

OPEN

Veno-arterial Extracorporeal Membrane Oxygenation as Bridge to Heart Transplantation: The Way Forward

Andrea Montisci, MD,¹ Francesco Donatelli, MD,^{2,3} Silvia Cirri, MD,¹ Enrico Coscioni, MD,⁴ Ciro Maiello, MD,⁵ and Claudio Napoli, MD, PhD, MBE^{6,7}

Abstract. Advanced heart failure (HF) represents a public health priority due to the increase of affected patients and the meaningful mortality. Durable mechanical circulatory support (MCS) and heart transplantation (HTx) are unique therapies for end-stage HF (ESHF), with positive early and long-term outcomes. The patients who underwent HTx have a 1-y survival of 91% and a median survival of 12–13 y, whereas the median survival of ESHF is <12 mo. Short-term MCS with veno-arterial extracorporeal membrane oxygenation (VA ECMO) can be used as a bridge to transplantation strategy. Patients bridged with VA ECMO have significantly lower survival in comparison with non-MCS bridged and left ventricular assist device-bridged patients. VA ECMO represents an effective, and sometimes unique, system to obtain rapid hemodynamic stabilization, but possible negative effects on patients' outcomes after HTx must be considered. Here, we discuss the use of VA ECMO as bridge to transplantation.

(*Transplantation Direct* 2021;7: e720; doi: 10.1097/TXD.0000000000001172. Published online 8 July, 2021.)

Received 8 January 2021. Revision received 6 April 2021.

Accepted 7 April 2021.

¹ Department of Anesthesia and Intensive Care, Cardiothoracic Center, Istituto Clinico Sant'Ambrogio, Milan, Italy.

² Department of Cardiac Surgery, Cardiothoracic Center, Istituto Clinico Sant'Ambrogio, Milan, Italy.

³ Department of Clinical Sciences and Community Health, University of Milan, Milan, Italy.

⁴ Department of Cardiac Surgery, AOU San Giovanni di Dio e Ruggi d'Aragona, Salerno, Italy.

⁵ Cardiac Transplantation Unit, Department of Cardiac Surgery and Transplantation, Ospedali dei Colli, Naples, Italy.

⁶ Clinical Department of Internal Medicine and Specialistic Units, Regional Referring Centre for Clinical Immunology of Organ Transplantation (LIT), University Department of Advanced Medical and Surgical Sciences, University of Campania "Luigi Vanvitelli," Naples, Italy.

⁷ IRCCS-SDN, Istituto di Ricovero e Cura a Carattere Scientifico, Naples, Italy.

The authors declare no funding or conflicts of interest.

A.M. participated in the writing of the article and the critical review. F.D. did the conception of the work, writing of the article, and critical review. S.C. did critical review. E.C. and C.M. did writing of the article and critical review. C.N. participated in conception of the work, writing of the article and critical review.

Correspondence: Andrea Montisci, MD, Department of Anesthesia and Intensive Care, Cardiothoracic Center, Istituto Clinico Sant'Ambrogio, Milan, Italy. (montisci.andrea@yahoo.it).

Copyright © 2021 The Author(s). *Transplantation Direct*. Published by Wolters Kluwer Health, Inc. This is an open-access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

ISSN: 2373-8731

DOI: 10.1097/TXD.0000000000001172

EPIDEMIOLOGY AND DEFINITION OF ADVANCED HEART FAILURE

Heart failure (HF) affects an estimated 64.3 million people worldwide,¹ with a prevalence of 1%–2% in the general population and in 2016, caused approximately 300 000 deaths.²

Despite significant improvements in the medical management of HF, a substantial proportion of patients still progresses to the advanced stages of the disease.

Advanced HF affects approximately 1%–10% of the entire population of HF patients, with a prevalence destined to rise as a consequence of more effective therapies.³

The updated European Society of Cardiology definition of advanced HF includes the presence of severe and persistent symptoms of HF (New York Heart Association NYHA advanced III or IV class), reduced LVEF $\leq 30\%$ or isolated right ventricular failure, episodes of pulmonary or systemic congestion requiring high-dose intravenous diuretics (or diuretic combinations) or episodes of low cardiac output requiring inotropes or vasoactive drugs or malignant arrhythmias, severe impairment of exercise capacity with an inability to exercise, or low 6-min walking test distance (6MWT) (<300 m) or peak oxygen consumption (VO_2) <12–14 mL/kg/min.^{3,4}

The aim of the present narrative review is to outline the results of the studies on the use of veno-arterial Extracorporeal Membrane Oxygenation (VA ECMO) in patients on the waitlist for heart transplantation (HTx). The implementation of mechanical circulatory support (MCS) induced by the recent changes in heart allocation policies will also be discussed.

MECHANICAL CIRCULATORY SUPPORT FOR ADVANCED HF

The therapeutic panel of advanced HF includes orthotopic heart transplantation (HTx) and long-term MCS (LT-MCS).

