Chapter

ECMO as Bridge to Heart Transplantation

Andrea Lechiancole, Massimo Maiani, Igor Vendramin, Sandro Sponga and Ugolino Livi

Abstract

Extracorporeal membrane oxygenation (ECMO) is increasingly employed to support patients affected by refractory cardiogenic shock. When patients cannot be weaned from ECMO because of severe heart dysfunction, heart transplantation (HTx) or implantation of a durable mechanical circulatory support should be considered. Traditionally, the use of ECMO as a direct bridge to HTx was burdened by high mortality. However, during these last years, the widespread employment of ECMO increased centers' experience in the management of this device, and new allocation policies provided the highest priority level for ECMO HTx candidates. Therefore, these factors could have mitigated the negative outcomes previously reported. The aim of this chapter is to describe the role of ECMO as a direct bridge to HTx, analyzing results of this strategy, and how to determine candidacy and risk stratification among the severely ill population of patients supported by this mechanical circulatory support.

Keywords: ECMO, heart transplantation, bridge, cardiogenic shock, candidacy

1. Introduction

Venoarterial extracorporeal membrane oxygenation (ECMO) is a short-term mechanical circulatory support (MCS) that enables cardiopulmonary support. Thanks to the easily reproducible technique of implantation and its biventricular and respiratory support, ECMO can be deployed in a relatively short time in almost all cardiopulmonary failures. For this reason, it is a well-accepted therapeutic option for patients with refractory cardiogenic shock [1, 2].

Like all temporary MCS, ECMO is generally employed as a bridge to decision treatment [3]. The possible clinical scenarios after ECMO support are represented by: 1—weaning from the device secondary to the recovery of cardiac function, 2—bridge to a durable MCS (left or biventricular assist devices) or bridge to heart transplantation (HTx), or 3—ECMO discontinuation because of irreversible multiorgan failure.

Patients supported by ECMO have traditionally been considered as high-risk candidates for HTx, with the poor outcome on the waiting list and after transplantation [3–7]. Many institutions advocates favoring the bridge to a durable left ventricular assist device (LVAD) if the function of the right ventricle improves during

ECMO support. This strategy was largely adopted in the United States, aiming to consider HTx after the complete recovery of patient clinical conditions [8, 9]. However, the results of this so-called "double bridge to HTx" are controversial [9].

The United Network for Organ Sharing (UNOS) has recently changed the heart allocation policy and conferred the highest priority status to patients supported by ECMO [10], in line with other transplant organizations [11]. Therefore, the number of patients that cannot be weaned from ECMO support and are considered for direct heart transplantation (HTx) is increasing.

1.1 Candidacy for HTx in patients supported with ECMO

Bridging to a durable mechanical circulatory support or HTx is considered when patients could not be weaned from the ECMO support because of a missed recovery of the myocardial function. Several weaning protocols are described in the literature [12, 13] and almost universally consist in the gradual reduction of the ECMO support, while hemodynamics and echocardiography parameters are monitored. If the cardiac function is deemed severely and irreversibly impaired, a rapid assessment of the patient clinical conditions should be performed before listing for HTx.

The first step when considering a candidacy for HTx is the evaluation of neurological function since de-novo disabling cerebrovascular accidents generally prevent patients from being listed. Severe neurological complications could occur as a consequence of cardiogenic shock, particularly after cardiac arrest and cardiopulmonary resuscitation, or during cannulation and duration of ECMO support. However, severe hypoperfusion and prolonged immobilization could result in critical illness with severe impairment of musculoskeletal function. A thorough examination is essential to discriminate between this potentially reversible condition to others. Cerebral imaging, usually by means of computed tomography (CT), is usually performed to exclude acute cerebrovascular accidents (strokes or hemorrhages) or neoplasms.

