

Extracorporeal membrane oxygenation evolution: Left ventricular unloading strategies

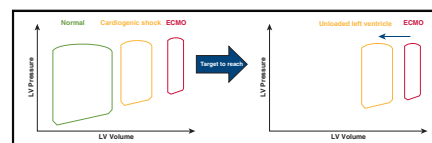


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Cardiogenic shock and acute heart failure are still the leading causes of death in Western countries.¹ Possible treatment options include vasopressors, inotropes, calcium sensitizers, nitric oxide synthase inhibitors, and different kinds of short- and long-term mechanical circulatory support devices.² So far, for all these treatment modalities, none has proven to be superior to the others, with overall limited evidence.² Venoarterial (VA) extracorporeal membrane oxygenation (ECMO) has evolved in recent years for the treatment of cardiogenic shock and cardiopulmonary resuscitation^{3,4} (Figure 1). Survival and adverse event rates are inversely associated with the size of the program. The main adverse events include bleeding and thromboembolic complications and limb ischemia.⁵ In most cases, the cannulas are inserted in the femoral vessels percutaneously, which is a fast and safe option even under resuscitation. However, the femoral-inserted arterial ECMO cannula leads to a retrograde flow in the aorta. This increases the afterload of the left ventricle (LV) and may lead to LV distension. We describe strategies to unload the LV.

PATHOPHYSIOLOGY OF VA ECMO AND LV DISTENSION

In cardiogenic shock, the pressure–volume (PV) curve of the LV is shifted to the right compared with the normal physiological state (Figure 2). The retrograde arterial flow of VA ECMO leads to an even stronger right shift of the PV loop of the failing LV. This correlates with an increase of LV end-diastolic pressure and a reduced stroke volume. Clinically, this is associated with LV distension, increase in LV wall stress, a closed aortic valve, blood stasis in the LV with possible thrombus formation, and pulmonary congestion. However, the goal that should be aimed for in patients experiencing cardiogenic shock is to shift the PV loop to the left to reduce LV wall tension and prevent complications associated with LV distension (Figure 2). Blood



Pressure volume loops of the LV of patients with cardiogenic shock and ECMO.

CENTRAL MESSAGE

Early unloading of the left ventricle using a transaortic microaxial pump might be beneficial in patients on peripherally placed arteriovenous extracorporeal membrane oxygenation.

stasis due to aortic valve closure can lead to aortic root and ascending aorta thrombosis.^{6–8} LV wall tension itself is associated with an increase of myocardial oxygen consumption and negatively associated with the chances of native heart recovery. Therefore, reduction of the LV wall tension increases the chances of weaning patients from VA ECMO.

OPTIONS TO PREVENT OR TREAT LV DISTENSION

It is important to identify patients who are at risk of LV distension or in need of LV unloading. This can be either diagnosed by clinical observation, radiograph of the chest, echocardiography, or direct or indirect measurements. In some patients, LV distension may be treated by either conservative treatment, such as blood pressure control, inotropic support, or fluid management; however, in some patients, this approach is not sufficient.^{9,10} Patients who have a closed aortic valve, aortic regurgitation, increase in LV diameters, mitral regurgitation, congested lungs on radiograph of the chest, elevated wedge pressure in Swan-Ganz catheter (Edwards LifeSciences, Irvine, Calif) measurements, or elevated LV end-diastolic pressure direct measurements using a catheter crossing the aortic valve should undergo LV unloading.¹¹ Different techniques that are used are either central cannulation strategies with or without placement of an LV vent using the right upper pulmonary vein, implantation of pulmonary artery cannula, transapical cannula, creating an atrial septal defect, direct