HTx represents the treatment of choice for appropriately selected patients, with a 1-y survival of 90%, median survival of 12.2 y, and a significant and sustained improvement of functional status and quality of life.⁵

HTx, unfortunately, cannot represent the answer to the pandemics of HF, as the increase of the number of patients requiring advanced therapies collides with a limited supply of donors' hearts. LT-MCS is a therapeutic tool for advanced HF with positive results in terms of survival and improvement of functional status. The recently published Society of Thoracic Surgeons INTERMACS database annual report showed, indeed, that 1-y survival for isolated continuous-flow left ventricular assist device (LVAD) was 83% and 5-y survival was 46%,⁶ compared with a median survival of ESHF patients lower than 12 mo.⁷

The outcomes of patients treated with HTx or LT-MCS are highly dependent on the clinical status at the time of surgery. INTERMACS classification is the most common method to describe the clinical status of patients candidate to LT-MCS, ranging from the INTERMACS class 1 to 7, that include, respectively, patients with critical cardiogenic shock and advanced NYHA class IV.⁸ Several studies reported higher mortality rates for INTERMACS 1 patients and for those bridged to LT-MCS with short-term MCS.⁶

This relationship has been demonstrated even for patients undergoing HTx, as pretransplant clinical instability is a strong predictor of negative posttransplant outcomes.

Due to these unsatisfactory results, ST-MCS represents a reasonable strategy to stabilize extremely sick patients (bridge

to transplantation [BTT] strategy) (Figure 1) or to allow time for hemodynamic stabilization, end-organ damage recovery, and a thorough evaluation of HTx candidacy (bridge to decision, BTD or bridge to candidacy, BTC strategy).

The BTT strategy is of particular value in light of the results reported in patients listed for emergent HTx, who experience an increased load of complications as primary graft failure, need for postoperative dialysis, and in-hospital mortality.⁹

The heart allocation systems significantly diverge based on urgency criteria assignment and have to deal with chronic organ shortage and increasing demand. These factors may influence the BTT strategy.

The adopted solutions are different across countries.

ORGAN ALLOCATION POLICIES

The World Health Organization defines the allocation policy as the assignment of human cells, tissues, and organs to a transplant candidate based on a set of rules.¹⁰

The increase of the heart transplant waiting list and the significant proportion of patients either dying or deteriorating while waiting for transplant forced to expand the pool of suitable donors. The recent modifications of allocation policies in many countries reflect the need for more precise identification of the patients' clinical and urgency status to decrease mortality in the cohort with the highest risk. Table 1 describes the main allocation policies across the different United States and European countries.

In 2018 in the United States, United Network for Organ Sharing (UNOS) criteria have been modified from a former 3- to a new 6-tier system in the attempt to decrease the mortality rate for the sickest recipients on the waitlist.

The highest priority (UNOS 1) is attributed to patients on VA ECMO.¹¹

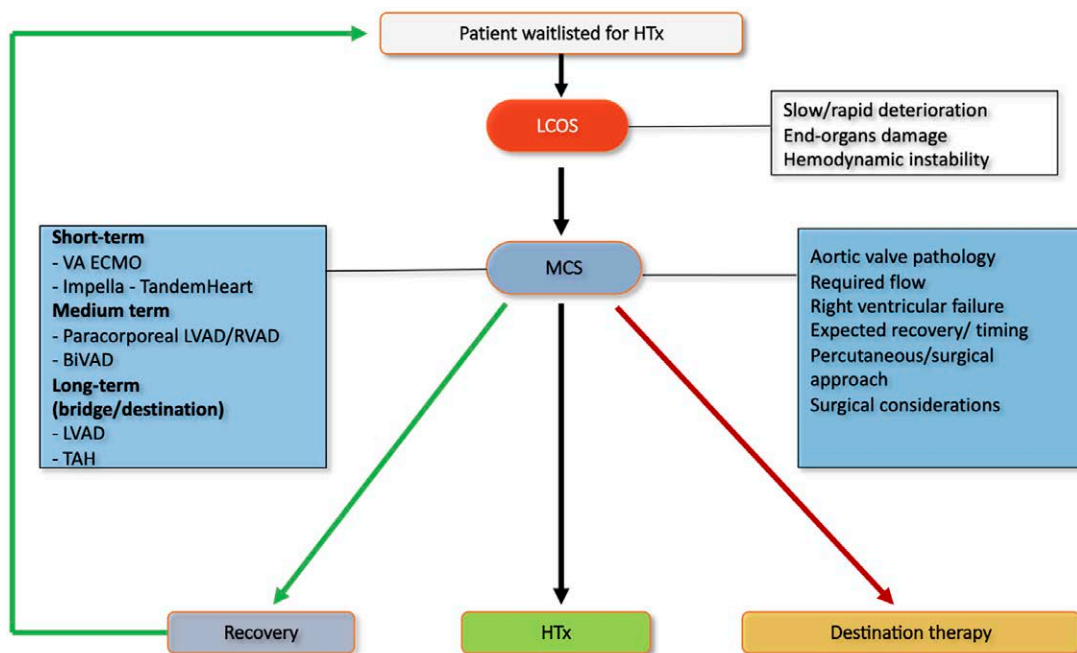


FIGURE 1. MCS-based bridging strategies. BiVAD, biventricular assist device; HTx, heart transplantation; LVAD, left ventricular assist device; MCS, mechanical circulatory support; RVAD, right ventricular assist device; TAH, total artificial heart; VA ECMO, veno-arterial Extracorporeal Membrane Oxygenation.