Patients already on the waitlist for HTx at the time of ECMO implantation generally do not need any additional diagnostic exams. However, patients who are evaluated for HTx candidacy, while on ECMO support, are generally screened by means of a whole-body CT scan, and also all pathological conditions should be assessed. In fact, persistent end-organ dysfunction, while on ECMO support, has been strongly associated with poor prognosis after HTx [14–16]. Lastly, when considering patient age limits, they could vary according to clinical status, but generally an age > 70 years preclude an HTx eligibility (**Figure 1**).

1.2 ECMO as BTT management

Once weaning attempts have confirmed an irreversible severe heart impairment, the ultimate goal of ECMO support is to permit adequate perfusion for end-organ recovery.

Typically, venoarterial ECMO is effective in reducing the right atrial pressure and in increasing the mean arterial blood pressure. The systemic arterio-venous pressure gradient is fundamental in enhancing tissue of organs with portal circulation, such as the liver and kidney. Thus, a relatively high ECMO-generated blood flow is of paramount importance to allow end-organ function improvement.

However, the major risk of this strategy is left ventricular overdistension. In fact, the failing left ventricle (LV) contraction could not be able to generate an adequate

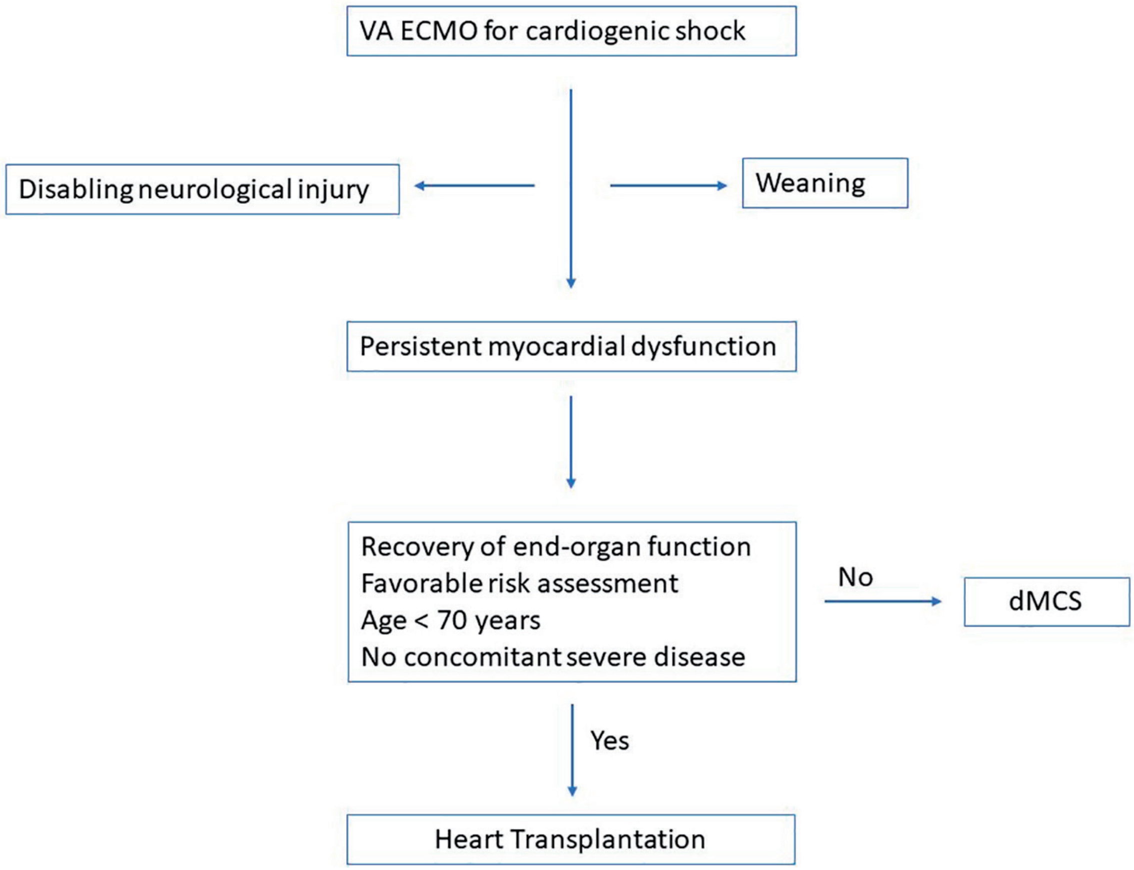

Figure 1.
Proposed decisional algorithm for patients supported by ECMO. VA ECMO: venoarterial extracorporeal membrane oxygenation and dMCS: durable mechanical circulatory support.

