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Advanced Heart Failure and Management Strategies

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ABSTRACT

The global healthcare burden attributable to heart failure is ever increasing. Patients presenting with refractory heart failure should be evaluated for compliance with medical regimens and sodium and/or fluid restriction, and every attempt should be made to optimize conventional strategies. Reversible causes such as ischemia should be identified and revascularization considered in persistently symptomatic patients, particularly those with a viable myocardium. Carefully selected patients who continue to deteriorate clinically in spite of optimization of medical therapy may be considered for advanced treatment strategies, such as continuous inotropic infusions, mechanical circulatory support devices, cardiac transplantation, or referral to hospice care. We discuss the clinical presentation and management of patients with advanced/refractory (Stage D) heart failure.

INTRODUCTION

Heart failure is associated with very high morbidity and mortality, particularly in the elderly population, and accounts for a substantial portion of healthcare expenses in the United States and worldwide. This could be attributed to increasing life expectancy and overall prevalence of heart failure. Eighty percent of men and 70% of women <65 years of age diagnosed with heart failure will die within 8 years. Following an initial hospitalization for heart failure, there is a 50% readmission rate at 6 months and nearly 20% incidence of death within 12 months.[1] The American College of Cardiology Foundation/American Heart Association (ACCF/AHA) guidelines identify four stages in the clinical course of heart failure: Stage A—patients with coronary artery disease, hypertension, or diabetes mellitus who do not yet demonstrate left ventricular hypertrophy, geometric chamber distortion, or function impairment; Stage B—those who are asymptomatic but demonstrate left ventricular hypertrophy and/or impaired left ventricular function; Stage C—patients with current or past symptoms of heart failure associated with underlying structural heart disease; and Stage D (advanced or refractory)—patients who continue to experience symptoms on minimal exertion or at rest in spite of optimal medical therapy and deteriorate clinically requiring repeated hospitalizations. Stage D patients may require advanced treatment strategies, such as special fluid removal procedures, continuous inotropic infusions, mechanical circulatory support devices, cardiac transplantation, or referral to hospice care.[2]

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CLINICAL PRESENTATION AND EVALUATION OF PATIENTS WITH ADVANCED HEART FAILURE

Fluid retention, dyspnea, and exercise intolerance are the cardinal symptoms of heart failure. Patients with advanced heart failure may present with manifestations of low cardiac output such as early satiety, poor appetite, abdominal pains, nausea, renal insufficiency, decreased mentation, memory problems, or cognitive impairment with or without fluid retention, which are often reversible with the treatment of heart failure. Patients presenting with refractory heart failure should be evaluated for compliance with medical regimens and sodium and/or fluid restriction, and every attempt should be made to optimize conventional strategies. Reversible causes such as ischemia should be identified and revascularization considered in persistently symptomatic patients, particularly in those with viable myocardium. Myocardial viability can be assessed using various modalities, such as positron emission tomography with fluorodeoxyglucose imaging, single photon emission tomography with thallium-201, technetium-99m sestamibi or technetium-99m tetrofosmin imaging, dobutamine stress echocardiography, or magnetic resonance imaging with gadolinium.[2]

MANAGEMENT

Diuretics, preferably loop diuretics (oral or intravenous), are used for management of fluid overload, largely for symptom relief and based on anecdotal

experience. However, diuretics have not been shown to affect mortality in patients with heart failure.[3] Electrolyte abnormalities and renal insufficiency often complicate treatment of heart failure, particularly in the acute setting. Decreased cardiac output and renal blood flow in heart failure contribute to a decrease in glomerular filtration rate (GFR) with resultant reduced delivery of solute and water to the distal diluting segment of the nephron, thus impairing the kidney's ability to excrete dilute urine. In addition, decreased cardiac output and ineffective circulating volume promote arterial baroreceptor activation, which results in sympathetic nervous system (SNS) and renin angiotensin aldosterone system (RAAS) activation. SNS activation enhances sodium and water retention, while RAAS activation results in both an increase in angiotensin II levels and arginine-vasopressin (AVP) release. AVP promotes further free fluid retention and, in some cases, hyponatremia. Heart failure therapy, particularly diuretics, may also contribute to both worsening GFR and hyponatremia. Renal dysfunction in patients with chronic heart failure has been associated with increased risk of hospitalization for decompensated heart failure, cardiovascular death, and all-cause mortality.[4] In the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure trial, there was a direct relationship between serum creatinine and in-hospital mortality, with an 18% increase in in-hospital mortality for every 0.3 mg/dL increase in serum creatinine up to 3.5 mg/dL.[3] The presence of hyponatremia in patients with heart failure has also been identified as a poor prognostic indicator and associated with increased mortality.[5]