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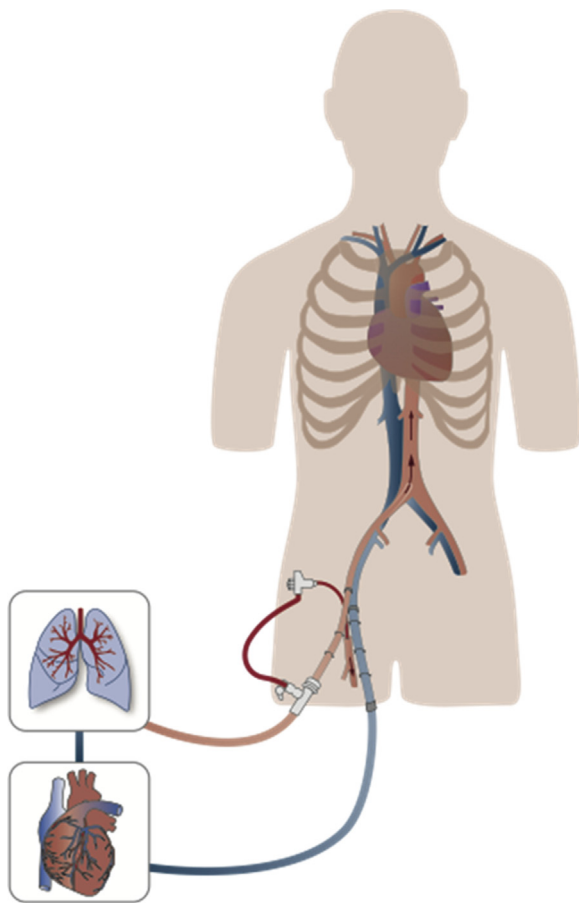


FIGURE 1. Femoral inserted venoarterial extracorporeal membrane oxygenation.

unloading of the left atrium, or insertion of additional short-term devices such as an intra-aortic balloon pump (IABP) or a transaortic microaxial pump (Impella devices; Abiomed, Danvers, Mass)¹²⁻¹⁴ (Table 1).

Central cannulation strategies are often used in patients with postcardiotomy failure. Schmack and colleagues¹⁵

reported their retrospective single-center experience with central cannulation with and without additional LV unloading using the right upper pulmonary vein. ECMO-supported patients with LV unloading showed favorable 30-day survival compared with those without unloading ($P = .034$).¹⁵ However, whether a central cannulation strategy approach is superior to peripheral femoral cannulation is unclear.¹⁶ However, an additional draining LA or LV catheter may clot after a few days of support. The frequency of this has not been reported, and therefore no general recommendations of a change of anticoagulation exist.

Some centers create an iatrogenic atrioseptostomy to create a left-to-right shunt and prevent or treat pulmonary congestion. However, reported evidence is mainly limited to smaller single-center studies or case series. Alternatively, a transseptal cannula in the left atrium can be placed and connected to the venous ECMO cannula.¹⁷ In patients on ECMO with a femoral insertion, an additional IABP has been routinely use in many centers due to its simple implant technique and cost-effectiveness. Deflation of the balloon lowers the afterload for the LV, leading to decompression of the LV. In previous studies, it has shown to improve survival compared with patients without unloading on ECMO. In a large national inpatient database from Japan, 1650 patients with cardiogenic shock were treated with an ECMO and an additional IABP ($n = 604$) or an ECMO without unloading ($n = 1064$) and were compared using propensity matching. The 28-day mortality and in-hospital mortality were significantly lower in the IABP unloading group than in the ECMO-alone group (48.4% vs 58.2%; $P = .001$ and 55.9% vs 64.5%; $P = .004$, respectively). Successful weaning from ECMO occurred more often in patients on ECMO unloaded with an additional IABP (82.6% vs 73.4%; $P < .001$).¹⁸

Insertion of an additional Impella is the so-called ECMELLA concept (Figure 3). In one of the earliest studies, 2 European centers retrospectively analyzed their experience in ECMO recipients for cardiogenic shock with and

