MESTRADO INTEGRADO EM MEDICINA – TRABALHO FINAL

INÊS TATIANA DE BRITO E CRUZ

EXTRACORPOREAL MEMBRANE OXYGENATION AS BRIDGE TO HEART TRANSPLANTATION

ARITIGO DE REVISÃO

ÁREA CIENTÍFICA DE MEDICINA INTENSIVA

Trabalho realizado sob a orientação de:

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NOVEMBRO / 2021

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Agradecimentos

Ao meu orientador, Professor Doutor Paulo Martins, pela disponibilidade, dedicação, empenho e gentileza com que me acompanhou durante todo este processo.

Aos meus pais, ao meu irmão e à minha cunhada, por tornarem Coimbra ainda mais perto, pela paciência e pelo apoio incondicional.

Ao meu avô, a minha estrelinha mais amada, por ter sido um exemplo de superação e a minha maior fonte de força. Não me pudeste acompanhar fisicamente nesta aventura, mas acredita que só foi um pouco mais difícil do que ganhar-te no Dominó.

Ao João, pelo carinho, admiração e suporte em todas as horas.

Aos meus amigos, especialmente à Sara e ao António, e aos meus afilhados, por tornarem esta jornada mais bonita, por me darem a motivação que às vezes nem vocês tinham e, pelo caminho que sei que ainda vamos percorrer juntos.

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Resumo

Nestas últimas três décadas, a Insuficiência cardíaca (IC) tornou-se um grande problema de saúde em todo o mundo, devido à sua crescente incidência, e consequente mortalidade. O transplante cardíaco (TC) continua a ser o gold-standard no tratamento de IC avançada. Apesar disso, o TC não é suficiente para dar resposta a todos os doentes e o número de pacientes que fazem ponte para transplante sob suporte circulatório mecânico (SCM) está a aumentar progressivamente. A Oxigenação por Membrana Extracorporal veno-arterial (ECMO-VA) fornece suporte cardiorrespiratório completo, restaurando a perfusão sistémica e permitindo a recuperação da função do órgão-alvo, mas acarreta uma alta taxa de complicações que têm forte impacto no prognóstico. Pacientes que fazem ponte com ECMO-VA parecem associar uma mortalidade pós-transplante significativa e ter piores resultados quando comparados aos pacientes cuja ponte foi feita com dispositivos de assistência ventricular esquerda de longa duração, assim como recetores sem ponte com SCM. A ECMO-VA é uma abordagem salva-vidas, permitindo um TC bem-sucedido na maioria dos pacientes, com uma sobrevivência aceitável a curto e a longo prazo, numa população com um prognóstico, de outra forma, reservado. Neste estudo, comparamos a ECMO-VA com a terapêutica convencional existente e com outras técnicas de SCM, com o objetivo de verificar se esta deve ser usada como ponte direta para o transplante de coração.

Palavras-Chave

ECMO-VA, OXIGENAÇÃO POR MEMBRANA EXTRACORPORAL, TRANSPLANTE CARDÍACO, SUPORTE CIRCULATÓRIO MECÂNICO, PONTE PARA TRANSPLANTE

Abstract

Heart failure (HF) has become a major health problem worldwide, due to its increasing incidence and associated mortality, over the last three decades. Heart transplantation (HT) continues to be the gold standard treatment to advanced HF. HT is not enough to address it, and the number of patients who are bridge to HT under mechanical circulatory support (MCS) is progressively increasing. Veno-arterial Extracorporeal Membrane Oxygenation (VA-ECMO) provides full cardiorespiratory support, restoring systemic perfusion and allowing end-organ function recovering, but it is haunted by a high burden of complications that have a strong impact on prognosis. Patients bridged with VA-ECMO appear to be associated with a significant post transplantation mortality and to be inferior when compared to reported outcomes of patients bridged with long-term left ventricular assistance devices, as well as non-bridged recipients. VA-ECMO is a lifesaving approach allowing successful HT in most of the patients, with an acceptable short and long-term survival in, an otherwise, ominous prognosis population. In this study, we compare VA-ECMO with existing conventional therapy and other MCS techniques, to sought if it should be used as a direct bridge to heart transplantation.

Keywords

VA-ECMO, EXTRACORPOREAL MEMBRANE OXYGENATION, HEART TRANSPLANTION, MECHANICAL CIRCULATORY SUPPORT, BRIDGE TO TRANSPLANT

Introduction

Heart failure (HF) has become a major health problem worldwide. Despite recent improvements in both medical and device treatments, advanced HF remains with a meaningful mortality and heart transplantation (HT) continues to be the gold standard treatment.[1]

Nevertheless, due to scarcity of donor organs, long waiting list times and growing incidence of terminal HF, the number of patients who are bridge to HT under mechanical circulatory support (MCS) is progressively increasing, either with veno-arterial extracorporeal membranous oxygenation (VA-ECMO) or ventricular assist devices (VADs).

VA-ECMO has been increasingly used as short-term circulatory support in patients with refractory heart failure, under the premise that it is a bridge to recovery, to a more durable bridge, to definitive treatment, or to decision.[2] However, performing an HT directly of VA ECMO only represents 1% of global transplantation, and, although there is still lack of scientific evidence, has been associated with poor posttransplant survival.[3]

Thereby, the aim of this narrative review is to compare VA-ECMO with existing conventional therapy and other MCS techniques, to sought if it should be used as a direct bridge to heart transplantation.

