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Review Article

Current indications for heart transplantation and left ventricular assist device: A practical point of view

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ABSTRACT

Heart transplantation (HTx) is considered the "gold standard" therapy of refractory heart failure (HF), but it is accessible only to few patients because of the paucity of suitable heart donors. On the other hand, left ventricular assist devices (LVADs) have proven to be effective in improving survival and quality of life in patients with refractory HF. The challenge encountered by multidisciplinary teams in dealing with advanced HF lies in identifying patients who could benefit more from HTx as compared to LVAD implantation and the appropriate timing. The decision-making is based on clinical parameters, imaging-based data and risk scores. Current outcome of HF patients supported by LVAD (2-year survival around 70%) is rapidly improving and leads the way to a new therapeutic strategy. Patients who have a low likelihood to gain access to the heart graft pool could benefit more from LVAD implantation (defined as bridge to transplantation indication) than from remaining on HTx waiting list with the likely risk of clinical deterioration or removal from the list because patients are no longer suitable for transplantation. LVAD has also demonstrated to be effective in patients who are not considered eligible candidates for HTx with a destination therapy indication. HTx should be reserved to those patients for whom the maximum clinical benefit can be expected, such as young patients with no comorbidities. Here we discuss the current listing criteria for HTx and indications to implant of LVAD for patients with refractory acute and chronic HF based on the guidelines and the practical experience of our center.

1. Introduction

Medical therapy, cardiac defibrillators and devices for cardiac resynchronization therapy have been shown to improve the prognosis of patients with left ventricular systolic heart failure (HF) both in Europe and the United States [1,2]. Despite the combined use of the best therapies, HF usually advances progressively and in some cases it becomes unresponsive to conventional treatments to the extent that surgical revascularization [3,4], ventriculoplasty [5] and mitral surgery become worthless or poorly useful [6,7]. Patients with acute HF requiring inotropic therapy have an approximately 6-month mortality of 25% based on clinical trials, and the European and Italian registries on acute HF [8–10]. These data underscore the need for further treatment options for advanced HF capable of improving symptoms, hospitalizations and improving survival.

The clinical profile of a patient with refractory HF often exhibits at least some of the following characteristics despite optimal therapy: (1) severe symptoms (NYHA class III to IV); (2) episodes with clinical signs of fluid retention and/or peripheral hypoperfusion; (3) objective evidence of severe cardiac dysfunction, that can be demonstrated by at least one of the following: left ventricular ejection fraction (LVEF) <30%; restrictive mitral inflow pattern at Doppler-echocardiography; high left and/or right ventricular filling pressures; and elevated B-type natriuretic peptides; (4) evidence of systemic organ injury, in particular renal and hepatic dysfunctions, underlined by an increase in creatinine and bilirubin levels; (5) severe impairment of functional capacity

Abbreviations: HF, Heart failure; NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; LVAD, left ventricular assist device; HTx, heart transplantation; ISHLT, International Society of Heart and Lung Transplantation; VAD, assist device; BTT, bridge to transplantation; ESC, European Society of Cardiology; Bi-VAD, Biventricular assist device; QoL, quality of life; DT, destination therapy; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; pVO_2, peak oxygen consumption; BMI, body mass index; V_E/VCO_2, ventilation equivalent for carbon dioxide; HFSS, Heart Failure Survival Score; SHFM, Seattle Heart Failure Model; IABP, intra-aortic balloon pump; BTD, bridge to decision; BTC, bridge to candidacy; BSA, body surface area; TAH, total artificial heart; LVEDD, left ventricular end diastolic diameter; TAPSE, tricuspid annular plane systolic excursion; MELD, Model for End-stage Liver Disease; INR, International Normalized Ratio.

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demonstrated by either inability to exercise, a 6-minute walk test distance <300 m or a peak oxygen uptake <12–14 ml/kg/min; and (6) history of >1 HF hospitalization in the past 6 months [11]. This definition identifies a group of patients with a high risk of clinical events. These patients, with compromised quality of life and poor prognosis, deserve effective therapeutic options and should be considered for left ventricular assist device (LVAD) or heart transplantation (HTx). The correct timing to refer such patients to centers specializing in HTx and LVAD is fundamental for their survival.

2. Epidemiological transition

HTx is considered the gold standard for the treatment of refractory HF [11], but it is available only to a minority of patients because of the paucity of heart donors and of the contraindications or risk factors in several patients with HF [12]. Increasing the pool of heart donors by including older donors might reduce the likelihood of HTx success [13]. From the mid '80s until today in our center the age of donors has doubled reaching an average age of 40 years or older, a trend also observed in other Italian and European centers. It is well known that the donor's age is one of the major prognostic determinants in heart transplant patients (the higher the age, the higher the risk at 1-year and long term mortality) [14]. Patients on waiting list for HTx have a waiting list time in Italy of about 2.3 years (estimated from the time lapse between 2006 and 2010; http://www.trapianti.salute.gov.it/) during which they experience progressive clinical deterioration and an annual mortality of 8–10%. Moreover, 10–15% of HTx candidates are withdrawn from the waiting list every year because they are no longer suitable candidates. Statistics from the *Eurotransplant International Foundation* coordinating the transplantation activity in Austria, Belgium, Croatia, Germany, Luxemburg, Holland and Slovenia have shown that the percentage of HTx candidates receiving a graft at the end of every year has decreased from 63% in 2006 to 45% in 2011, thus highlighting that the lack of organs is emerging as the main issue capable of nullifying the clinical benefit of a clinical procedure such as HTx (http://www.eurotransplant.org). The 2013 report of the International Society for Heart and Lung Transplantation (ISHLT) based on data submitted by 407 centers worldwide concerning 103,299 pediatric and adult HTx between 1982 and June 2011 showed that 1-year survival is 81%, and 5-year survival is 69%, with median survival of 11 years for all and 13 years for those surviving the first year (www.ishlt.org/registries) [14].