TABLE 1.
Different allocation policies across United States and European countries

UNOS (old)		UNOS (2018)		Eurotransplant		France		Italy	
Status	Criteria	Status	Criteria	Status	Criteria	Status	Criteria	Status	Criteria
1A	(a) MCS with acute hemodynamic decompensation - ECMO - IABP - THA - VAD (b) MCS with objective evidence of device-related complications (c) Continuous mechanical ventilation	1	- VA ECMO - Nondischargable BIVAD - MCS with life-threatening arrhythmias - Dischargeable LVAD/RVAD/TAH - Nondischargable LVAD - IABP or percutaneous MCS - MCS with malfunctioning - Sustained VT/VF	HU	-Inotrope-dependency -MCS with complications -Short-term MCS (individual motivation required)	Score: (a) Candidate risk score (0–1151 points) - VA ECMO- - Natriuretic peptides - Renal function - Total bilirubin (b) Exceptions: - durable MCS with device-related complications - uncomplicated BIVAD and TAH. (c) Donor-recipient matching (d) Traveling time	1	(a) Mechanical circulatory support due to acute hemodynamic failure with at least: - RVAD or BIVAD with centrifugal pump - LVAD with complications (thromboembolism, device infection, mechanical failure, ventricular arrhythmias. - TAH - IABP - ECMO (b) Mechanical ventilation National emergency Program access f: Status 1 PLUS - Short-term (<1 mo) MCS, CP, or ECMO - Long-term MCS, with complications - TAH with complications - Mechanical ventilation + IV inotropes + IABP	
1B	(a) Continuous infusion of single or multiple inotropes in addition to hemodynamic monitoring - IV inotropes - LVAD, stable - CHD, Restrictive CM, Retransplant (b) LVAD/RVAD in place (c) Continuous IV inotropes (d) LVAD/RVAD in place (e) All other candidates	5	Combined organ transplant All other candidates	HU 1B (only Nederland)	Stabilized patient still on high dose of inotropes.	2A - LVAD, uncomplicated - IV inotropes - ICD and recurrent malignant ventricular arrhythmias Candidates not on 1 or 2A status Suspended while on waitlist	2A 2B 3		
2	All other candidates	T	Transplantable	T	Transplantable				

BIVAD, biventricular assist device; CHD, congenital heart disease; CM, cardiomyopathy; CP, centrifugal pump; ECMO, Extracorporeal Membrane Oxygenation; IABP, intra-aortic balloon pump; IV, intravenous; LVAD, left ventricular assist device; MCS, mechanical circulatory support; RVAD, right ventricular assist device; TAH, total artificial heart; UNOS, United Network for Organ Sharing; VAD, ventricular assist device.

Eurotransplant¹² is an international collaborative organization that is responsible for the organ transplant in Austria, Belgium, Croatia, Germany, Hungary, Luxembourg, the Netherlands, and Slovenia. Eurotransplant allocation rules for HTx are based on urgency status and expected outcomes and do not assign priority status to VA ECMO patients.¹³ The rationale of this approach relies on the evaluation that the urgency criterium should meet the chance of a good post-transplant outcome.¹⁴

In France, the candidate risk score is the fundamental rule for heart allocation; it is based on 4 parameters: (1) the patient's objective risk of death on the waiting list, (2) the measure of medical urgency, (3) the donor-recipient matching based on criteria other than blood type, and (4) the national graft sharing taking travel time between procurement and transplant hospitals. The use of short-term MCS confers a hazard ratio of 3.7 (2.5–5.5) for 1-y mortality in the waitlist, and VA ECMO represents an urgency criterion.¹³

In Italy, the highest priority of status 1 is attributed to patients on MCS for acute hemodynamic instability. The subset of status 1 patients with a short-term MCS or long-term MCS/total artificial heart with complications can access the national emergency program, with an absolute priority on the first ABO compatible donor.¹⁵

MCS AND VENO-ARTERIAL EXTRACORPOREAL MEMBRANE OXYGENATION

Many MCS systems are available, with different technical characteristics and clinical applications.

