

## END STAGE HEART FAILURE – TRANSPLANTATION OR LVAD?

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### Summary

Heart failure is a complex clinical syndrome that can result from any structural or functional cardiac disorder that impairs the ability of the ventricle to fill or eject blood. According to the data from the International Society for Heart and Lung Transplantation registry, the half-life of patient survival after heart transplantation has progressively improved from 8.9 years in 1982 to a projected half-life of approximately 11 years from 2002 to 2006. The peak VO<sub>2</sub> (VO<sub>2</sub>max) is the most objective assessment of functional capacity in patients with heart failure, and may be the best predictor of when to list a patient for cardiac transplantation. Mechanical cardiac support devices may be implanted in patients, in whose cases all other pharmacological therapies (oral medications and intravenous inotropes) for severe heart failure, as well as non-pharmacological support with intraaortic balloon pump counterpulsation, have failed. Left ventricular assist device provide support of the left ventricular function, causing reverse ventricular remodeling and permanent improvement of left ventricular function. End stage heart failure is not an end of life, since heart transplantation, better medications and devices, including ventricular assist devices implantations, offer patients a better quality and an appreciable extension of life.

**Key words:** heart failure; heart transplantation; LVAD

### 1 The definition of heart failure

Heart failure (HF) is a complex clinical syndrome that can result from any structural or functional cardiac disorder that impairs the ability of the ventricle to fill or eject blood [1]. The most common cause of heart failure is the left ventricular systolic dysfunction (about 60%).

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The right ventricular systolic dysfunction is usually due to the left ventricular systolic dysfunction. However, it can also develop as a consequence of ventricular infarction, pulmonary hypertension, chronic severe tricuspid regurgitation, or arrhythmogenic right ventricular dysplasia. The diastolic left ventricular dysfunction has become a more common reason of heart failure. The American College of Cardiology and American Heart Association (ACC/AHA) have developed a classification of heart failure based upon the evolution and progression of the disease. Stage A includes patients at risk of developing heart failure, but who have no structural heart disease at present. The management strategy is the prevention of heart failure. Stage B includes patients with structural heart disease without symptoms. The management goal is the prevention of left ventricular remodeling leading to heart failure. Stage C includes patients with a structural heart disease with current or prior symptomatic heart failure. They may be treated with pharmacological therapy. Cardiac resynchronization therapy may be added. Stage D includes patients with severe refractory heart failure [1]. This classification system is a complement and does not replace the New York Heart Association (NYHA) functional classification. The important goal of it is that the risk factors and structural changes for the development of HF and the therapeutic interventions performed even before the appearance of the left ventricular dysfunction or symptoms should reduce the morbidity and mortality from HF.

The NYHA functional classification scheme is used to assess the severity of functional limitations, and it correlates fairly well with the prognosis.

## 2 Indication for transplantation

In the 2008 report from the Registry of the International Society for Heart and Lung Transplantation (ISHLT), it is estimated that annually, more than 5,000 heart transplants are performed worldwide (including more than 2,000 not reported) [2]. The majority of centers perform between 10 and 19 heart transplants per year. The average recipients' age ranges from 50 to 59.

The ACC/AHA and European Society of Cardiology (ESC) guidelines include the following indications for cardiac transplantation: [1,3].

Absolute indications:

- 1) Hemodynamic disorder due to HF
- 2) Refractory cardiogenic shock
- 3) Dependence on intravenous inotropic support to maintain organ perfusion
- 4) Peak VO<sub>2</sub> lower than 10 mL/kg per minute
- 5) Severe symptoms of ischemia that consistently limit routine activity and are not

amenable to coronary artery bypass surgery or percutaneous coronary intervention

- 6) Recurrent symptomatic ventricular arrhythmias refractory to all therapeutical modalities

Relative indications:

- 1) Peak  $\text{VO}_2$  of 11 to 14 mL/kg per minute (or 55 % predicted) and major limitation of a patient's daily activities
- 2) Recurrent unstable ischemia not amenable to other intervention
- 3) Recurrent instability of fluid balance/renal function not due to patient non-compliance with medical regimen

Insufficient indications:

- 1) Low left ventricular ejection fraction
- 2) History of functional class II or IV symptoms of HF
- 3) Peak  $\text{VO}_2$  over 15 mL/kg per minute (or over 55% predicted) with no other indications

Ventricular assist devices (VADs) can provide mechanical support to “bridge” selected patients to transplantation; especially those on the waiting list with a high level of mortality expectation.

### 3 Prognosis after heart transplantation

After transplantation, there is significant mortality prospect in the first six months, followed by a mortality rate of about 3.5 percent per year. According to the data from the ISHLT registry, the half-life of patient survival after heart transplantation has progressively improved from 8.9 years from 1982 to 1991 to 10.3 years from 1992 to 2001, and to a projected half-life of approximately 11 years from 2002 to 2006 [2]. The controlled trials of patients with stable NYHA class III to IV HF have demonstrated mortality benefit from medical management including angiotensin converting enzyme (ACE) inhibitor therapy, beta-blocker therapy, aldosterone antagonist therapy, implantable cardioverter-defibrillator (ICD) and cardiac resynchronization therapy (CRT); often a combination of CRT+ICD [4]. The predictors of death within two months of status 1 candidates included status 1A, mechanical ventilation, inotropic and intra-aortic balloon pump support, pulmonary capillary wedge  $>20$  mmHg and serum creatinine  $>1.5$  mg/dl, failed cardiac transplant, valvular cardiomyopathy, age  $>60$  years, weight  $\leq 70$  kg, and lack of ICD on the day of listing. One-year survival for status 1 candidates improved from 49.5 to 69.0 percent; for status 2 candidates, it improved from 81.8 to 89.4 percent. The peak  $\text{VO}_2$  ( $\text{VO}_{2\text{max}}$ ) is the

