Device Therapy in Refractory Heart Failure

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Advanced heart failure (HF) has been defined as persistent symptoms that limit daily life despite optical medical therapy, corresponding to New York Heart Association (NYHA) class III/IV symptoms or to the newer classification of stage D HF (ACC/AHA staging classification). It affects 10% of the HF population and is associated with a poor quality of life, recurrent hospitalizations and a mortality approaching 50% at 1 year and 80% at 5 years.[1,2] Despite the widespread use of angiotensin converting enzyme (ACE) inhibitors, beta adrenergic blocking agents and spironolactone which improve the prognosis in mild to moderate stages, HF remains a progressive disease leading to decompensation and demand of both inotropic agents (class III recommendation according to ACC/AHA guidelines, considered solely for palliation in patients with end-stage disease) and diuretics to treat hypotension, impaired renal function and pulmonary congestion.[3]

Heart transplantation (HT) is associated with nearly 90% 1-year survival, 60% 10-year survival and 95% freedom from symptoms and activity limitations in survivors throughout the follow-up period.[1] Nevertheless, the lack of available donors and the large number of patients, who do not meet the criteria for transplantation, have spurred interest in cardiac resynchronization therapy (CRT) and mechanical circulatory support (MCS), providing alternatives for patients waiting for HT (bridge to transplantation, BTT), patients who are ineligible for HT (destination therapy, DT) or patients who are anticipated to recover after left ventricular unloading (bridge to recovery, BTR).

- **Cardiac Resynchronization Therapy** (CRT) in NYHA functional class III/IV

The progression of heart failure results in dilated ventricles and impaired conduction between different segments of ventricular wall. QRS duration over 120 ms is present in 25-40% of patients with advanced HF, with left bundle branch block (LBBB) being the most common conduction abnormality of both ischemic and non-ischemic cardiomyopathy. The transvenous insertion of both ventricular pacing leads has been proved beneficial on the basis of clinical improvement for over half of patients with inter-ventricular dyssynchrony undergoing CRT.[4] Although a wide QRS does not always indicate marked dyssynchrony, it is currently the most convenient descriptor for considering biventricular pacing to confer symptomatic benefit mainly in patients with median QRS duration 150-170 ms. Echocardiographic parameters have not been adopted, although real-time 3D echo appears quite promising in quantifying mechanical dyssynchrony by assessing novel parameters, such as the systolic dyssynchrony index (SDI).[5,6]

CRT has been recommended as a class IA indication by both major HF and pacing guidelines for advanced HF patients (NYHA III/IV) with QRS ≥ 120 ms, ejection fraction (EF) ≤ 35% and sinus rhythm, refractory to optimal medical therapy.[7] A large number of randomized multi-center trials have evaluated CRT-pacing (CRT-P) and CRT-defibrillator (ICD) devices (CRT-D) on symptoms, exercise tolerance, morbidity and mortality in patients with refractory HF. In the COMPANION trial, CRT-P decreased the risk of death from or hospitalization for HF (primary endpoint) by 34% and the risk of death from any cause (secondary endpoint) by 24%, while CRT-D was associated with decreased risk of primary and secondary endpoints by 40% and 36% respectively.[8] The CARE-HF study showed a reduction in the risk of death due to advanced HF (hazard ratio 0.55, P=0.003) and sudden death (hazard ratio 0.54, P=0.005) in patients with CRT-P who were followed up for a mean period of 37.4 months[9] and also demonstrated improved quality of life by 13% at 18 months and by 23% at study-end for patients assigned to CRT.[10]

According to the results from the MUSTIC study, patients with NYHA III and intraventricular conduction delay who were followed up at 9 and 12 months after CRT-P implantation displayed major clinical and echocardiographic improvements, e.g. the 6-minute walk distance increased by 20% (patients in sinus rhythm, SR) and 17% (patients in atrial fibrillation, AF) / peak VO2 increased by 11% (SR) and 9% (AF) / quality of life improved by 36% (SR) and 32% (AF) / NYHA class improved by 25% (SR) and 27% (AF) / EF improved by 5% (SR) and 4% (AF), mitral regurgitation decreased by 45% (SR) and 50% (AF).[11] Similarly, CRT reduced the interventricular mechanical delay, the end-systolic volume index, the area of the mitral regurgitation and increased the mean EF by 3.7% at 3 months to 6.9% at 18 months in a sub-analysis of the CARE-HF.[12] Effects were significantly greater in patients with non-ischemic than in ischemic heart disease while prolonged PR interval and right bundle branch block were predictors of non-favorable outcome.[13] Less than two thirds of patients enrolled in the MIRACLE or MIRACLE-ICD trials responded to CRT, with just more than half responding within the first month of CRT-P or CRT-D implantation (patients with improvement ≥ 1 NYHA class from baseline to 6 month follow-up were considered

responders and those with no change or worse NYHA class were classified as non-responders).[14]