Diuretic resistance is defined as decreased natriuresis and diuresis. Ultrafiltration is a mode of mechanical sodium and fluid removal developed to overcome diuretic resistance and electrolyte abnormalities associated with diuretic treatments. Ultrafiltration using a simplified device (Aquadex flex flow fluid removal system by CHF Solutions, Inc., Brooklyn Park, MN) is being studied and increasingly used in heart failure management. Ultrafiltration has shown promise by increasing diuresis without causing significant electrolyte disturbances as well as by decreasing length of stay.[6,7] The Ultrafiltration versus Intravenous Diuretics for Patients Hospitalized for Acute Decompensated Congestive Heart Failure trial was a prospective, randomized, multicenter trial of early ultrafiltration versus intravenous diuretics in patients hospitalized with heart failure and hypervolemia (n=200). At 48 hours, weight (5±3.1 vs. 3.1±3.5 kg; $P=0.001$) and net fluid loss (4.6 vs. 3.1 L; $P=0.001$) were greater in the ultrafiltration group. At 90 days, fewer rehospitalizations (18% vs. 32%; $P=0.037$) for heart failure and rehospitalization days per patient (1.4±4.2 vs. 3.8±8.5; $P=0.022$) were noted in the group randomized to ultrafiltration. No differences in serum creatinine were noted between groups. Advantages of ultrafiltration over diuretic-based approaches include adjustable fluid removal volumes and rates, minimal effect on serum electrolytes, and decreased neurohormonal activity. Aquapharesis may be considered in patients with fluid overload (at least 5 lbs above dry weight), inadequate diuretic response, and serum creatinine ≤3 mg/dL. A special 5 Fr. single lumen extended length catheter (ELC)—in combination with an 18G intravenous catheter, a 6 Fr. dual lumen peripheral ELC, or a 7–8 Fr. dual lumen central catheter access—is required for aquapharesis, and patients should be anticoagulated with intravenous unfractionated heparin.

Beta blockers and angiotensin converting enzyme inhibitors (ACEIs) (angiotensin receptor blockers in patients intolerant to ACEIs) should be maximized as tolerated.[2] Aldosterone antagonists (spironolactone or eplerenone) have been shown to improve survival and decrease the frequency of hospitalization in patients with New York Heart Association (NYHA) class III–IV symptoms when added to ACEIs, beta blockers, and diuretics.[8,9] Vasodilators (hydralazine and isosorbide dinitrate) should be considered in African Americans.[10] In patients with severe systolic heart failure with persistent symptoms in spite of maximal therapy with ACEIs, beta blockers, and diuretics, digoxin has been shown to reduce symptoms and decrease hospitalizations.[11] The Multicenter Automatic Defibrillator Implantation Trial II,[12] Sudden Cardiac Death in Heart Failure Trial,[13] and Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure[14] trials have clearly proved the mortality benefit of an implantable cardioverter defibrillator (ICD) in addition to conventional medical therapy in patients with ischemic and nonischemic dilated cardiomyopathy with left ventricular ejection fraction <35% and in whom survival with good functional capacity is otherwise anticipated to extend beyond 1 year. All patients with NYHA class III–IV heart failure with evidence of atrioventricular dyssynchrony by electrocardiogram (QRS duration >120 ms) should be considered for cardiac resynchronization therapy.[2,14,15]