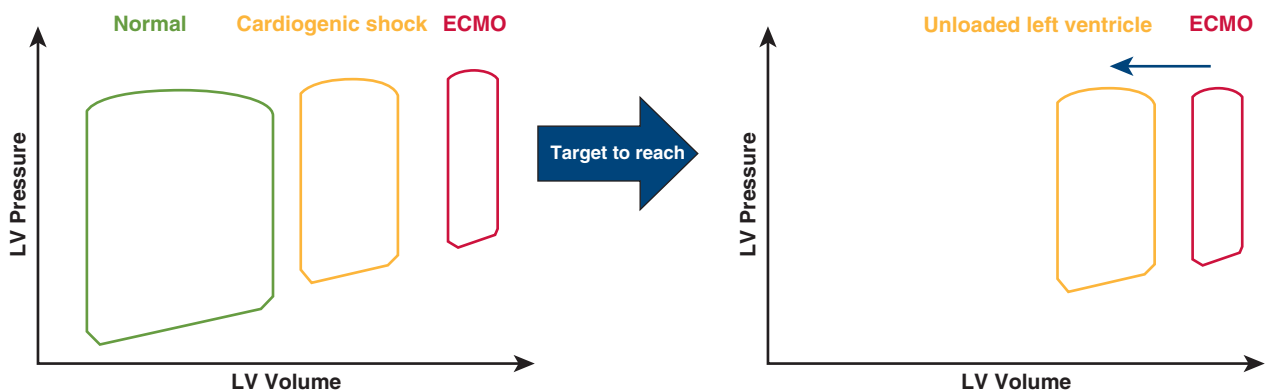


FIGURE 2. Early unloading of the left ventricle using a transaortic microaxial pump might be beneficial in patients on femoral inserted arteriovenous extracorporeal membrane oxygenation. ECMO, Extracorporeal membrane oxygenation; LV, left ventricular.

TABLE 1. Comparison of different unloading and venting strategies for venoarterial ECMO

ECMO unloading device	Impella 2.5/CP	Impella 5.0/5.5	IABP	Atrial septostomy	Surgical LV venting	Pulmonary artery venting
Degree of unloading	++	+++	+	++	+++	++
Logistic requirements for implantation	++	+++	+	+++	+++	++
Bleeding risk	++	+	+	+	+++	+
Hemolysis	++	+	+	+	+	+
Costs	++	+++	+	+	+	+
Access	Femoral	Axillary	Femoral/axillary	Femoral vein	Thoracic pulmonary vein or left apical	Jugular vein

ECMO, Extracorporeal membrane oxygenation; IABP, intra-aortic balloon pump; LV, left ventricular.

without additional Impella 2.5 implantation. These 157 patients were propensity score–matched in a 2:1 fashion. The main finding was that mortality and rate of successful weaning due to a recovered native heart function was greater in the ECMELLA group.¹⁹

Only a few studies have compared the effect of different additional unloading devices. Recently, a retrospective single-center study evaluated 49 patients using the ECMELLA approach and compared them with 91 patients

with ECMO and IABP. Both groups showed comparable measures of unloading and comparable 30-day mortality (39% vs 39%, $P = .56$). Patients in the ECMELLA group showed a greater rate of access-site bleeding (22% vs 0, $P < .01$) and major hemolysis (18% vs 0, $P < .01$).²⁰

A recent meta-analysis divided these different strategies to unload the LV during VA ECMO treatment into 3 groups: those with preload reduction, afterload reduction, and without unloading. The largest effect on unloading and outcome has been observed in the preload reduction strategies and the worst outcomes in patients without unloading strategies.²¹