Materials and Methods

The initial bibliographic research of this narrative review began on March 29, 2021 and consisted in three parts: two searches in *PubMed* database, separated by a period of 3 months, and one in other well-known electronic databases. The first search used “VA-ECMO”, “ECMO”, “Bridge to heart transplantation”, and “heart failure” as keywords and the second was carried out with “VA-ECMO as a bridge to cardiac transplantation”, resulting in obtained 49 and 33 articles, respectively. The third search used the same keywords as the first, resorting to *Science Direct*, in which the first 5 of 275 papers were selected, based on relevance, and *The Cochrane Library*, adding more 7 papers. In all surveys, the following filters were applied: publication date between 2005 and 2021; language in English, Portuguese, or Spanish. As a result, 94 papers were obtained in the initial search.

Studies included in the review met the following criteria: i) published in English, Spanish or Portuguese from January 2005 to July 2021; ii) were case studies, meta-analysis, randomized controlled trial or cohort studies; iii) were papers directly related with ECMO-VA as a direct bridge to heart transplantation; iv) excluded if were studies with patients under 18 years old, patients who were listed to multi-organ transplant or re-transplantation and patients with a double bridge to transplantation.

The narrative review was conducted in two phases. In phase 1, abstracts were read and assessed against the review criteria, resulting on the exclusion of 68 papers. For abstracts that met the review criteria in phase 1, which were 26, full articles were read and were evaluated for inclusion or exclusion. The reference lists of the included papers were checked to search for further relevant papers; where such articles were considered relevant, they were included in the review. In the end, 17 papers were included in the final review, including 15 retrospective cohort studies, 1 case report, and 1 prospective study.

The search process is shown in Figure 1.

Definition and Epidemiology of Heart Failure

Due to its increasing incidence and associated mortality over the last three decades,[4] HF has become a major health problem worldwide. Currently, the prevalence of HF seems to be 1 to 2% of the general adult population, affecting an estimated 64,3 million people.[1,5]

Even if the implementation of evidence-based therapy has improved outcomes in some patients, they still need to be meticulously characterized, described, and treated since a substantial proportion of HF patients progresses to an advanced stage of the disease. Patients with advanced HF appear to be 1 to 10% of the whole heart failure population,[5] with a prevalence destined to rise due to the growing number of patients with HF and improved survival after diagnosis.

The updated Heart Failure Association-European Society of Cardiology (HFA-ESC) criteria for defining advanced HF includes the presence of: 1. Severe and persistent symptoms of HF [New York Heart Association NYHA class III (advanced) or IV]; 2. Severe cardiac dysfunction defined by reduced LVEF ≤30%, isolated right ventricular failure or non-operable severe valve; 3. Episodes of pulmonary or systemic congestion requiring high-dose intravenous diuretics (or diuretic combinations) or episodes of low output requiring inotropes or vasoactive drugs or malignant arrhythmias causing >1 unplanned visit or hospitalization in the last 12 months and 4. Severe impairment of exercise capacity with an inability to exercise or low 6-min walking test distance (6MWTD) (<300 m) or peak oxygen consumption (VO2) <12–14 mL/kg/min or <50% predicted value estimated to be of cardiac origin.[1,5]

The main problem is advanced HF remains with poor prognosis, with a meaningful morbidity and mortality, since, even with recent advances in both medical and device treatments, 1-year survival only range from 25 to 75%.[5]

Management of Advanced Heart Failure

Heart transplantation and Long-term MCS

The maximal standard therapy to chronic HF is, by definition, insufficient in patients with advanced HF. Therefore, HT continues to be the gold standard treatment, in absence of contraindications, with a post-transplant 1-year survival of around 90%, a median survival of 12.5-years and a significant improvement of quality of life and functional status.[1,5]

Due to scarcity in donor organs, long waiting list times and growing incidence of terminal HF, HT is not enough to address this worldwide health problem. Therefore, the number of patients who are bridge to HT under mechanical circulatory support (MCS) is progressively increasing.

Long term MCS, and specifically left ventricular assist devices (LVADs), have made significant strides in providing circulatory support, while also improving quality of life, and proved to be a good alternative when HT is not possible.[6] LVADs can either be used as a bridge to transplantation or as destination therapy, with an actuarial survival reported of 80% at 1-year and 70% at 2-years.[5]

However, the decision between HT and LVAD is never straightforward and must be unique to each patient. Eligibility for each option depends on several conditions of each patient, which may possibly change over time.[5] In Table 1, we provide a suggestive list of potential indications for HT or LVAD.

Although, the main long-term therapies for advanced HF are LVAD and HT, these patients are often critically ill, with a high expected mortality, requiring advanced hemodynamic stabilization as a bridge to further treatment.[7] In these cases, short-term MCS should be used as a temporary therapy to allow an evaluation of candidacy and work as a bridge to decision.

Indications for short- and long-term MCS should be based on the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) profiles, displayed in table 2.[1,5]

Heart Allocation Policies in Portugal, Europe, and USA

Although HT is the most effective treatment for selected patients with advanced HF, access to transplant is limited by the shortage of heart donors, resulting in high waitlist mortality.[8] Therefore, the heart allocation systems play a fundamental role in the judicious choice of the heart's recipient.

However, different countries have different selection criteria. Whereas some heart allocation systems grant priority status to candidates according to therapy, others use distinct methods such as scores based on objective candidate characteristics and the evaluation of the urgency status and expected outcomes. These factors may influence the bridge to transplant strategy.[11]

In Portugal, the allocation of organs is based on the health legislation system that prioritizes patients with circulatory support and retransplantation (I), followed by cardiogenic shock (II).[9] In Austria, Belgium, Croatia, Germany, Hungary, Luxembourg, the Netherlands, and Slovenia, the organization responsible for the organ transplant is Eurotransplant[10], whose offers hearts successively to candidates with international high-urgency (IHU) status, then to candidates with national HU status, and finally to elective candidates. Finally, United Network for Organ Sharing (UNOS)[11] administers the only Organ Procurement and Transplantation Network (OPTN) in the United States, which chooses the recipient based on his status from 1 to 6.

