place several days. Its achievement justifies multidisciplinary skills and expertise (interventional cardiology, cardiac imaging and perfusionist) for fluoroscopy/echocardiography guidance assuring safe septal defect realization and correct cannula positioning, but also close circuit monitoring during the ECMO run (balance between venous drainage by LA and usual cavo-atrial cannulas, and risk of intra-cardiac and peripheral clotting).³ The benefit/risk ratio of this active LA venting is controversial regarding the passive atrial venting effects reported in preclinical models with significant reduction in preload and myocardial work.¹⁰ Several clinical paediatric and adult case series reported significant and quick decrease in LA pressure (change from -5 to -16 mmHg) ¹¹⁻¹⁴ and for some, potential clinical beneficial effect (mechanical ventilation weaning or even improved survival).¹¹ The atrioseptostomy seems very attractive as affordable, widely available, and quick to achieve (30-45min) without introducing artificial bodies or challenging the aortic valve, giving hopes for fewer complications (drain mispositioning, catheter obstruction, clots, cardiac perforation).^{11,13} Nevertheless, three specific questions need attention: (1) a risk of insufficient drainage and of early occlusion in case of small balloon size, even if no need for an additional LHD was reported in a recent case series ¹¹ (2) an increased risk of thrombus formation (LV or aortic root) secondary to blood stasis favoured by the reduction of preload and myocardial work with potential devastating consequences justifying adequate anticoagulation and close monitoring; and (3) the potential septal defect persistence which concerned 17-100% of survivors needing additional closure in up to 50% of the case.^{11-13, 15} Fourth, the utilization of LA venting for LV unloading prompts inquiries regarding its effectiveness, particularly in scenarios devoid of significant mitral regurgitation. This approach addresses the LV preload but it disregards the intricate contributions of venous return via Thebesian veins, bronchial veins, and retro-aortic circulation, elements that assume prominence in cases involving aortic insufficiency. Consequently, the suggested technique may inadvertently overlook crucial facets of cardiac physiology and intricate dynamics of the circulation.

Table 1 Published, active and future studies testing left ventricular venting strategies for venoarterial extracorporeal membrane oxygenation-supported cardiogenic shock patients.

| NCT | Country | Type of CS | Status | Acronym | n | Protocol, timing and type of LHD | Primary endpoint |
|-------------|---------|------------|--------------------|--------------|-----|--|--|
| NCT03740711 | Korea | All | Published | EVOLVE-ECMO | 60 | Early active left atrial venting when B-line on TTE vs. refractory pulmonary congestion on chest radiograph or inadequate AV opening on serial TTE | Weaning of VA-ECMO support |
| NCT03431467 | USA | All | Recruiting | REVERSE | 98 | Impella-CP within 10 h after ECMO initiation vs. ECMO alone | 30-day survival free from mechanical circulatory support, heart transplantation or inotropic support |
| NCT04775472 | Korea | All | Not yet recruiting | EARLY-UNLOAD | 116 | Early left atrioseptostomy within 12 h after ECMO initiation vs. conventional approach (atrioseptostomy in case of LVEDP increase ^a) | 30-day all-cause mortality |
| NCT05577195 | Germany | All | Recruiting | UNLOAD-ECMO | 198 | Impella CP at time of ECMO initiation vs. ECMO alone | Time to death from any-cause within 30 days after randomization |

Research on [ClinicalTrials.gov](https://clinicaltrials.gov) was made on 5 September 2023. All studies exclude post-cardiotomy CS.

CS, cardiogenic shock; ECMO, extracorporeal membrane oxygenation; LHD, left heart decompression; LVEDP, left ventricular end-diastolic pressure; TTE, transthoracic echocardiography; VA, venoarterial.

^aDefined by refractory pulmonary oedema, abnormal opening of the aortic valve, left ventricular dilatation, refractory ventricular tachycardia or fibrillation.

Thus, the study by Park et al. 9 cannot answer current clinical questions but the authors lays the foundation for further exploration of LHD techniques based on more robust research protocols. Given the array of LV unloading methods that have been utilized, several of which have shown promising potential, a series of randomized controlled trials is ongoing (Tab/e 7). Whereas, the REVERSE and the UNLOAD-ECMO trials aim to assess the impact of Impella-CP[®] in association with ECMO compared to ECMO alone on short-term survival with different timing of LV venting (insertion within 10h after ECMO initiation or at ECMO initiation, respectively), the EARLY-UNLOAD trial will investigate early atrioseptostomy within 12 h after ECMO initiation versus a conventional approach. These trials collectively aim to provide valuable insights into the efficacy and optimal timing of W unloading interventions in the management of CS patients supported by ECMO.

In conclusion, while the suitability of this technique remains uncertain. it is imperative to investigate the potential of systematic and early LV unloading with ECMO support. In light of the existence of alternative LV unloading techniques, it is essential to study the relevance of these various approaches initiating a robust randomized controlled trial about LHD. Indeed, a multi-arm clinical trial, comparing several unloading techniques and various strategies (timing, escalations, associations, etc.), would offer the potential to refine our understanding of LHD strategies. This trial should include a comparative analysis between different LHD types (including early active or passive LA venting, Impella-CP[®] insertion and IABP) and no LHD approaches. By examining the outcomes associated with different strategies, coupled with distinct initiation timeframes post- ECMO placement, this trial could answer the question.

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