Recently, a large multicenter study has been published with the largest evidence on unloading on ECMO to date²²: This international, multicenter cohort study included 686 consecutive patients from 16 tertiary-care centers in 4 countries with cardiogenic shock treated with VA-ECMO with or without LV unloading using a femoral-inserted Impella. These patients were 1:1 propensity score–matched. The primary end point was 30-day mortality. In the matched as well as in the unmatched cohort, survival was significantly greater for the ECMELLA group. In the unmatched cohort, 30-day mortality was 60.2% (95% confidence interval [CI], 54.5%-65.3%) versus 66.2% (95% CI, 60.6%-70.9%). The corresponding unadjusted hazard ratio (HR) for ECMELLA use was 0.82 (95% CI, 0.68-1.00; $P = .05$). In the matched cohort, 30-day mortality was 58.3% (95% CI, 51.6%-64.1%) versus 65.7% (95% CI, 59.2%-71.2%), with an HR for ECMELLA use of 0.79 (95% CI, 0.63-0.98; $P = .03$). A subgroup analysis investigated the timing of implanting the additional Impella device. Based on clinical practice, patients were divided in those receiving the Impella before or 2 hours after ECMO implantation and were compared with those without unloading.²² Compared with patients receiving ECMO without unloading, early LV unloading was associated with lower 30-day mortality (HR, 0.76; 95% CI, 0.60-0.97; $P = .03$), whereas delayed LV unloading was not (HR, 0.77; 95% CI, 0.51-1.16; $P = .22$). However, addition of a second device was also associated with an increase in adverse events.

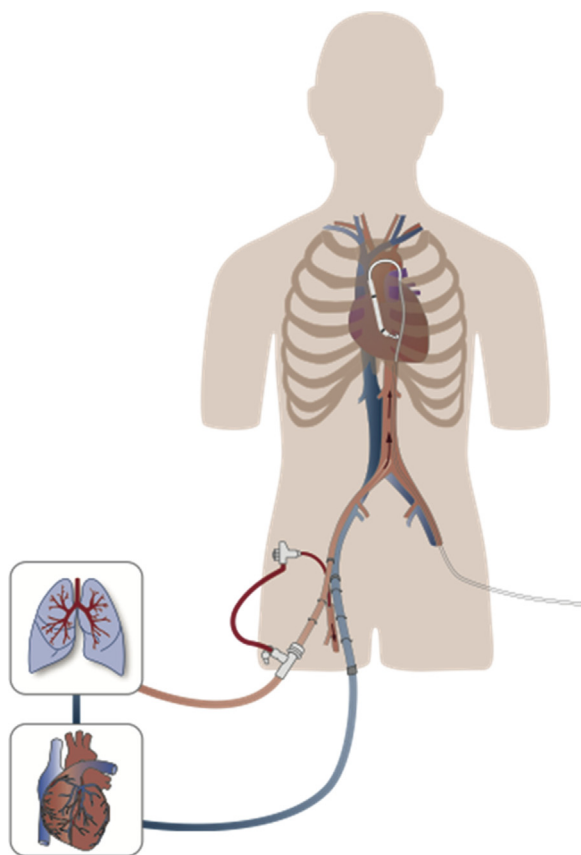


FIGURE 3. ECMELLA concept: femoral placed venoarterial extracorporeal membrane oxygenation and Impella device on the other side.

In the matched cohort, bleeding complications and hemolysis occurred more frequently in patients treated with ECMELLA versus patients treated with VA-ECMO; severe bleeding was observed in 38.4% of the patients treated with ECMELLA versus 17.9% in the patients treated with VA-ECMO and hemolysis was observed 33.6% of the patients treated with ECMELLA versus 22.4% of the patients treated with VA-ECMO.²²

DEGREE OF UNLOADING

A clinically unanswered question so far is if more LV unloading leads to better survival in ECMO recipients. A simulation study on hemodynamic effects of different kinds of short-term mechanical circulatory support devices and their combination showed that ECMO alone leads to the greatest LV load. The combination with an IABP is slightly reducing this load. The direct unloading using an Impella 2.5 improved the unloading, but the combination from ECMO and Impella 5.0 showed the greatest degree of unloading of the LV.^{23,24}