In the acute setting, positive inotropes (dobutamine, a ß-adrenergic agonist, or milrinone, a phosphodiesterase inhibitor) have been shown to improve hemodynamics and symptoms, particularly in patients presenting with cardiogenic shock.[16,17] Both of these agents can only be administered intravenously and are proarrhythmic. Long-term intermittent (at infusion centers) or continuous home infusion of inotropes as a bridge to heart transplantation has been shown to improve symptoms and decrease hospitalization and requirements for mechanical treatments such as intra-aortic

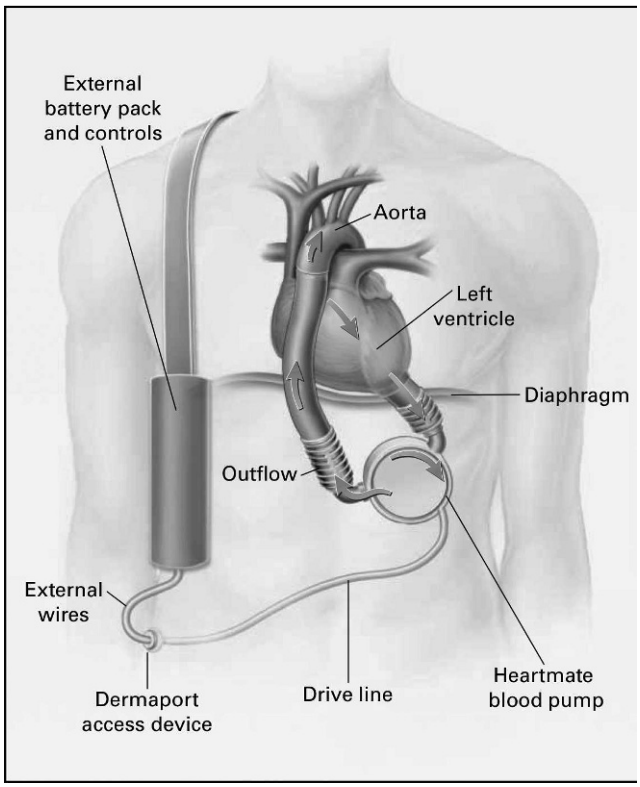

Figure. An intracorporeal left ventricular assist device and its components. The inflow canula is inserted into the apex of the left ventricle, and the outflow canula is anastomosed to the ascending aorta. Blood returns from the lungs to the left side of the heart and exits through the left ventricular apex and across an inflow valve into the pumping chamber. Blood is then actively pumped through an outflow valve into the ascending aorta. The pumping chamber is placed within the abdominal wall. One transcutaneous line carries the electrical cable and air vent to the battery pack and electronic controls, which are worn on a shoulder holster or belt. (Reprinted with permission from Goldstein DJ et al. *NEJM.* 1998).[21]

balloon pumps.[18–20] However, no mortality benefits have been noted in these studies. They are not routinely recommended in any heart failure patients. Inotropes may also be considered for palliation in patients with refractory heart failure who are not eligible for a more definitive therapy such as heart transplantation.

Mechanical circulatory support devices, such as an intra-aortic balloon pump (IABP) or ventricular assist devices (VADs), are increasingly used in the management of heart failure. IABP has emerged as the single most effective and widely used circulatory assist device. It is mainly used in patients with advanced heart failure presenting with low cardiac output state as a bridge to recovery or transplantation. The use of IABP is limited by the invasive nature of the procedure, restriction of patient mobility, and risks of thromboembolism, bleeding, and infection.

VADs are mechanical pumps that assist the failing ventricle (left or right) in maintaining adequate circulation (Figure).[21] They are characterized as pulsatile or continuous flow based on their mechanism of action and as extracorporeal, paracorporeal, or intracorporeal based on the implantation site (Table 1). Left ventricular assist devices (LVAD) are more commonly used than right ventricular assist devices. The Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure[22] trial randomized 129 patients with NYHA class IV heart failure symptoms who were deemed ineligible for cardiac transplantation to LVAD implantation (n=68) or standard medical management (n=61). There was a 48% significant reduction in mortality from any cause in the LVAD group compared to the medical therapy group (relative risk, 0.52; 95% confidence interval [CI], 0.34–0.78; $P=0.001$). Quality of life was significantly improved at 1 year in the device group. The 1-year survival rate was significantly higher in the LVAD group than in the medical therapy group: 52% and 25%, respectively ($P=0.002$). The 2-year survival rates were not significantly different at 23% and 8%, respectively. Infection, bleeding, and device malfunction were 2.4 times more likely to occur in the LVAD group than in the medical therapy group.