A prolonged QRS is widely regarded as a prerequisite for CRT but approximately 30-40% of all CRT patients are regarded as non-responders; it has been suggested that almost 30-40% of HF patients with wide QRS do not exhibit ventricular dyssynchrony (non-responders) and 27% of HF patients with narrow QRS show mechanical dyssynchrony and response to CRT.[15] In a sub-analysis of the PROSPECT trial, patients with narrow QRS complex and mechanical dyssynchrony assessed by echocardiography, demonstrated benefit by CRT, yet in the RethinQ trial patients with similar inclusion criteria did not show improved peak oxygen consumption after CRT.[16,17] Larger studies are needed to clearly define criteria for identifying patients likely to benefit from such a complex invasive and costly treatment.

Female sex and advanced age should not be contra-indications for CRT when appropriate indications exist, while patients with right bundle branch block or right ventricular dysfunction would probably have a lower response to CRT.[18] In patients with AF, atrioventricular node (AVN) ablation and implantation of CRT provides 100% biventricular pacing and great improvement in NYHA class and survival benefit[19] and as a result, it is included in the latest guidelines for patients with AF who meet criteria for CRT (EF<35%, NYHA III/IV and refractory to drug therapy) as a class IIa recommendation.

Mechanical Circulatory Support

In recent years, technological advancements have emerged to help assist the failing heart, alter hemodynamics and improve cardiac output. Initial reports of mechanical support of the heart date back to the 1960s with the development of the intra-aortic balloon pump (IABP), and later in 1971 Dr. Michael DeBakey reported the first clinical use of a left ventricular assist device (LVAD).[20] Different devices have been developed since then, classified into percutaneous and surgical therapies; the former are indicated for short-term use in acutely decompensated HF or perioperatively and include the IABP, and continuous aortic flow augmentation (CAFA) and catheter-based pumps; the latter are intended for long-term treatment of chronic HF and comprise ventricular assist devices (VADs) and total artificial hearts (TAHs)].[21]

1. Percutaneous therapies

The IABP has been in use since the early 1960s, with a balloon catheter being inserted through the femoral artery and externally controlled, inflated during diastole and deflated during systole. It is associated with a 2.8% rate of significant complications and a 0.05% rate of in-hospital mortality which probably reflects the critical condition of patients who are selected for IABP therapy. The CAFA pump was first tested in the Cancion System which circulates blood from catheterized bilateral femoral arteries to an extracorporeal pump and then into the descending aorta. It was associated with improvement in cardiac index but major bleeding in the MOMENTUM trial prevented its commercial use.[22] A new CAFA device, the Exeleras system (fully implantable, intended for long-term treatment of HF) is now under development and will be the subject of future studies.

Among different percutaneous catheter-based pumps that have been designed to provide short-term hemodynamic support in patients with cardiogenic shock, the Impella 2.5 is a minimally invasive catheter-based cardiac assist device, inserted into the left ventricle via the femoral artery with a micro-axial pump continuously pumping blood from the left ventricle into the ascending aorta at a maximum rate of 2.5 L/min. The TandemHeart Percutaneous Transseptal Ventricular Assist (PTVA) system is another catheter-based pump which is inserted into the left atrium via transseptal puncture with an extracorporeal pump (maximum flow rate 5.0 L/min) and an outflow catheter positioned into the descending aorta. Both the Impella and the TandemHeart PTVA systems provide hemodynamic support (improvement in cardiac index, increase in mean blood pressure, reduction in pulmonary capillary wedge pressure), although no difference was found in 30-day mortality between either of these systems and IABP. It also seems that outcome is better in their prophylactic use for high risk percutaneous coronary intervention, while severe adverse effects inlcude bleeding and limb ischemia.[21,23,24]