ECMELLA THERAPY USING AXILLARY IMPELLA 5.0/5.5 DEVICES AND BRIDGING OPTIONS

The Impella 5.0 has been designed for femoral implantation using a prosthesis to the femoral artery. Many centers implant the device in the axillary artery that facilitates mobilization and ambulation of these patients. In 2018, the Impella 5.5 received CE mark in Germany for longer-term support and showed promising early results.^{25,26} The newly designed device is lacking the pigtail catheter and its design allows more precise placement in the LV, potentially leading to lower rates of hemolysis.²⁷ In the initial series of 46 patients from 6 German centers who received an Impella 5.5, the 30-day survival was 73.9% with an overall favorable adverse events profile.²⁶ Later, the Food and Drug Administration approved the device in the United States.²⁸ The Impella 5.5 is designed for an axillary approach only. These surgically inserted devices have been shown to prevent or overcome ECMO-related complications such as bleeding and the need for blood transfusions.^{29,30} Many patients who undergo ECMO implantation for cardiogenic shock have pre-existing heart failure and suffer from acute on chronic decompensation. In these patients, the need of a durable left ventricular assist device (LVAD) is more likely compared with patients who previously had a preserved LV ejection fraction. Right ventricular (RV) failure is a leading cause of death after durable LVAD implantation.³¹ The unloaded RV during ECMO treatment makes an evaluation of RV function and prediction of a RV failure post-LVAD implantation difficult. In a recent large retrospective multicenter study on LVAD recipients who had been bridged by an ECMO, the need of right-sided support was up to 45.1%.³² Using an axillary placed Impella to first unload

the LV during ECMO and, after explantation of the ECMO, evaluating the right ventricular function under LVAD like conditions has been shown to be feasible and safe.³³ In a first feasibility trial in patients who had first an ECMO for profound cardiogenic shock and then an Impella 5.0 for RV evaluation and preconditioning, the 1-year survival post-LVAD implantation was close to 90% with a post-LVAD RV failure rate of 11.1%.³³ The axillary Impella devices can either being placed as a first-line unloading device or at a later stage if the patient has been stabilized in the acute setting by another short-term device. However, some patients may not even be LVAD candidates on ECMO because of potential contraindications while on the device, such as unclear neurologic status or systemic infections. For these patients, initial unloading on ECMO with a surgically placed axillary Impella device and explantation of the ECMO in case of sufficient RV and lung function gives a good bridge-to-bridge or bridge-to-decision option for these patients.³⁴ The axillary approach allows mobilization and ambulation. In the post-CE mark series in Germany, up to two-thirds of patients are mobilized at least to a chair, and one-third of patients are able to walk around.²⁶ New technical developments and features of the Impella CP and 5.5 device display LV end-diastolic pressure and native heart cardiac output. These diagnostic options may help in the future to stratify whether a patient can safely be weaned from the short-term device or may benefit from durable LVAD implantation.

CONCLUSIONS

The mortality of patients in acute cardiogenic shock is still high. ECMO is indicated for severe cardiogenic shock and increasingly implanted in recent years. A femoral-placed ECMO increases afterload of the LV, making recovery less likely and may lead to pulmonary congestion. Different additional devices are used for unloading. The largest evidence exists for Impella devices to unload the LV during ECMO (ECMELLA), and they have been shown to improve survival in patients receiving ECMO. Axillary Impella 5.0/5.5 allows unloading during ECMO therapy and provides a good bridge-to-bridge (eg, weaning, LVAD) option.

Conflict of Interest Statement

Dr Bernhardt has received honoraria, travel grants, consultancy fees, and/or research support from Abbott, Abiomed, AstraZeneca, Berlin Heart, Medtronic, and Novartis. Dr Schrage has received honoraria, travel grants, consultancy fees, and/or research support from AstraZeneca and Abiomed. Dr Westermann has received honoraria, travel grants, consultancy fees, and/or research support from Abiomed, AstraZeneca, Berlin-Chemie, Novartis, and Medtronic. Dr Reichenspurner has received honoraria,

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The *Journal* policy requires editors and reviewers to disclose conflicts of interest and to decline handling or reviewing manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

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Key Words: cardiogenic shock, extracorporeal membrane oxygenation, short-term device, mechanical circulatory support, unloading, venting, pulmonary edema, left ventricular distension