pressure to overcome the ECMO-derived afterload, and at the end to open the aortic valve. This condition could hesitate to blood stasis within the LV, with increased pressure inside the chamber and eventually pulmonary edema. Chest radiography and echo imaging are useful in promptly recognizing and monitoring these conditions and sequelae. However, the employment of a pulmonary artery catheter represents the most direct and time-sensitive means of detecting LV loading and permits to measure the pulmonary capillary wedge pressure (PCWP) and pulmonary artery pressure.

Once there is evidence of elevated PCWP or LV overdistension and pulmonary edema, a LV venting strategy should be introduced. It is worth of note that many centers employed a LV unloading strategy in an early phase of the ECMO course to prevent or limit as most as possible pulmonary congestion, while assuring adequate blood flow and pressure in the systemic circulation.

There are different strategies described for LV unloading, and clinical practice is generally guided by local expertise and experience. A combination of reduction of ECMO flow, vasodilators, and inotropes could facilitate the opening of the aortic valve, but peripheral perfusion could be compromised and noneffective in assure end-organ recovery.

Intra-aortic balloon pump (IABP) is the most widely used ancillary invasive support. It could be deployed at the bedside and generally with no difficulties. IABP reduces blood pressure into the aortic root during systole, enhancing aortic valve opening and LV ejection. However, IABP is effective in LV unloading only when some residual contractility of the LV is present, and its role in affecting outcomes among patients supported by ECMO is still not clarified [17].

Direct LV venting could be accomplished by means of a cannula surgically placed into the LV and connected to the venous line of the ECMO circuit or through the deployment of the impella (abiomed, danvers, and MA), a percutaneous transaortic ventricular assist device that provides an antegrade micro-axial flow. The ECPELLA strategy (ECMO + Impella) has emerged as an attractive solution since it combines the positive effect of high-flow arterial support with an efficient LV unloading [18]. A certain level of expertise and technical skills are the main limitation of direct LV venting strategies, that are generally offered in facilities specialized in ECMO support.

1.3 Outcomes of BTT with ECMO

The scientific evidence about the use of VA ECMO as a bridge to HTx is limited, and most studies are single-center or based on the analysis of the UNOS registry.

Despite the improvement of ECMO technology and increased experience in managing supported patients, HTx bridged by ECMO continues to be suboptimal when compared to patients bridged with left ventricular assist devices (LVAD) or without the need of MCS, and still burdened by significant mortality. In fact, 1 year after HTX, the overall survival rate for this group of patients is reported to be 60–70% [5, 6]. In particular, survival probability decreases abruptly within the first 30 days after HTx, when the mortality rate is reported as high as 20–40%. Multiorgan failure, primary graft failure, and sepsis account for a great part of early deaths [4–6].

Since the main limitation of HTx is the shortage of the donor pool, an accurate risk stratification among HTx candidates on ECMO support could limit as most as possible any shifting of available organs avoiding futile treatments. The severe hypoperfusion that accompanies cardiogenic shock affects the function of end-organs, by means of metabolic alterations at the cellular and extracellular levels whose severity is strictly related to the duration and degree of hypoperfusion, and to baseline pathological alterations.

It has been reported that persistent or worsening end-organ failure is strongly related to poor outcomes after HTX. Renal failure and mechanical ventilation were strong predictors of mortality according to Zalawadiya et al. [14], who analyzed the UNOS registry to report the outcomes of BTT with VA ECMO from 2000 to 2015.