Table 3 illustrates the urgency criteria from heart allocation systems across Portugal, other European countries, and United States of America.[9-11]

Short-term MCS

Short-term MCS devices may be indicated in the setting of cardiogenic shock, to allow cardiac recovery and reverse critical end-organ hypoperfusion and hypoxia. These devices should be used in patients with INTERMACS profiles 1 to 3, as a bridge to decision (BTD), bridge to recovery (BTR), bridge to bridge (BTB) for long-term MCS or bridge to transplant (BTT). However, they can only be used for a short and limited period, ranging from a few days up to several weeks.[5]

Several MCS system are available, including paracorporeal and percutaneous devices with different technical characteristics and clinical applications, as presented in table 4.[2,12,13]

Although there is no single ideal device, extracorporeal membrane oxygenation (ECMO) has become the favourite choice for short-term hemodynamic support, because it is cheaper than others, allows quick improvement in oxygenation and is the only one suitable for patients with severe biventricular failure.[14] Specifically, VA-ECMO has been increasingly used as short-term circulatory support in patients with refractory heart failure.

Veno-arterial Extracorporeal Membrane Oxygenation Overview

VA-ECMO is a portable cardiopulmonary bypass device modified for easier and longer use and transport, which addresses both right and left ventricular dysfunction, systemic oxygenation ($p0_2$), and acid-base balance via modulation of the partial pressure of CO_2.[1,2] This device can only be used for days to weeks and does not treat the underlying condition.

The ECMO circuit is composed by a centrifugal blood pump, a blood gas exchange unit, which includes a membrane oxygenator and a heat exchanger; inflow and outflow cannulas, and tubing set.[15,16] It withdraws deoxygenated blood from the venous system, pumps the blood through the oxygenator to exchange blood gases, and returns the blood to the arterial circulation.[2]

Even though VA-ECMO provides full cardiorespiratory support, restoring systemic perfusion and allowing end-organ function recovering, it is haunted by a high burden of complications that have a strong impact on prognosis.[15] A Systematic review and meta-analysis[17] with more than 100 patients receiving ECMO, showed that the most common complications associated with ECMO were: renal failure requiring continuous veno-venous hemofiltration (occurring in 52%), bacterial pneumonia (33%), any bleeding (33%), oxygenator dysfunction requiring replacement (29%), sepsis (26%), haemolysis (18%), liver dysfunction (16%), limb ischaemia (10%), venous thrombosis (10%), central nervous system complications (8%), gastrointestinal bleeding (7%), aspiration pneumonia (5%), and disseminated intravascular coagulation (5%). Furthermore, it is a complex intervention that requires well-trained healthcare providers, teamwork, and clearly defined roles, and is associated with high costs. Therefore, it is essential to define which patients can benefit from its placement.

Despite the Interim Guideline Consensus Statement[18] from Extracorporeal Life Support Organization (ELSO), protocols and guidelines struggle to identify patients most likely to survive with favourable outcomes. However, it is known that these critically patients benefit from a transversal approach to ventricular assistance, not only limited to VA-ECMO, but encompassing a set of complementary strategies ranging from intra-aortic balloon pump to LVAD.

Patient selection at Coimbra Hospital and University Center

The decision on VA-ECMO placement is made case by case and centred on locally agreed inclusion criteria formulated by a multidisciplinary team of intensive medicine, cardiology, and cardiothoracic surgery, based on the ELSO consensus statement.[18]

At the ECMO center of Coimbra Hospital and University Center (CHUC), patients are considered to VA-ECMO if: 1. Patients with refractory cardiogenic shock (CS), defined by evidence of low cardiac output, such as cardiac index <2.2 L/min/m^2, systolic pressures <90 mmHg, oliguria or anuria, pulmonary edema and increased lactate, despite optimized fluid resuscitation and high dose of inotropic agents/ vasopressors, like noradrenaline >0.5 micrograms/kg/min, in the context of acute myocardial infarction (AMI) Killip-Kimball class IV, electrical storm, acute valve disease, catastrophic complication of an invasive procedure, fulminant myocarditis, postpartum cardiomyopathy, advanced HF INTERMACS 1-3, postcardiotomy shock, support for high risk procedures, such as complex angioplasty and catheter ablation for ventricular arrhythmias; 2. Age <70 years old; 3. Survival after Veno-Arterial ECMO (SAVE) Score ≥0 (0 = 50% in-hospital survival), which assesses risk based on the diagnosis, age, circulatory and ventilation parameters, secondary organ dysfunction and pre-existing comorbidities.[16]

VA-ECMO is considered the first line of therapy if patients present right ventricular failure, severe respiratory dysfunction, or severe hemodynamic instability.

In this context, VA-ECMO should be seen as a BTR, BTB or bridge to long-term mechanical circulatory support, such as VADs, depending on the underlying pathology of CS. BTR is selected in case of AMI after revascularization, myocarditis, postcardiotomy, while BTT is used in non-resvascularizable AMI, advanced HF INTERMACS 1-3, and electrical storm.

Previous studies on VA-ECMO as a direct bridge to Heart transplantation

The use of ECMO has considerably increased in the last two decades,[14] under the premise that it provides time for the patient recovery or for the medical team find a long-term solution, such as HT. Nevertheless, using VA-ECMO as direct bridge to HT has been extremely infrequent in adults, representing only 1% of global transplantation, and, although there is still a lack of scientific evidence, has been associated with poor posttransplant survival.[3]

The following studies examined the impact of VA-ECMO as bridge to heart transplantation on posttransplant survival (Table 5).