Mechanical ventricular assist devices (VADs) have shown in the last years to be effective in improving survival and quality of life of patients with refractory HF and could represent a valid alternative to HTx. LVADs are continuous flow devices made of a pump, which unload the left ventricle of the blood by the presence of an inflow cannula and pump it to the aorta through an outflow cannula. LVADs are placed in the anterior mediastinum and are powered through a wire that exits the body usually at the abdomen level and connects to a controller and to an energy source (battery or *control unit* connected to the electricity supply) (Fig. 1). VAD therapy is a strategy approved in patients with refractory HF who become clinically unstable while on a waiting list for HTx as a bridge to transplantation (BTT) indication and recently inserted in the 2012 European Society of Cardiology (ESC) guidelines on acute and chronic HF [7]. The guidelines also recommend the use of Biventricular (Bi)-VAD (devices designed to assist both the right and left ventricles) as BTT therapy in patients with severe biventricular dysfunction or at high risk of developing right ventricular failure after LVAD implantation [7,15,16]. Because of the high biologic cost and the poor quality of life (QoL) of patients on Bi-VAD, this treatment is not commonly used. Continuous-flow LVADs have also demonstrated to improve the prognosis and QoL in patients with advanced HF who are not considered eligible candidates for HTx (destination therapy [DT]) [17,18]. In the United States of America, a higher number of centers as compared to Europe have exploited an early LVAD implantation strategy in patients meeting the criteria to be placed on HTx list [19]. The north American INTERMACS (Interagency Registry for Mechanically Assisted Circulatory Support) registry, including over 6000 LVAD implantations, has shown a survival rate of 80% at 1 year and 70% at 2 years in patients implanted with continuous flow LVADs between 2006 and 2012 [20]. It must be noticed that most patients from the INTERMACS registry until 2011 had received a VAD as BTT and that an important percentage of these patients (higher than 50% in 2010, around 40% in 2011) has received a heart graft in the year after VAD implantation [20]. From a trial using Thoratec Heart-Mate II continuous-flow LVAD as DT treatment it is known that the current survival at one year is 73% [21]. In another trial using Heartware LVAD as BTT the survival at one year was 85% [22].

The aim of this review is to improve and standardize the referral of potential HTx candidates in order to guarantee equity in the access to a valuable and scarcely available therapy. On the other hand, mechanical VADs, despite its effectivity, are costly and have a heavy impact on patients' everyday life and quality of life due to the complexity of its management. This concept calls for the need of a better knowledge of the indications and outcomes of such therapy. Here we report a detailed analysis of the patients' subpopulations we consider suitable for HTx and LVAD, in the light of the recent changes in the treatment strategies of refractory HF.

3. Current indication for HTx

The recent European guidelines on HF consider suitable for HTx patients with a cardiomyopathy in an advanced stage, severe symptoms, unfavorable prognosis, motivated, emotionally stable and considered capable of coping with the complex post-operative period [7,23]. These observations are definitely based on common sense but they do not suffice in clearly identifying the potential HTx candidate [7]. Probably, the most accurate guidelines on HTx eligibility have been published in 2006 by the ISHLT [24].

In ambulatory patients with refractory HF despite optimal medical therapy, a peak oxygen consumption (pVO_2) ≤14 ml/kg/min (patients who do not tolerate beta-blockers) on cardiopulmonary test represents a class I (level of evidence B) indication for HTx. In patients on B-blocker therapy, the value below which HTx should be considered is ≤12 ml/kg/min (class IIa, level of evidence B). The cardiopulmonary test should be maximal (respiratory quotient >1.05) and the anaerobic threshold should be reached. In patients younger than 50 years old and in women, the percentage of the predicted peak oxygen consumption should also be used, with a reference threshold value of ≤50% (recommendation IIb, level of evidence B). In obese patients, with a body mass index (BMI) >30 kg/m^2, oxygen peak consumption should be referred to the lean body mass (threshold 19 ml/kg/min) (level of evidence C). If the test is submaximal, the slope of the relationship ventilation/exhaled CO_2 (ventilation equivalent for carbon dioxide — V_E/VCO_2 slope >35) can be applied as the threshold for HTx eligibility [24].

In ambiguous situations (e.g. when the peak oxygen consumption value falls between 12 and 14), a multiparametric score such as the Heart Failure Survival Score (HFSS) is useful in estimating the patient's prognosis and determine the eligibility to HTx [25]. It must be noted, as the guidelines themselves stress, that the peak oxygen consumption cannot be considered as the sole criterion to consider a patient suitable for HTx and that the decision-making should be based on multiple variables [24]. In Table 1 the main contraindications, divided to major and minor, are listed. They are universally recognized, even though differences can arise on the additive effect of multiple minor contraindications, which are reported