Jansseron et al. [11] and Coutance et al. [16] further confirm the negative role of renal impairment on survival after BTT with ECMO. According to the France experience, patients with a glomerular filtration rate < 40 mg/dl or in renal replacement treatment are no longer considered as HTx candidates. Moreover, patients are recommended to be awakened and extubated during ECMO support in order to prevent pulmonary complications related to prolonged mechanical ventilation.

Other conditions that were reported to be risk factors for death are infection, high levels of lactate, and liver dysfunction [5, 6–19].

Scoring systems have been advocated by some authors for risk assessment, since they permit to stratify clinical status of patients in an objective and reproducible way, taking into account several clinical variables. Since they permit to comprehensively consider different clinical and biochemical values, risk scores could be considered as a surrogate of disease, and have proved to effectively predict survival in HTx bridged with ECMO.

In a previous study of our group, the acutephysiology, age, and chronic health evaluation (APACHE) IV score was demonstrated to be a powerful predictor of survival, with a receiving operative curve of 0.98. In particular, patients with an APACHE IV score > 47, 30 days and 1 year survival were 40% and 26.6%, respectively, significantly higher than the group with an APACHE IV score < 47 (30 days and 1 year survival of 100% and 89.7%, respectively) [20].

The alternative scoring system effectively employed in risk stratification among BTT with ECMO were sequential organ failure assessment (SOFA) and the model for end-stage liver disease excluding international normalize ratio (MELD-XI) [7, 21].

Large multicentric prospective studies are necessary to determine the accuracy and efficacy of these risk scores, and cut-off values that could discriminate between favorable or poor outcomes.

1.4 Listing ECMO patients

Since patients supported with ECMO have the highest risk for mortality on the transplant waitlist, they were given a preferential status at listing in many countries. Since October 2018 even in the United States BTT with ECMO reached the highest priority status, and the number of patients who are being bridged to HT with ECMO is constantly increasing [8]. As reported in a recent analysis using the UNOS database, the introduction of the new allocation system enhanced the access to available organs for HTx candidates supported with ECMO, resulting in a higher rate of HTx with lower time on the waiting list [10]. Moreover, the post-HTx survival of ECMO-bridged recipients significantly improved, reaching 90% at months [10]. A similar survival result, 85% at one post-HTx year, was reported by a French group after the introduction of the new national French allocation protocol, that conferred the highest priority status for ECMO-supported patients and excluded for HTx patients with severely impaired renal function [16].

An alternative possible explanation for improved post-transplant survival of ECMO-supported patients with the new allocations systems could be related to the utilization of ECMO on a different cohort of patients. In fact, since patients supported with ECMO have a high likelihood of being transplanted, ECMO could be increasingly considered as the short-term MCS of choice to bridge patients.

On the other hand, patients supported with ECMO who could not be weaned and have major risk factors may warrant consideration for an alternative to HT, such as LVAD implantation. In fact, it has been argued that perhaps a strategy of transitioning ECMO supported patients to durable MCS may provide the stabilization required to guarantee better post HT outcomes and more judicious use of transplanted hearts [9, 19], but limited and controversial evidence does not permit to generate recommendations.

2. Udine experience

Out of 410 Htx performed at the University Hospital of Udine since 2005, a total of 41 (10%) patients were directly bridged to HTx with ECMO. The ECMO circuit consisted of a centrifugal blood pump (Rotaflow, Maquet, Hirrlingen, Germany) with a hollow fiber oxygenator (Quadrox). Tubes (33 mL of priming), as well as the oxygenator and the pump, were coated with bioline (maquet), which combines polypeptides and heparin.