DeFilippis *et al*.[19] evaluated posttransplant mortality in 319 patients bridge from ECMO to HT, listed in UNOS database from 2006 to 2019. In their series, the incidence of mortality in the patients with ECMO bridged directly to transplant was 29.3% at 1-year, 33.4% at 2-years, and 38.2% at 5-years and there was no difference in the posttransplant mortality compared with those who were bridged from ECMO to LVAD.

In Argentina, Giordanino *et al*.[7] described the outcomes of a small cohort of patients who were supported with VA-ECMO or Centrifugal pump to bridge to HT. Mortality was 23.3% at 30 days, similar in both groups. They conclude that both are a lifesaving approach, allowing successful transplantation in most of the cases, with good short- and long-term survival.

Moonsamy *et al*.[20] explored the results of 117 patients who were bridge with ECMO from a cohort of 24 905 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 described in recent studies. Gonzales *et al*.[21] contrasted the waitlist and posttransplant outcomes of ECMO-supported patients among the new and old UNOS system. Between 2015 and 2019, there were a total of 185 heart transplant recipient with pre-transplant MCS by VA-ECMO. The 6-month survival post transplantation was 74.6% and 90.6% for the old and new era patients, respectively. Lui[22] and colleagues also analysed the UNOS database, but from 2001 to 2018. During this period,118 patients supported with ECMO prior to transplantation were registered, among a total of 29 644 heart transplants performed. The authors found a statistically significant decrease in 1-year survival for patients who

were bridged from ECMO to transplantation compared to those who were bridged to an LVAD prior to subsequent transplantation.

In a single-center cohort conducted in Russia, Poptspov et al.[23] enrolled 166 patients bridge on VA ECMO support, in a period of 4-years (January 2013 – December 2017). Post-transplant survival at home discharge and at 6 months, 1, 2, 4 and 5-years was 86.1%, 84.2%, 83.3%, 75.1%, 72.3% and 72.3%, respectively. These results are less successful when compared to recipients without pre-transplant MCS.

Coutance et al.[3] performed a large observational single-center retrospective study based on the comparison of posttransplant outcomes of patients supported or not by ECMO at the time of heart transplantation. Among the 415 transplanted patients, 118 (28.4%) used ECMO as bridge to transplant. Posttransplant survival did not differ significantly between the two groups: ECMO (1-year: 85.5% and 3-year: 80.3%) and non-ECMO patients (1-year: 80.7% and 3-year: 72%).

In Spain, Barge-Caballero *et al*.[24] conducted a retrospective multi-center study, in 16 institutions, during a 5-year period, including 129 patients who underwent HT directly from VA-ECMO, to compare events during the different short-term MCS and after HT. In-hospital posttransplant mortality was 33.3% and overall survival from listing to discharge was 54.5% for patients bridge on VA-ECMO. The authors observed that patients treat with VA-ECMO showed the highest incidence rate of adverse clinical events associated with temporary MCS.

Fukuhara *et al*.[25] scrutinized 107 patients transplanted directly from VA-ECMO, among 25168 adult heart transplant recipients, registered in the UNOS database between 2003 and 2016. The analysis of the propensity-matched cohort demonstrated a lower survival in ECMO group at 90 days (74.8% vs 88.8%; P= 0.025) and 3-years (69.3% vs 82.2%; P= 0.054), when compared to bridge with continuous flow LVAD. Results showed that bridge to transplant with VA-ECMO was associated with increased early/ midterm mortality, especially in patients with a high Model for End-stage Liver Disease XI (MELD-XI) score (>17).

In Italy, Lechiancole *et al*.[26] analysed the outcomes of 32 patients who were bridge with VA-ECMO. Overall, patients showed a high post-transplant mortality (18.7%, <30 days). This single-center retrospective study demonstrated that acute physiology, age, and chronic health evaluation IV (APACHE IV) could be considered a powerful predictor of survival in patients bridged by ECMO to HT.

Zalawadiya *et al*.[27] examined the post transplantation-mortality in 157 ECMO-supported adults undergoing HT, reported to UNOS, between 2000 and 2015. Survival at 1-year of

57.8% was mostly caused by hight 30 days posttransplant mortality. For patients surviving the first 30 days after HT, long-term survival was acceptable, with 82.3% at 1 year and 76.2% at 5-years. Also, renal failure and mechanical ventilation were predictors of 30 days and long-term mortality.

In France, Jasseron *et al*.[28] compared 42 heart transplant recipients bridged with VA-ECMO reported to the national registry CRISTAL, during a 2 year-period. One-year posttransplant survival was 70% and 81% in the comparison group, which included patients without MCS and with long-term MCS or IABP.

Mishra[4] and colleagues from Norway guided a retrospective single-center study, between 2005 and 2012, comparing the posttransplantation outcomes of 15 patients bridged with ECMO with patients bridged with LVAD or non-bridged. One and five- years survival rates were 70% and 70% for ECMO patients, 96% and 83% for LVAD patients, and 92% and 81% for non-bridged HT patients, respectively.

A series from Korea[29] reported the outcomes of 25 patients who underwent transplantation directly from VA-ECMO. Seven patients (28%) died within 1-year after transplantation. Also, in this multivariate analysis, the MELD score modified by UNOS was the only independent predictor of posttransplant mortality, with an expected 1-year survival of 91%, in patients with 24 or less.

Karamlou *et al*.[13] tracked status 1 HT outcomes, from UNOS database, between 2000 and 2010. The authors reported a 1-year and 5-year posttransplant survival of 62% and 54%, respectively, in patients bridged on ECMO support.

Chung *et al*.[6] sought to compare the outcomes of patients supported with ECMO prior to transplantation. They found a statistically significant decrease in 1y survival for patients who were bridged from ECMO to transplantation compared to those who were bridged to an LVAD prior to subsequent transplantation.