VA ECMO can be defined as a modified cardiopulmonary bypass machine that ensures full hemodynamic and respiratory support. The system includes a centrifugal blood pump, a gas exchange unit with a membrane oxygenator and a heat exchanger, inflow and outflow cannulas, and a tubing set. The pump and the gas exchange unit allow the drainage of venous blood from the right atrium or the vena cava and the rein-fusion of oxygenated, nonpulsatile blood flow in the arterial system.¹⁶

Central ECMO entails the cannulation of the intrathoracic vessels, whereas the most common peripheral configuration involves the cannulation of the femoral artery and the femoral vein. The main hemodynamic effects of VA ECMO are the increase of mean arterial pressure and coronary perfusion pressure and the reduction of cardiac preload. Cardiac filling pressures are not invariably reduced: indeed, the retrograde extracorporeal flow in the common peripheral configuration augments left ventricular afterload, possibly leading to an increase of left ventricular end-diastolic pressure and wall stress.

VA ECMO restores systemic perfusion and allows time for end-organ function recovery after cardiogenic shock, but at the same time, it is plagued by a high burden of complications that strongly impacts patients' prognosis.¹⁷

ADVANCED HEART FAILURE AND THE WAITING LIST FOR HEART TRANSPLANTATION: THE ROLE OF ECMO AS A BRIDGE TO TRANSPLANTATION

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

The following studies examined the impact of pretransplant VA ECMO bridging on posttransplant survival (Table 2).

Jasseron et al¹⁸ compared 80 heart transplant recipients bridged with VA ECMO reported to the CRISTAL French national registry between January 1, 2010, and December 31, 2011, with a comparison group of 786 patients, including 703 patients without MCS, 60 with long-term MCS (51 on VAD and 9 on total artificial heart), and 23 on short-term MCS with an intra-aortic balloon pump.

Patients listed on VA ECMO showed a 1-y overall survival rate of 52.2%, significantly lower compared with the comparison group (75.5%) ($P < 0.01$). One-y posttransplant survival was 70% in the VA ECMO group and 81% in the comparison group ($P = 0.06$). Interestingly, 1 mo after transplantation, survival of recipients was not significantly different among the groups (88.3% [74.2%–95.0%] versus 91.6% [88.6%–93.7%], $P = 0.5$).

Mishra et al¹⁹ reported a single-center experience in which they compared the posttransplantation outcomes of 15 patients bridged with ECMO, 26 patients bridged with LVAD and 206 nonbridged patients during 2005–2012. One-year and 5-y survival rates were 70% and 70% for ECMO patients, 96% and 83% for LVAD patients, and 92% and 81% for nonbridged HTx patients (P value for overall survival < 0.001), respectively.

Zalawadiya et al²⁰ analyzed the UNOS Registry to report the outcomes of 157 patients bridged to HTx with VA ECMO from 2000 to 2015. They reported a survival at 1 y of 57.8%. A higher mortality was observed in the first 30-d posttransplant. For patients who survived the first 30 d after transplant, long-term survival was 82.3% at 1 y and 76.2% at 5 y. Renal failure (acute or chronic) and mechanical ventilation were predictors of 30-d and long-term mortality both in the short and long term.

Lechiancole et al²¹ conducted a single-center retrospective study that analyzed the outcomes of 32 patients bridged to HTx with VA ECMO. Early posttransplant mortality was 18.7% (< 30 d). The mean acute physiology, age, and chronic health evaluation (APACHE IV) were found to be a strong predictor of mortality in such a cohort of patients. Indeed, in the group with an APACHE IV score > 47 , 30-d, 1- and 5-y survival were 40% and 26.6%, respectively, and significantly higher than the group of patients with an APACHE IV score < 47 (no early mortality, survival 89.7% at 1 y and 81.5% at 5 y).

Fukuhara et al²² identified in the UNOS Registry 107 heart transplant recipients bridged with VA ECMO and 6148 patients bridged to transplantation with a durable continuous-flow LVAD, from a total cohort of 25 168 adult heart transplant recipients between 2003 and 2016. The analysis of the propensity-matched cohort demonstrated a lower survival in ECMO group at 90 days (74.8% versus 88.8%; $P = 0.025$) and 3 years (69.3% versus 82.2%; $P = 0.054$). Multivariable and Cox analysis showed the model for end-stage liver disease excluding international normalized ratio (MELD-XI) score to be the sole predictor to both 90-d (odds ratio, 1.94; 95% confidence interval, 1.00–3.76; $P = 0.050$) and 3-y mortality (hazard ratio, 1.47; 95% confidence interval, 1.16–1.88; $P = 0.002$).