Clinical characteristics of the population at the time of HTx are shown in **Table 1**. In brief, the median age was 57 years (range 38–73 years), and 80% (n = 33) were male patients. The median creatinine level was 1.6 mg/dl (range 0.8–3.5 mg/dl), and the rate of renal replacement treatment was 15% (n = 6). 25 patients (61%) were mechanically

	Overall population (n = 41)	Low-risk (n = 30)	High-risk (n = 11)	P
Median age (range), years	57 (38–73)	56 (38–69)	58 (41–73)	0.2
Male sex, n (%)	33 (80)	24 (80)	9 (82)	0.9
Median creatinine (range), mg/dl	1.6 (0.8–3.5)	1.6 (0.8–2.3)	1.7 (0.8–3.5)	0.5
Hemodialysis, n (%)	6 (15)	3 (10)	3 (27)	0.2
IABP, n (%)	32 (78)	23 (77)	9 (82)	0.8
Impella, n (%)	2 (5)	2 (7)	0 (0)	0.6
Mechanical ventilation, n (%)	25 (61)	15 (50)	10 (91)	0.02
Median duration of ECMO support (range), days	10 (3–21)	11 (5–21)	9 (2–19)	0.9
Donor age	47 (21–63)	46 (29–58)	49 (21–63)	0.2
Median ischemic graft time (range), minutes	210 (145–290)	220 (155–290)	200 (145–250)	0.3

Table 1.
Baseline clinical characteristics of patients bridged to HTx with ECMO support.

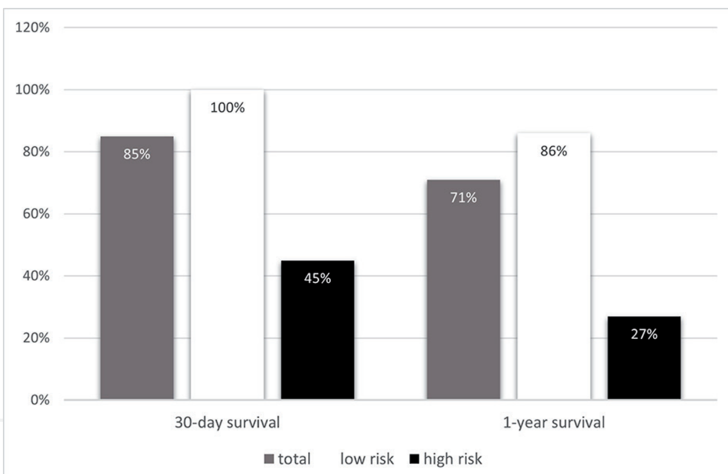

Figure 2.
Survival at 30 days and at 1 year of the overall population (total), APACHE IV score < 47 population (low-risk) and APACHE IV score ≥ 47 population (high-risk).

ventilated, 32 (78%) had IABP, and 2 (5%) an impella support for LV unloading. The median duration of ECMO support was 10 days (range 3–21 days).

After HTx, 30 days mortality was 15% (n = 6), and 1 year survival was 71% (six patients died after a median time from HTx of 73 days, range 42–237 days).

Since our previous experience revealed very poor outcomes for patients with values of APACHE IV score ≥ 47 [], we further extensively adopted this tool to stratify patients into two groups: low-risk (if APACHE IV score value was <47) and high-risk (APACHE IV score ≥ 47).

The low-risk group (n = 30) and the high-risk group (n = 11) had a median APACHE IV score of 34 (range 28–45) and 52 (47–60), respectively (p < 0.001).

As shown in the **Figure 2**, compared to other patients, those having an APACHE IV score had a significantly lower 30 days survival ($p < 0.001$) and 1 year-survival ($p < 0.001$).

3. Conclusions

VA ECMO as a BTT strategy is increasingly used after the change of allocation policies in many countries, particularly in the United States. Indeed, since patients supported with ECMO receive the highest priority status, this MCS has emerged as an attractive therapy to obtain at the same time cardiopulmonary support and to facilitate HTx.