In Turkey, Gedik *et al*.[30] presented 3 case reports of patients who received the VA-ECMO as a bridge to heart transplant, out of 31 patients who underwent transplant from January 2014 and June 2016. Although, patients 1 and 2 are still alive and periodically supervised by their center, patient 3 died 29 days after discharge from hospital at home.

Heart transplantation results of patients bridged with VA ECMO appear to be associated with a significant post transplantation mortality and to be inferior when compared to reported outcomes of patients bridged with durable LVADs as well as non-bridged recipients. However, the scientific evidence regarding the use of pretransplant VA-ECMO as a direct bridge is still limited.

A search for better results

Although the outcomes of using pretransplant ECMO bridging are associated with survival rates still below expectations, several of the mentioned studies presented beneficial strategies for reducing mortality.

First, objective risk markers and scores, especially as part of a comprehensive assessment performed by the HF team, are valuable for prognostication, prioritization, and triage for either selection for MCS or any other advanced HF interventions.[1] Therefore, identification of mortality predictors and selection of adequate candidates for a bridge to HT on ECMO is critical to improve their outcomes in the future.

Fukuhara[25] and colleagues showed MELD-XI score to be a contributor to both 90-day (odds ratio, 1.94; 95% confidence interval, 1.00-3.76; P= 0.050) and 3-year mortality (hazard ratio, 1.47; 95%; confidence interval, 1.16-1.88; P= 0.002). Within the ECMO group, whereas recipients with MELD-XI score <13 had 85.0 ± 6.2% 90-day and 73.5 ± 8.2% 3-year survival; patients with MELD-XI score >17 had 54.0 ± 8.8% 90-day and 49.5 ± 9.4% 3-year survival (P <0.001). Additionally, Cho[27] reported that patients whose MELD score modified by UNOS were 24 or less, had an expected 1-year posttransplant survival of 91%.

Lechiancole[26] demonstrated that APACHE IV had an adverse impact on survival (HR 1.23 [1.08–1.39, 95% C.I.]) and can be account for a better selection of patients on ECMO supported at the time of listing. Indeed, in the group with an APACHE IV score <47 no early mortality was reported, and the estimated survival rate was 89.7% at 1-year and 81.5% at 5-years, which was significantly higher than the group of patients with an APACHE IV score ≥47, where 30-day mortality was 60% and survival probability was 26.6% at both 1 and 5-years.

Jha *et al*.[31] point out that frailty, defined as >3 physical domains of the Fried Frailty Phenotype (FFP) or >2 physical domains of the FFP plus cognitive impairment defined as a score of <26/30 on the Montreal Cognitive Assessment (MoCA), was an independent predictor of all-cause mortality after HT with 1 y survival 74 + 9% in the frail group, compared to 98 + 2% in the non-frail group (P= 0.0003).

Secondly, possible changes in the criteria of organ allocation systems should be adjusted to the quantity of available hearts, to the progress of the MCS, with the goal of facilitate access to organs and reduce waiting list times.

For example, in USA, ECMO supported patients are given the highest priority for HT with the new HT allocation system. Gonzalez[21] and colleagues demonstrated that the short-term post-transplant survival of ECMO bridged patients is significantly better and reaches

90% at 6 months with the new system. This improvement could be explained by a significant decrease in the waitlist time and by an increased access to organs, as demonstrated by a longer distance between the donor and transplant centers. However, a major increase in the number of patients listed as status 1, would raise concern for compromising these favorable outcomes through increasing waiting time on ECMO.

Lastly, these critically ill patients require management by a well-experienced and multidisciplinary ECMO team, including intensivists, cardiologists, cardiothoracic surgeons, and anaesthesiologists, in order to achieve better results. Even though VA-ECMO's optimal implementation and management in patients with advanced HF has not been defined yet, outcomes of patients undergoing VA-ECMO, especially in-hospital mortality, are fairly different from centre to centre, suggesting that variations in practice patterns in management of the patients may play a major role. These might include different schemes of timing of cardiogenic shock recognition, customized escalation to MCS, centralization of care, and haemodynamic control.[32]

Briefly, further studies are required to determine, more objectively, patient risk profiles, more suitable selection of candidates, and ultimately optimize the allocation systems. These findings, along with centers expertise in VA ECMO management may be of paramount value significantly increasing survival of these demanding patients.

Conclusion

Even though the number of treatments with ECMO have increased globally over the last 20 years, its routine use for urgent heart transplantation is still not widely accepted in most transplant centers, due to the limited duration of this support and lack of scientific evidence, still with uncertain results.[30]

VA-ECMO represents an effective and viable last resort to obtain rapid hemodynamic stabilization in patients with advanced HF. However, the prevalence of complications and adverse effects on patients' outcomes after HT should be considered, and when possible, minimized.

The use of VA-ECMO as direct bridge to heart transplantation could have similar survival outcomes compared with those not supported by ECMO, with a careful candidate selection, in the context of an efficient donor allocation system that ensures accessibility to suitable grafts within few days after listing.

In summary, even with the pledge to improve post-transplant outcomes, VA-ECMO is a lifesaving approach allowing successful HT in most of the patients, with an acceptable short and long-term survival in an otherwise ominous prognosis population.