Barge-Caballero et al²³ conducted a retrospective multi-center study in 16 Spanish hospitals, including 169 patients bridged to HTx under VA ECMO support from 2010 to 2015. In-hospital postoperative mortality and overall survival

TABLE 2.**Main characteristics of the studies on VA ECMO before heart transplantation**

Author	Period	Country	Total number of HTx patients	Patient transplanted on ECMO	Days on waitlist	Survival
Jasseron	January 1, 2010 December 31, 2011	France	866	46	9 (IQR 6–15)	30 d: 61.6% (CI 49.8%–71.4%) 90 d: 57.6% (CI 45.8%–67.7%) 1 y: 52.2% (CI 40.5%–62.6%)
Mishra	2005–2012	Norway	259	15	NA	1 y: 70% 5 y: 70%
Zalawadiya	January 1, 2000 June 30, 2015	United States	NA	157	Total days on waitlist 82.9 ± 139.8	30 d: 72.6% Before 2009: 1 y 55.6%, 3 y 51.6%, 5 y 51.6% After 2009: 1 y 59.1%, 3 y 56.8%, 5 y 52.6%
Lechiancole	2005–2017	Italy	300	32	NA	30 d 81.3% APACHE > 47: 1 y 26.6%, 5 y 26.6% APACHE < 47: 1 y 89.7%, 5 y 81.5%
Fukuhara	January 2003 March 2016	United States	25 168	40	NA	90 d: 73.1% 3 y: 67.4%
Barge-Caballero	January 1, 2010 December 31, 2015	Spain		129	7.6 ± 8.5	In-hospital: 33.3% 1 y: 54.7%
Potspov	January 1, 2013 December 31, 2017	Russia	786	166	NA	In-hospital: 143 (86.1%) 180 d: 84.2%; 1 y: 83.3%; 2 y: 75.1%; 3 y: 74.2%; 4 y: 72.3%; 5 y: 72.3%
Carter	January 1, 1999– March 31, 2018	United States	26 918	146	26 (IQR 6–92)	30 d: 89.3% (CI 88.1%–91.5%) 4 y: 70.3% (CI 68.5%–72.5%) 8 y: 59.1% (CI 57.2%–61.2%) 12 y: 50.9% (CI 49.2%–53.1%) 16 y: 47.4% (CI 45.6%–49.5%)
Giordanino	April 2006–April 2018	Argentina	333	14	On ECMO 6.5 (CI 5–14.5)	30 d: 12 (85.7) No further deaths at 4 y follow-up
Lui	April 28, 1996 June 30, 2018	United States	29 644	118	24.7 ± 71.2 (5, 2–13)	30 d: 79% 60 d: 77% 180 d: 69% 360 d: 68%
Gonzales	January 11, 2015 09/20/2019	United States	NA	185	2015–2018 7 (5–31) 2018–2019 3 (2–5)	2015–2018, 180 d: 74.6% 2018–2019, 180 d: 91.2%
Moonsamy	2005–2017	United States	24 905	177	Total d on waitlist 89 ± 214	30 d: 79 ± 2%; 180 d: 63 ± 3%; 1 y: 61 ± 3% 5 y: 52 ± 9%

CI, confidence interval; ECMO, Extracorporeal Membrane Oxygenation; HTx, heart transplantation; IQR, interquartile range; VA ECMO, veno-arterial Extracorporeal Membrane Oxygenation.

from listing to hospital discharge after transplantation were, respectively, 33.3% and 54.4% for patients bridged on VA ECMO. Patients treated with VA ECMO showed the highest incidence rate of adverse clinical events associated with T-MCS.

Potspov et al²⁴ enrolled 182 patients supported with VA ECMO in the period from January 1, 2013, to December 31, 2017, accounting for 23.2% of all the waiting list (n = 786). Posttransplant survival among heart transplant recipient with pretransplant ECMO versus control was 84.2% versus 90.1% (6 mo), 83.3% versus 91.8% (1 y), 75.1% versus 86.1% (2 y), 74.2% versus 85.8% (3 y), 72.3% versus 84.7% (4 y), 72.3% versus 83.5% (5 y), respectively ($P < 0.0001$).

Carter et al²⁵ interrogated the UNOS Registry from January 1, 1999, to March 31, 2018, for heart transplant recipients. They compared the patients bridged with any form of MCS and those bridged with VA ECMO. Twenty-six thousand nine hundred eighteen recipients were included. MCS patients included 9321 with LVAD (34.6%), 53 with right ventricular assist devices (0.2%), 258 with total artificial hearts (1.0%), 686 with biventricular assist devices (2.6%), 1378 with intra-aortic balloon pumps (5.1%), and 146 who required ECMO (0.5%). The primary endpoint was restricted mean survival time through 16.7 y. Recipients bridged with ECMO were

estimated to survive 16.6 mo less than non-MCS recipients, similar to patients receiving total artificial hearts or right ventricular assist devices.

Giordanino et al²⁶ reported the outcomes of a small cohort of patients who underwent HTx on VA ECMO or Levitronix centrifugal pump (CP) ensuring univentricular or biventricular support as a BTT strategy. Fourteen and 13 received ECMO or CP, respectively. Thirty patients ultimately underwent HTx, with a 23.3% mortality rate in the ECMO group, not significantly different compared with the CP group.