However, since the ECMO-BTT strategy was traditionally burdened by high mortality, preventing any possible shifts of the limited available donor organ pool represents a major concern. Based on international experience, the key factors for obtaining successful HTx in patients supported with ECMO are as follows: 1—a thorough ECMO management aimed to prevent possible complications, while permitting end-organ recovery, 2—risk stratification and accurate selection of candidates at the time of listing, and 3—obtaining a compatible donor heart in relatively short time.

Otherwise, in high-risk conditions, transition to durable MCS should be considered to favor patient full recovery, permitting a judicious use of the limited donor pool.

Conflict of interest

The authors have no conflicts to declare.

Author details

Andrea Lechiancole*, Massimo Maiani, Igor Vendramin, Sandro Sponga and Ugolino Livi
Cardiothoracic Department, University Hospital of Udine, Italy

*Address all correspondence to: andrea.lechiancole@asufc.sanita.fvg.it

References

[1] Keebler ME, Haddad EV, Choi CW, McGrane S, Zalawadiya S, Schlendorf KH, et al. Venoarterial extracorporeal membrane oxygenation in cardiogenic shock. JACC: Heart Failure. 2018;**6**(6):503-516. DOI: 10.1016/j.jchf.2017.11.017

[2] Tsangaris A, Alexy T, Kalra R, Kosmopoulos M, Elliott A, Bartos JA, et al. Overview of veno-arterial extracorporeal membrane oxygenation (VA-ECMO) support for the management of cardiogenic shock. Frontiers in Cardiovascular Medicine. 2021;**7**(8):686558. DOI: 10.3389/fcvm.2021.686558

[3] Rousse N, Juthier F, Pinçon C, Hysi I, Banfi C, Robin E, et al. ECMO as a bridge to decision: Recovery, VAD, or heart transplantation? International Journal of Cardiology. 2015;**187**:620-627. DOI: 10.1016/j.ijcard.2015.03.283. Epub 2015 Mar 20

[4] Moonsamy P, Axtell AL, Ibrahim NE, Funamoto M, Tolis G, Lewis GD, et al. Survival after heart transplantation in patients bridged with mechanical circulatory support. Journal of the American College of Cardiology. 2020;**75**(23):2892-2905. DOI: 10.1016/j.jacc.2020.04.037

[5] Urban M, Siddique A, Merritt-Genore H, Um J. What are the results of venoarterial extracorporeal membrane oxygenation bridging to heart transplantation? Interactive Cardiovascular and Thoracic Surgery. 2019;**29**(4):632-634. DOI: 10.1093/icvts/ivz096

[6] Montisci A, Donatelli F, Cirri S, Coscioni E, Maiello C, Napoli C. Veno-arterial extracorporeal membrane oxygenation as bridge to heart transplantation: The way forward. Transplantation direct. 2021;**7**(8):e720. DOI: 10.1097/TXD.0000000000001172

[7] Fukuhara S, Takeda K, Kurlansky PA, Naka Y, Takayama H. Extracorporeal membrane oxygenation as a direct bridge to heart transplantation in adults. The Journal of Thoracic and Cardiovascular Surgery. 2018;**155**(4):1607-1618.e6. DOI: 10.1016/j.jtcvs.2017.10.152

[8] DeFilippis EM, Clerkin K, Truby LK, Francke M, Fried J, Masoumi A, et al. ECMO as a bridge to left ventricular assist device or heart transplantation. JACC Heart Failure. 2021;**9**(4):281-289. DOI: 10.1016/j.jchf.2020.12.012

[9] Coeckelenbergh S, Valente F, Mortier J, Engelman E, Roussoulières A, El Oumeiri B, et al. Long-term outcome after venoarterial extracorporeal membrane oxygenation as bridge to left ventricular assist device preceding heart transplantation. Journal of Cardiothoracic and Vascular Anesthesia. 2022;**36**(6):1694-1702. DOI: 10.1053/j.jvca.2021.06.035

[10] Gonzalez MH, Acharya D, Lee S, Leacche M, Boeve T, Manandhar-Shrestha N, et al. Improved survival after heart transplantation in patients bridged with extracorporeal membrane oxygenation in the new allocation system. The Journal of Heart and Lung Transplantation. 2021;**40**(2):149-157. DOI: 10.1016/j.healun.2020.11.004