Figures and Tables

Figure 1. Literature Search process and number of papers identified, excluded, and included in each phase of this review

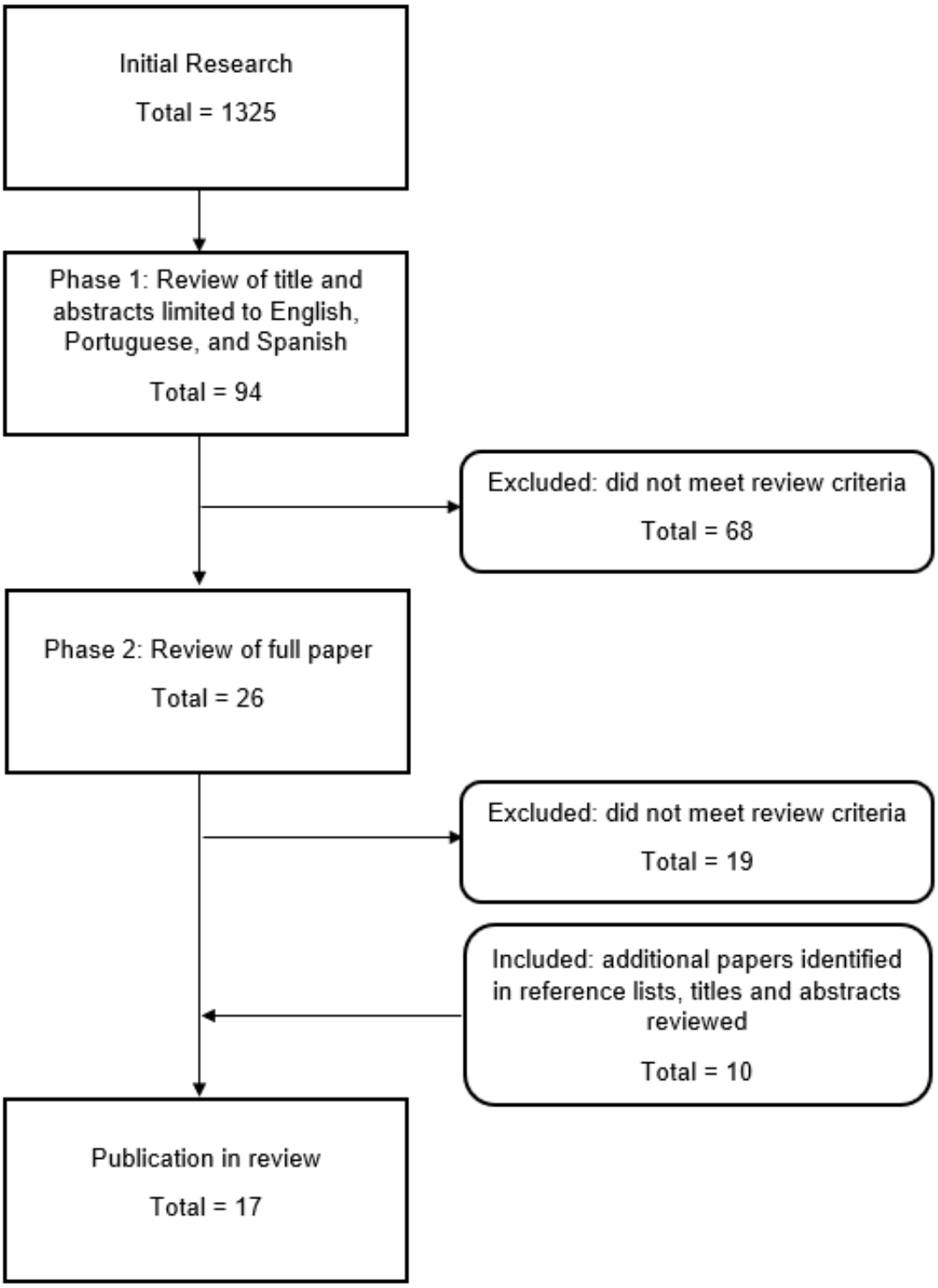

Table 1. Indications and Contraindications to Heart Transplant or Left Ventricular Assist Devices

Treatment	Patients to consider	Contraindications
Heart Transplant	1) End-stage HF with severe symptoms, a poor prognosis, and no remaining alternative treatment options, except for LVAD as BTT 2) Motivated, well informed, and emotionally stable 3) Capable of complying with the intensive treatment required postoperatively	1) Active infection 2) Several peripheral arterial or cerebrovascular disease 3) Pharmacologic irreversible pulmonar hypertension 4) Cancer with poor prognosis 5) Irreversible liver or renal dysfunction 6) Systemic disease with multiorgan involvement 7) Other serious comorbidity with poor prognosis 8) Pre-transplant BMI> 35Kg/m2 9) Current alcohol or drug abuse 10) Psychologic instability that jeopardizes proper follow-up and intensive therapeutic regime after HT or social supports deemed insufficient to achieve compliant care in outpatient setting
LVAD	Patients with avanced-HF, with a stable psychosocial background and and who have at least one of the following: 1) LVEF <25% and unable to exercise for HF or, if able to perform cardiopulmonary 2) Exercise testing, with peak VO2 <12 mL/kg/min and/or <50% predicted value) 3) ≥3 HF hospitalizations in previous 12 months without an obvious precipitating cause) 4) Dependence on i)v) inotropic therapy or temporary MCS) 5) Progressive end-organ dysfunction due to reduced perfusion and not to inadequately low ventricular filling pressure)	1) Contraindication to long-term oral anticoagulation 2) Active infection 3) Severe renal dysfunction 4) Ventricular arrhythmias 5) Severe RV dysfunction and/or severe TR 6) Living alone and poor psychosocial background

HF = Heart Failure; **LVAD** = left ventricular assist devices; **BTT** = bridge to transplant; **BMI** = Body Mass index; **LVEF** = left ventricular ejection fraction; **i.v** = intravenous; **MCS** = Mechanical circulatory support; **RV** = right ventricular; **TR** = tricuspid regurgitation.