Lui et al²⁷ conducted a recent study to evaluate the effect of the new heart allocation system in the United States. The UNOS database was interrogated for all adult patients who required support with VA ECMO before heart transplantation from 2001 to 2018. Four groups were considered: (1) patients that required ECMO support at 1 point in their time on the waitlist but transplanted without MCS (n = 101); (2) patients on ECMO support until being transplanted (n = 118); (3) patients that required ECMO support while on the waitlist and were bridged to an LVAD before transplantation (n = 55). (4) Other heart transplant recipients without MCS or mechanical ventilation before Htx (n = 29 370). Kaplan–Meier curves showed a significant decrease in 1-y survival for patients bridged with VA ECMO to transplantation, compared with

those who were bridged to an LVAD before subsequent transplantation. The requirement of preoperative ECMO support, irrespective of the possibility of weaning before HTx, resulted in a significantly increased risk of posttransplant mortality, compared with recipients not requiring pretransplant MCS (HR 2.36, $P < 0.001$). The higher risk of mortality was carried by the direct bridging from ECMO to HTx (HR 3.03, $P < 0.001$).

The study by Moonsami et al²⁸ analyzed the outcomes of 7904 patients were bridged with durable LVADs, 177 (0.7%) with ECMO, 203 (0.8%) with nonendovascular-VAD, 44 (0.2%) with percutaneous endovascular devices, and 8 (0.03%) with TandemHeart, from a cohort of 24905 adult patients registered in the UNOS database between 2005 and 2017. Unadjusted survival at 1 and 5 y posttransplant was 68% ± 3% and 61% ± 8% for ECMO, respectively, significantly lower than all other types of pretransplant

The effect of the new UNOS heart allocation system has been recently described. Gonzales et al compared the waitlist and posttransplant outcomes of ECMO-supported patients in the new and old UNOS allocation systems.²⁹ From November 1, 2015, and September 30, 2019, a total of 296 ECMO-supported patients were listed for HTx, 191 and 105 listed according to the old- and new-allocation system, respectively. Patients listed in the new system were more likely to be transplanted and had a lower incidence of death or removal ($P = 0.001$) from the transplant list. The 6-mo survival after transplantation was 74.6% and 90.6% for the old- and new-era patients, respectively ($P = 0.002$).

CAUSES OF DEATH IN VA ECMO PATIENTS

The overall evidence coming from the aforementioned studies indicates a significantly higher mortality for patients bridged to HTx with VA ECMO.

VA ECMO is associated with many complications. A large systematic review¹⁷ including 1866 patients showed that the most frequent complications were as follows: lower extremity ischemia, 16.9% (12.5%–22.6%); fasciotomy or compartment syndrome, 10.3% (7.3%–14.5%); lower extremity amputation, 4.7% (2.3%–9.3%); stroke, 5.9% (4.2%–8.3%); neurologic complications, 13.3% (9.9%–17.7%); acute kidney injury, 55.6% (35.5%–74.0%); renal replacement therapy, 46.0% (36.7%–55.5%); major or significant bleeding, 40.8% (26.8%–56.6%); rethoracotomy for bleeding or tamponade in postcardiotomy patients, 41.9% (24.3%–61.8%); and significant infection, 30.4% (19.5%–44.0%).

The most frequent causes of death in patients bridged to HTx with VA ECMO are multiorgan failure (MOF) and primary graft dysfunction (PGD). MOF represents a generic cause of death reflecting multiple injuries and subtending several causes, from cardiogenic shock to sepsis. PGD, defined as the early onset of a severe ventricular dysfunction of the donor graft, is the leading cause of early mortality in the posttransplant period.³⁰ Pretransplant MCS is almost universally reported as a risk factor for PGD. The pathophysiologic link may be the summative effect of the ischemia-reperfusion injury of the graft and the dysregulated inflammatory cascade already present in ECMO patients, fueled by the interaction between blood and foreign surfaces.

CONCLUSIONS

In the last 10 y, the number of ECMO treatments increased worldwide and, subsequently, the clinicians' confidence with extracorporeal life support.

VA ECMO as a BTT strategy is increasingly used after the change of the heart allocation rules in the United States. Indeed, the attribution of the highest priority status to patients on ECMO prompted a more frequent use of this MCS before HTx,³¹ making ECMO an attractive therapy to obtain hemodynamic stabilization and to get a heart quickly.

Furthermore, the new system of heart allocation was developed to expand the number of categories and to avoid the classification of patients with different clinical conditions into the same group. The expansion of VA ECMO-bridged patients with unsatisfying outcomes,³¹ however, could have led to unintended consequences.

This trend should be questioned in light of the universal reporting that the patients bridged with VA ECMO experience poor early and midterm outcomes. The possibility of a waste of organs in the setting of global donor organ shortage exists.¹¹

The management of cardiogenic shock is changing towards new concepts and strategies,³²⁻³⁴ and the acute decompensation of a patient in the waitlist poses significant clinical challenges.