most objective assessment of functional capacity in patients with HF, and may be the best predictor of when to list a patient for cardiac transplantation. The 2002 task force of the ACC/AHA recommended the use of exercise testing with ventilatory gas analysis for this purpose [5]. The others risk models are Heart Failure Survival Score (HFSS), including: presence or absence of coronary artery disease; resting heart rate; left ventricular ejection fraction; mean arterial blood pressure; presence or absence of an interventricular conduction delay on ECG; serum sodium; peak VO<sub>2</sub>; and an invasive version with pulmonary capillary wedge pressure. Seattle Heart Failure Model in contrast of HFSS included ICDs and CRT.

#### 4 Indication for left ventricular assist device (LVAD)

In the 2006 Heart Failure Society of America (HFSA) guidelines, the 2005 ACC/AHA HF guidelines with 2009 focused update, and the 2008 ESC HF guidelines recommended [1,3] that patients awaiting heart transplantation, who have become refractory to all means of medical circulatory support, should be considered for a mechanical support device as a **bridge to** transplantation [6]. **Destination therapy** has been recommended for highly selected patients with severe HF refractory to conventional therapy, who are not candidates for heart transplantation, and particularly those who cannot have any improvement from intravenous inotropic support at an experienced HF center [6]. The 2008 ESC guidelines (although experience is limited) considered these devices for long-term use when no definite procedure is planned [3]. Mechanical cardiac support devices may be implanted in patients who have experienced no clinical improvement from pharmacological therapies for severe HF, including oral medications, and intravenous inotropes, and non-pharmacological support with intraaortic balloon pump counterpulsation. The main criteria for selection of patients are as follows: a) active heart transplant candidate; b) maximal inotropic support, with or without Intra-aortic balloon pump (IABP); c) systolic blood pressure <80 mmHg with a cardiac index below 2.0 L/min per m<sup>2</sup> or a pulmonary capillary wedge pressure over 20 mmHg [7].

#### 5 Prognosis after LVAD implantation

The LVADs are associated with the least morbidity and the best chance for rehabilitation and recovery before and after transplantation in patients requiring a prolonged support. An important consideration is that the device be implanted before developing secondary end-organ damage. In case of irreversible end-organ damage (especially renal dysfunction), there will be no improvement of a patient's clinical status. A screening risk score to predict operative mortality after device

implantation are as follows: indication for ventilator support (4 points); postcardiotomy shock (2 points); the implantation of temporary LVAD prior to HeartMate (2 points); central venous pressure >16 mmHg (1 point) and prothrombin time >16 seconds (1 point). A risk score >5 were associated with a significantly greater operative mortality than lower score (46 versus 12 percent). Patients with low (0 to 4), intermediate (5 to 7) or high (8 to 10) risk score had increasing mortality rates (8, 32, and 49 percent) and decreasing rates of successful bridging to transplantation (89, 65, and 49 percent) [8].

LVAD provide support of the left ventricular function only; the management of the right ventricular function is therefore very important, and the goal has to be the management of pulmonary vascular resistance. LVAD support reverse ventricular remodeling and cause permanent improvement in left ventricle function, causing regression of myocyte hypertrophy and fibrosis, improvement in myocyte contractility, restoration of beta-adrenergic receptors, normalization of calcium metabolism, altered expression of genes involved in processes such as myocyte metabolism and apoptosis [9-13]. This structural reverse remodeling is complete by about 40 days, with evidence of clinical benefit and an improvement in the quality of life [14]. These data suggest that human myocytes have the capability of undergoing beneficial functional and electrophysiological changes and an increase in contractility and hemodynamic improvement [12,13,15].

End stage heart failure is not an end of life, since heart transplantation, better medications and devices, including VADs implantations, offer patients a better quality and an appreciable extension of life.

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## Sažetak

### **Terminalna faza zatajenja srca – transplantacija ili LVAD**

Zatajenje srca kompleksni je klinički sindrom, a može se razviti kao posljedica bilo kojeg strukturalnog ili funkcionalnog poremećaja koji utječe na punjenje klijetki i ispumpavanje krvi. Prema podacima ISHLT registra, poluvrijeme preživljavanja nakon srčane transplantacije produžilo se s 8,9 godina u 1982. na oko 11 godina u razdoblju između 2002. i 2006. Vršni VO<sub>2</sub> (VO<sub>2</sub>max) najobjektivniji je parametar u procjeni težine zatajenja srca i mogao bi biti najbolji prediktor stavljanja bolesnika na transplantacijsku listu. Mehanička srčana potpora indicirana je u bolesnika u kojih se farmakološkom terapijom (oralnom i parenteralnom) te nefarmakološkom s intraaortnom balon pumpom ne ostvari adekvatno poboljšanje kliničkog statusa bolesnika. LVAD potpora je lijevom srcu, a može dovesti do remodeliranja i trajnog poboljšanja funkcije lijeve klijetke. Terminalna faza zatajenja srca nije i kraj života jer transplantacija, noviji farmakološki pripravci i mehanička potpora, uključujući i VAD, bolesnicima omogućuju bolju kvalitetu i **produžetak života**.

**Ključne riječi:** zatajenje srca; transplantacija srca; LVAD