Table 2. Interagency Registry for Mechanically Assisted Circulatory Support INTERMACS profiles

Profile	Definition	Description	Time frame for intervention
1	Critical cardiogenic shock "Crash and burn."	Life-threatening hypotension despite rapidly escalating inotropic support, with critical organ hypoperfusion	Definitive intervention needed within hours.
2	Progressive decline "Sliding on inotropes."	Declining function despite intravenous inotropic support	Definitive intervention needed within few days.
3	Stable on inotrope or inotrope-dependent "Dependent stability."	Stable on continuous intravenous inotropic support but demonstrating repeated failure to wean from support	Definitive intervention elective over a period of weeks to few months.
4	Frequent Flyer	Patient experiences daily symptoms of congestion at rest or during activities of daily living	Definitive intervention elective over a period of weeks to few months.
5	Housebound	Comfortable at rest and with activities of daily living but unable to engage in any other activity, living predominantly within the house	Variable urgency, depends upon maintenance of nutrition, organ function, and activity.
6	Exertion limited "Walking wounded."	Patient without evidence of fluid overload, comfortable at rest and with activities of daily living and minor activities outside the home but fatigues after the first few minutes of any meaningful activity	Variable, depends upon maintenance of nutrition, organ function, and activity level.
7	Advanced NYHA class III symptoms	Patient without current or recent episodes of unstable fluid balance, living comfortably with meaningful activity limited to mild physical exertion.	Heart transplantation or MCS may not be currently indicated.

INTERMACS = Interagency Registry for Mechanically Assisted Circulatory Support; **MCS** = Mechanical circulatory support.

Table 3. Heart Allocation Pollicies: Portugal, Eurotransplant and UNOS

	Portugal	Eurotransplant	UNOS
Population/ Nº HT centers	10,3/ 4	135,6/ 42	329,5/ 138
Urgency criteria			
VA-ECMO	Id	-	Status 1
IABP	Ic	-	Status 2
Percutaneous endovascular MCS	-	-	Status 2
TAH, BiVAD	Ia, Ib	-	Status 1, 2
Stable LVAD	Ib	-	Status 2, 3, 4
MCS with complications	-	IHU status	Status 2, 3
Ionotrope infusion	II	IHU status	Status 3, 4
VT/ VF	-	-	Status 1, 2
Transplant indication	-	IHU status	Status 4
Multiple organ transplant	-	-	Status 5
Acute retransplantation	Ie	-	-
Donor-recipient matching			
Age	-	+	-
Posttransplant risk	-	-	-
Geographic sharing	National	Multinational	Zonal
Waiting list	+	+	+

UNOS = United Network for Organ Sharing; **Nº** = number; **HT** = heart transplantation; **VA-ECMO** = Veno-arterial extrocorporeal membrane oxygenation; **IABP** = intra-aortic balloon pump; **MCS** = Mechanical circulatory support; **TAH** = total artificial heart; **BiVAD** = biventricular assist device; **LVAD** = left ventricular assist devices; **VT** = ventricular tachycardia; **VF** = ventricular fibrillation; **IHU** = international high urgency.

Table 4. Short-term Mecanical Circulatory Suporte Devices

Device:	VA-ECMO	IABP	IMPELLA CP®	IMPELLA RP®
Primary haemodynamic effect	Retrograde blood flow	Reduces LV afterload	Anterograde blood flow	Anterograde blood flow
Ventricles Supported	LV and RV	LV	LV or RV	LV or RV
Type of Implantation	Percutaneous or surgical	Percutaneous	Percutaneous	Percutaneous
Time for implantation	Moderate	Fast	Fast/ moderate	Fast
Duration of support (days)	5 to 20	< 7	5 to 10	10
Flow (L/min)	4 - 6	0,5 - 1	2,5 - 5	3 - 4
Cannula size (Fr)	Inflow 18-21 Outflow 15-22	7 - 9	14 - 22	23
Advantages	Complete cardiopulmonary sypport; high flow; independent of native cardiac function	Ease of use; good safety profile; fewer side effects	Ease of use; independent of native cardiac function	Ease of use; independent of native cardiac function
Disadvantages	Increases LV afterload	Limited haemodynamic effects	Frequent vascular complications	Frequent vascular complications
Contraindications	Severe irreversible noncardiac organ failure limiting survival; aortic dissection; irreversible HF if transplantation or VAD are not considered	Severe AR	LV thrombus or AR; mechanical prothesis	Pulmonary Hypertension
Complications	Bleedings; limb ischaemia; haemolysis; pulmonary oedema; sepsis	Bleedings	Bleedings; limb ischaemia; haemolysis	Bleedings; haemolysis
Cost	Moderate	Low	High	High

VA-ECMO = Veno-arterial extrocorporeal membrane oxygenation; **IABP** = intra-aortic balloon pump; **LV** = left ventricle/ventricular; **RV** = right ventricle; **HF** = heart failure; **VAD** = ventricular assist device; **AR** = aortic regurgitation.