The decision between different short- and long-term MCS systems on the acutely decompensated patient must take into account the superior results of the LVAD-bridged compared with ECMO-bridged patients.¹⁴

The field of advanced HF is rich in future developments. Durable MCS represents a concrete reality for patients with end-stage HF, and their outcomes are nowadays competing with HTx.³⁵

According to Fuchs et al,³⁶ it is reasonable that HTx will be a cornerstone of HF therapy for many years to come. Many topics for future research can be identified: increasing organ donations; expanding the donor pools with ex vivo perfusion systems and donation after circulatory death (DCD) procedures³⁷; improving organ allocation in light of the growing numbers of patients with MCS on the waiting list and their outcomes; improving organ retrieval, preservation, and future third-generation immunosuppression regimens to prevent rejection and adverse long-term outcomes. Finally, the coronavirus 2019 (COVID-19) pandemic may deserve further actions in the setting of cardiac surgery and heart transplantation.³⁸

Hence, VA ECMO represents an effective system to obtain a rapid hemodynamic stabilization, but detrimental effects on patients' outcomes after HTx need to be considered.

Institutional Review Board

This review study is exempt from Institutional Review Board approval.

ACKNOWLEDGMENTS

We are grateful to Silvia Sala, MD, for language editing and infographic preparation.

REFERENCES

1. James SL, Abate D, Abate KH, et al. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017:

- a systematic analysis for the global burden of disease study 2017. *Lancet*. 2018;392:1789–1858.
2. Groenewegen A, Rutten FH, Mosterd A, et al. Epidemiology of heart failure. *Eur J Heart Fail*. 2020;22:1342–1356.
 3. Crespo-Leiro MG, Metra M, Lund LH, et al. Advanced heart failure: a position statement of the heart failure association of the European Society of Cardiology. *Eur J Heart Fail*. 2018;20:1505–1535.
 4. Cacciatore F, Amarelli C, Ferrara N, et al. Protective effect of physical activity on mortality in older adults with advanced chronic heart failure: a prospective observational study. *Eur J Prev Cardiol*. 2019;26:481–488.
 5. Lund LH, Khush KK, Cherikh WS, et al. The registry of the international society for heart and lung transplantation: thirty-fourth adult heart transplantation report—2017; focus theme: allograft ischemic time. *J Heart Lung Transpl*. 2017;36:1037–1046.
 6. Teuteberg JJ, Cleveland JC Jr, Cowger J, et al. The society of thoracic surgeons intermacs 2019 annual report: the changing landscape of devices and indications. *Ann Thorac Surg*. 2020;109:649–660.
 7. Allen LA, Stevenson LW, Grady KL, et al; American Heart Association; Council on Quality of Care and Outcomes Research; Council on Cardiovascular Nursing; Council on Clinical Cardiology; Council on Cardiovascular Radiology and Intervention; Council on Cardiovascular Surgery and Anesthesia. Decision making in advanced heart failure: a scientific statement from the American Heart Association. *Circulation*. 2012;125:1928–1952.
 8. Stevenson LW, Pagani FD, Young JB, et al. INTERMACS profiles of advanced heart failure: the current picture. *J Heart Lung Transpl*. 2009;28:535–541.
 9. Mazzei M, Keshavamurthy S, Kashem A, et al. Heart transplantation in the era of the left ventricular assist devices. In: *Heart Transplantation*. IntechOpen; 2018.
 10. WHO: Transplantation of human cells, tissues and organs. WHO. Available at <http://www.who.int/transplantation/en/>. Accessed February 23, 2021.
 11. Liu J, Yang BQ, Itoh A, et al. Impact of new UNOS allocation criteria on heart transplant practices and outcomes. *Transplant Direct*. 2021;7:e642.
 12. Eurotransplant homepage. Eurotransplant. Available at <https://www.eurotransplant.org/>. Accessed January 4, 2021.
 13. Dorent R, Jasseron C, Audry B, et al. New french heart allocation system: comparison with Eurotransplant and US allocation systems. *Am J Transplant*. 2020;20:1236–1243.
 14. Bernhardt AM. The new tiered allocation system for heart transplantation in the United States—a Faustian bargain. *J Heart Lung Transpl*. 2019;38:870–871.
 15. della SM. Protocolli e linee di indirizzo. Available at <http://www.trapianti.salute.gov.it/trapianti/archivioProtocolliCnt.jsp>. Accessed January 4, 2021.
 16. Combes A, Price S, Slutsky AS, et al. Temporary circulatory support for cardiogenic shock. *Lancet*. 2020;396:199–212.