[11] Jasseron C, Lebreton G, Cantrelle C, Legeai C, Leprince P, Flecher E, et al. Impact of heart transplantation on survival in patients on venoarterial extracorporeal membrane oxygenation

at listing in France. Transplantation. 2016;**100**(9):1979-1987. DOI: 10.1097/TP.0000000000001265

[12] Vuthoori R, Heaney C, Lima B, Knisel A, Miller E, Kennedy K, et al. Assessment of cardiac recovery in patients supported with venoarterial extracorporeal membrane oxygenation. ESC Heart Failure. 22 Apr 2022. DOI: 10.1002/ehf2.13892

[13] Trahanas JM, Li SS, Crowley JC, Ton VK, Funamoto M, Cudemus Deseda GA, et al. How to turn it down: The evidence and opinions behind adult venoarterial extracorporeal membrane oxygenation weaning. ASAIO Journal. 2021;**67**(9):964-972. DOI: 10.1097/MAT.0000000000001375

[14] Zalawadiya S, Fudim M, Bhat G, Cotts W, Lindenfeld J. Extracorporeal membrane oxygenation support and post-heart transplant outcomes among United States adults. The Journal of Heart and Lung Transplantation. 2017;**36**(1):77-81. DOI: 10.1016/j.healun.2016.10.008. Epub 2016 Oct 15

[15] Ivey-Miranda JB, Maulion C, Farrero-Torres M, Griffin M, Posada-Martinez EL, Testani JM, et al. Risk stratification of patients listed for heart transplantation while supported with extracorporeal membrane oxygenation. The Journal of Thoracic and Cardiovascular Surgery. 2021;**S0022-5223**(21):00877-00871. DOI: 10.1016/j.jtcvs.2021.05.032

[16] Coutance G, Jacob N, Demondion P, Nguyen LS, Bouglé A, Bréchot N, et al. Favorable outcomes of a direct heart transplantation strategy in selected patients on extracorporeal membrane oxygenation support. Critical Care Medicine. 2020;**48**(4):498-506. DOI: 10.1097/CCM.0000000000004182

[17] Barge-Caballero G, Castel-Lavilla MA, Almenar-Bonet L, Garrido-Bravo IP, Delgado JF, Rangel-Sousa D, et al. Venoarterial extracorporeal membrane oxygenation with or without simultaneous intra-aortic balloon pump support as a direct bridge to heart transplantation: Results from a nationwide Spanish registry. Interactive Cardiovascular and Thoracic Surgery. 2019;**29**(5):670-677. DOI: 10.1093/icvts/ivz155

[18] Meani P, Lorusso R, Pappalardo F. ECPella: Concept, physiology and clinical applications. Journal of Cardiothoracic and Vascular Anesthesia. 2022;**36**(2):557-566. DOI: 10.1053/j.jvca.2021.01.056

[19] Sponga S, Nagpal AD, Vendramin I, Ferrara V, Lechiancole A, Maiani M, et al. Bridge to heart transplantation in patients with cardiogenic shock: A 20-year experience with two different surgical strategies. Journal of Cardiovascular Medicine (Hagerstown, Md.). 2021;**22**(5):388-395. DOI: 10.2459/JCM.0000000000001097

[20] Lechiancole A, Sponga S, Isola M, Vendramin I, Maiani M, Livi U. Heart transplantation in patients supported by ECMO: Is the APACHE IV score a predictor of survival? Artificial Organs. 2018;**42**(6):670-673. DOI: 10.1111/aor.13099

[21] Chung JC, Tsai PR, Chou NK, Chi NH, Wang SS, Ko WJ. Extracorporeal membrane oxygenation bridge to adult heart transplantation. Clinical Transplantation. 2010;**24**(3):375-380. DOI: 10.1111/j.1399-0012.2009.01084.x