Table 5. Best Evidence Papers

Author. Year and Country	Period	Nº of HTX patients	Nº of BTT with ECMO	BTT with ECMO: Survival Outcomes	Comparison	Duration of ECMO / Waitlist (days)	Comments
DeFilippis et al., 2021, USA	2006 - 2019	30 093	319	• 1y = 70.7% • 2y = 66.6% • 5y = 61.8%	vs ECMO to LVAD: • 1y = 69.2% • 2y = 62.6% • 5y = 56.5%	NA	There was no difference in mortality on pump support compared with posttransplant mortality among those bridged from ECMO to LVAD or HT.
Giordanino et al., 2020, Argentina	2006-2018	333	14	• 30 d=85.7%	vs T-CP: • 30d = 68.7%	6.5 / NA	
Moonsamy et al., 2020, USA	2005-2017	24 905	177	• 1y = 68 ± 3% • 5y = 61 ± 8%	vs T-LVAD. T-TCS-VAD. T-BiVAD: • 1y= 90 ± 0.4%. 84 ± 3% and 79 ± 9% • 5y= 77 ± 0.7%. 71 ± 4% and 73 ± 14%	NA / 89 ± 214	
Gonzalez et al., 2020, USA	2015-2019	NA	185	2015-2017 vs 2018-2019: • 6m = 74.6% vs 91.2%		2015-2017: 7 / NA 2018-2019: 3 / NA	With the new HT allocation system, ECMO supported patients have a shorter waitlist time, improved frequency of HT and improved short-term post-transplant survival
Lui et al., 2020, USA	1996-2018	29 644	118	•30 d ~ 79% •1 y ~ 67%		NA / 25 ±71	The higher risk of mortality was carried by the direct bridging from ECMO to HTx (HR 3.03, P < 0.001).
Potspov et al., 2019, Russia	2013-2017	594	166	• Hd = 86.1% • 6m = 84.2% • 1y = 83.3% • 2y = 75.1% • 4y = 72.3% • 5y = 72.3%	vs nonbridged-HTX. respectively : • Hd = 93.9% • 6M = 90.1% • 1Y = 91.8% • 2y = 86.1% • 4y = 84.7% • 5y = 83.5%	5.6 ± 3.2 / NA	Results of HT at recipients bridged with VA ECMO are less successful that recipients without pre-transplant MCS.
Countance et al., 2019, France	2012 - 2016	415	118	•1y= 85.5% •3y= 80.3%	vs BTT not-ECMO: • 1y = 80.7% • 3y = 72%	9 / NA	With the implementation of a specific protocol, patients bridge on ECMO had similar survival compared with those not supported by ECMO
Barge-Caballero et al., 2018, Spain	2010 - 2015	230	129	• Hd = 54.4% • 1y = 54.4%	vs T-LVAD and T-BiVAD : • Hd= 78.6% and 55.8%. • 1 y= 78.6% and 55.8%.	7.6 ± 8.5 / NA	Patients treated with VA-ECMO showed the highest incidence rate of adverse clinical events associated with T-MCS.
Fukuhara et al., 2018, USA	2003 - 2016	25 168	107	• 3m = 74.8% • 3y = 69.3%	vs BTT with continuous-flow LVAD: • 3M = 93.1% • 3y = 82.4%	NA / NA	BTT with VA-ECMO was associated with increased early/mid-term mortality, especially in patients with a high MELD-XI score (>17).

Lechiancole et al., 2018, Italy	2005 - 2017	300	32	• 30d = 81.3%	APACHE IV <47 vs APACHE IV ≥ 47 : • 30 d = 100% vs 60% • 1y = 89.7% vs 26.6% • 5y = 81.5% vs 26.6%	APACHE IV <47 = 10.4 ± 14.5 / NA APACHE IV ≥ 47 = 9.7 ± 7.5 / NA	The APACHE IV score is a powerful predictor of survival for patients with ECMO as BTT.
Zalawadiya et al., 2017, USA	2000 - 2015	NA	157	• 30d = 71.9% • 1y = 57.8%	Before 2009 vs After 2009: • 1y = 55.6% vs 59.1% • 3y = 51.6% vs 56.8% • 5y = 51.6% vs 52.6%	NA / 82.9 ± 139.8	Renal failure and mechanical ventilation were predictors of 30-d and long-term mortality.
Jasseron et al., 2016, France	2010 - 2011	672	46	• 1m = 79.9% • 3m = 77.8% • 1y = 70.4%		9 / NA	Cox proportional hazard analysis showed age >50 years at listing to be a significant predictor of mortality
Mishra et al., 2016, Norway	2005 - 2012	206	15	• 30d = 86.7% • 1y = 70% • 5y = 70% • 7y = 70%	vs non-bridged and T-LVAD: • 30d = 96% and 100% • 1y = 92% and 96% • 5y = 81% and 83% • 7y = 77 and 83%	9.1 ± 8.5 / NA	Patients managed with ECHTx experienced lower early survival than LVADHTx or HTx, at twice the cost of HTx, but late survival approached that of the other two groups.
Cho et al., 2015, Korea	2004 - 2013	NA	25	• 30 d = 80% • 1 y = 72%		7.8 / NA	The MELD UNOS score was an independently better predictor of death after transplantation compared with the duration of ECLS and the SOFA score.
Karamlou et al., 2013, USA	2000 - 2010	13 250	316	• 1y = 62% • 5y = 54%	vs T-BiVAD. T-RVAD. T-LVAD. T-IABP and T-inotropes : • 1y = 79%, 56%, 85%, 88% and 88% • 5y = 66%, 56%, 72%, 70% and 74%	NA / 62	Survival after HTx is optimized when ECMO or biventricular assist device support can be transitioned to LVAD-only support.
Chung et al., 2010, Taiwan	1995 - 2007	19	15	• Hd = 73.3% (100% of survival in the patients discharged home)	vs Double bridge with ECMO+VAD : • Hd = 100% (100% of survival in the patients discharged home)	220 ± 210 h / NA	
Gedik et al., 2016, Turkey	2014 - 2016	31	3	• Hd= 100% (1 patient died 29 days after discharge from hospital)		NA	

Hd = Hospital discharge; **LVAD** = Left Ventricular Assist Device; **CP** = Centrifugal Pump; **TCS-VAD** = Temporary Circulatory Support-Ventricular Assist Devices; **BiVAD** = Biventricular Assist Device; **RVAD** = Right Ventricular Assist Device; **IABP** = Intraaortic Balloon Pump; **MEDL-XI** = Model for End-stage Liver Disease XI; **APACHE IV** = Acute Physiology, Age, and Chronic Health Evaluation IV

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