 17. Cheng R, Hachamovitch R, Kittleson M, et al. Complications of extracorporeal membrane oxygenation for treatment of cardiogenic shock and cardiac arrest: a meta-analysis of 1,866 adult patients. *Ann Thorac Surg*. 2014;97:610–616.
 18. Jasseron C, Lebreton G, Cantrelle C, et al. Impact of heart transplantation on survival in patients on venoarterial extracorporeal membrane oxygenation at listing in France. *Transplantation*. 2016;100:1979–1987.
 19. Mishra V, Fiane AE, Winsnes BA, et al. Cardiac replacement therapies: outcomes and costs for heart transplantation versus circulatory assist. *Scand Cardiovasc J*. 2017;51:1–7.
 20. Zalawadiya S, Fudim M, Bhat G, et al. Extracorporeal membrane oxygenation support and post-heart transplant outcomes among United States adults. *J Heart Lung Transpl*. 2017;36:77–81.
 21. Lechiancole A, Sponga S, Isola M, et al. Heart transplantation in patients supported by ECMO: is the APACHE IV score a predictor of survival? *Artif Organs*. 2018;42:670–673.
 22. Fukuhara S, Takeda K, Kurlansky PA, et al. Extracorporeal membrane oxygenation as a direct bridge to heart transplantation in adults. *J Thorac Cardiovasc Surg*. 2018;155:1607–1618.e6.
 23. Barge-Caballero E, Almenar-Bonet L, Gonzalez-Vilchez F, et al. Clinical outcomes of temporary mechanical circulatory support as a direct bridge to heart transplantation: a nationwide Spanish registry. *Eur J Heart Fail*. 2018;20:178–186.
 24. Poptsov V, Spirina E, Dogonashaeva A, et al. Five years' experience with a peripheral veno-arterial ECMO for mechanical bridge to heart transplantation. *J Thorac Dis*. 2019;11:S889–S901.
 25. Carter KT, O'Brien R, Larson SB, et al. Venoarterial extracorporeal membrane oxygenation is a viable option as a bridge to heart transplant. *J Thorac Cardiovasc Surg*. [Epub ahead of print. August 16, 2020]. doi: 10.1016/j.jtcvs.2020.08.026.
 26. Giordanino EF, Absi DO, Favaloro LE, et al. Short-term mechanical circulatory support devices as bridge to heart transplantation: a prospective single-center experience in Argentina. *Clin Transplant*. 2020;34:e13888.
 27. Lui C, Fraser CD, Suarez-Pierre A, et al. Evaluation of extracorporeal membrane oxygenation therapy as a bridging method. *Ann Thorac Surg*. [Epub ahead of print. October 22, 2020]. doi: 10.1016/j.athoracsur.2020.08.041.
 28. Moonsamy P, Axtell AL, Ibrahim NE, et al. Survival after heart transplantation in patients bridged with mechanical circulatory support. *J Am Coll Cardiol*. 2020;75:2892–2905.
 29. Gonzalez MH, Acharya D, Lee S, et al. Improved survival after heart transplantation in patients bridged with extracorporeal membrane oxygenation in the new allocation system. *J Heart Lung Transpl*. 2021;40:149–157.
 30. Singh SSA, Dalzell JR, Berry C, et al. Primary graft dysfunction after heart transplantation: a thorn amongst the roses. *Heart Fail Rev*. 2019;24:805–820.
 31. Parker WF, Chung K, Anderson AS, et al. Practice changes at U.S. transplant centers after the new adult heart allocation policy. *J Am Coll Cardiol*. 2020;75:2906–2916.
 32. Montisci A, Micheletto G, Sibillio S, et al. Impella 5.0 supported oncological surgery as bridge to LVAD. *ESC Heart Fail*. 2021;8:167–170.
 33. Bertoldi LF, Pappalardo F, Lubos E, et al. Bridging INTERMACS 1 patients from VA-ECMO to LVAD via impella 5.0: de-escalate and ambulate. *J Crit Care*. 2020;57:259–263.
 34. Schrage B, Becher PM, Bernhardt A, et al. Left ventricular unloading is associated with lower mortality in patients with cardiogenic shock treated with venoarterial extracorporeal membrane oxygenation: results from an international, multicenter cohort study. *Circulation*. 2020;142:2095–2106.
 35. Mehra MR, Uriel N, Naka Y, et al; MOMENTUM 3 Investigators. A fully magnetically levitated left ventricular assist device—final report. *N Engl J Med*. 2019;380:1618–1627.
 36. Fuchs M, Schibilsky D, Zeh W, et al. Does the heart transplant have a future? *Eur J Cardiothorac Surg*. 2019;55:i38–i48.
 37. Messer S, Cernic S, Page A, et al. A 5-year single-center early experience of heart transplantation from donation after circulatory-determined death donors. *J Heart Lung Transpl*. 2020;39:1463–1475.
 38. Donatelli F, Miceli A, Glauber M, et al. Adult cardiovascular surgery and the coronavirus disease 2019 (COVID-19) pandemic: the Italian experience. *Interact Cardiovasc Thorac Surg*. 2020;31:755–762.