2. Surgical therapies

The limitations of medical therapy and the woeful shortage of organs for transplantation led to the development of ventricular assist devices, mechanical pumps that are surgically implanted to support the failing left ventricle (LVAD), or right ventricle (RVAD) or both (BiVAD). Apart from providing hemodynamic support, these devices result in reverse remodeling of the failing ventricle by reversing different genetic, cellular and neurohormonal pathways taking place in HF.[21]

There are three generations of these devices which became a cornerstone for the treatment of patients with refractory HF, while constant adjustments take place to increase their efficiency.[25,26] First-generation LVADs are large extracorporeal devices for temporary use, the Thoratec HeartMate XVE (later called HeartMate I) and the Novacor LVAS. The REMATCH study demonstrated increased 1- / 2-year survival and improved quality of life

for patients who received the HeartMate XVE with deaths being attributed to device failure and sepsis.[27] A non-randomized trial with the Novacor LVAS also demonstrated improved survival but 62% of patients receiving MCS suffered from a stroke or transient ischemic stroke.[28] Second-generation LVADs (HeartMate II, Jarvik 2000 and HeartAssist 5) are continuous-flow devices that work with an axial flow mechanism, have smaller size, need a more limited surgery, are less likely to be infected but need systemic anticoagulation. Although second-generation LVADs continue to improve, trials evaluating third-generation LVADs are taking place including HeartWare HVAD, HeartMate III and Synergy, usually using a magnetically levitated impeller for moving blood.[26]

It is estimated that 80-90% of LVADs are implanted in transplant candidates (BTT), although they are also used in patients who are deemed too sick to survive and have contraindications for transplant (DT) or even as 'bridge to decision' apart from BTR for those who require reevaluation and adequate support for improvement of end-organ perfusion. Patients with the following parameters have a strong indication for the implantation of a LVAD: NYHA IV for 60-90 days, optimal medical therapy and CRT-P/CRT-D if indicated, chronic inotrope dependence, LVEF <25%, PCWP ≥ 20 mmHg, SBP≤ 80-90 mmHg or cardiac index ≤2 L/min/m^2 or declining renal or right ventricular (RV) function.[1] Patients with severe renal, pulmonary, hepatic dysfunction or patients with active infection or cardiogenic shock should not be considered as candidates.

LVADs are associated with 5-10% peri-operative mortality and considerable morbidity due to multi-organ failure, embolic events, bleeding, infection, sepsis or acute RV failure. Certain complications may present over the long-term, such as embolic or hemorrhagic stroke, progression or de novo development of RV failure, human leucocyte antigen sensitization, renal insufficiency, device failure or infection requiring transplantation, explantation or replacement.[1] Risk for developing ventricular arrhythmias has also been reported and ICD therapy seems safe and effective in LVAD patients, associated with extended survival: (i) more than one-third of LVAD recipients experience appropriate ICD therapy in the first year, (ii) patients with a secondary prophylactic ICD indication have a two-fold increased risk for appropriate shocks compared with patients with a primary prophylactic ICD indication.[29,30]

The Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS, www.intermacs.org) is a comprehensive VAD registry in the USA with approximately 4800 VADs being enrolled until June of 2011.[31] Data collected in this registry made clear that preoperative hemodynamic status largely influences the prognosis after VAD implantation, leading to detection of 'profiles' and 'modifiers' in order to select patients and study outcomes in LVAD patients. The 1-year survival for LVADs continuously improved from 50% in the REMATCH trial to 74% at the second annual INTERMACS report and is close to 85% according to data presented at the International Society of Heart and Lung Transplantation annual meeting in 2010.[26]

The FDA has currently approved 2 different TAHs in the USA, the CardioWest Temporary Total Artificial Heart (as BTT) and the AbioCor Replacement Heart (as DT in patients with biventricular HF with no other medical or surgical treatment options). Yet, serious complications of these devices like bleeding, infection, stroke and difficulties regarding battery recharge still hold up their use.[21] A novel device of cardiac contractility modulation (CCM) was tested in FIX-HF-5, a multicentre randomized controlled trial in patients with advanced HF (NYHA III-IV, LVEF≤35%, narrow QRS) who were treated with optimal medical therapy (213 patients) versus optimal medical therapy plus CCM device (215 patients). Although no difference in the mean change of anaerobic threshold was found among the two groups, the trial revealed improved quality of life, peak VO_2 and NYHA class in patients receiving CCM therapy.[32] Further studies are needed to clarify how patients with end-stage HF should be treated in terms of when and which device should be implanted.

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