LVADs are currently used as a ''bridge'' to heart transplantation in patients listed for transplantation but clinically deteriorating before a donor heart is available or as a replacement (destination) therapy for failing hearts in patients who are not candidates for heart transplantation. At the present time, the Thoratec implantable VAD (Pleasanton, CA), HeartMate XVE (Thoratec), HeartMate II (Thoratec), and Novacor LVAS (WorldHeart, Salt Lake City, UT) are the approved devices for bridging to transplant, whereas HeartMate XVE is the only device approved for destination therapy. Major complications associated with LVADs include bleeding, infection, and device malfunction. Temporary right ventricular failure immediately following an LVAD placement can occur in 30% of patients requiring inotropes or right ventricular assist device.

Smaller size, greater durability, and lower risk of infection with the newer continuous flow devices—DeBakey VAD (MicroMed Cardiovascular, Houston, TX), HeartMate II, and JARVIK 2000 (Jarvik Heart, New York, NY)—offer an advantage over the pulsatile flow devices, which are limited by their large size and risk of disk failure and infection. JARVIK 2000, a newer axial-flow impeller pump currently under investigation, is smaller, totally implantable, and silent with potentially lower risk of infections, thrombosis, and hemolysis. These newer continuous flow devices are promising.

Routine right heart catheterization to assess the severity of heart failure is not recommended. Right heart catheterization and hemodynamic assessment

Table 1. Different Types of Ventricular Assist Devices

Device	Site	Mechanism of Action	Configuration
IABP	Extracorporeal	Pulsatile	LVAD
Impella	Extracorporeal	Continuous flow	LVAD
ABIOMED BVS	Extracorporeal	Pulsatile	LVAD/RVAD/BiVAD
JARVIK 2000	Intracorporeal	Continuous flow	LVAD
DeBakey VAD	Intracorporeal	Continuous flow	LVAD
Novacor LVAS	Intracorporeal	Pulsatile	LVAD
Thoratec	Intracorporeal	Pulsatile	LVAD/RVAD/BiVAD
HeartMate XVE	Intracorporeal	Pulsatile	LVAD
HeartMate II	Intracorporeal	Continuous flow	LVAD

IABP: intra-aortic balloon pump; LVAD: left ventricular assist device; RVAD: right ventricular assist device; BiVAD: biventricular assist device

are useful in tailoring therapy in advanced heart failure and in acute settings.[23] In preparation for listing for cardiac transplantation, a right heart catheterization should be performed on all candidates to assess for pulmonary hypertension and cardiac output. A pulmonary artery systolic pressure (PASP) >50 mmHg or transpulmonary gradient >15 or the pulmonary vascular resistance (PVR) >3 warrants a vasodilator challenge with inhaled nitric oxide or intravenous nitrates to determine reactivity. Reactivity may not be obvious in the acute setting, in which case in-hospital treatment with inotropes and continuous hemodynamic monitoring may be required, as often the PVR will decline after 24–48 hours of treatment. Irreversible pulmonary hypertension in spite of adequate therapy with diuretics, vasodilators, and/or mechanical cardiac support devices (IABP, LVAD) is a poor prognosticator in patients with advanced heart failure and is a relative contraindication for listing for heart transplantation.

Table 2. Calculation of Heart Failure Survival Score (HFSS)

Clinical Characteristic	Value (χ)	Coefficient (β)	Product
Ischemic cardiomyopathy	1	+0.6931	+0.6931
Resting heart rate	90	+0.0216	+1.9440
LVEF	17	−0.0464	−0.7888
Mean BP	80	−0.0255	−2.0400
IVCD	0	+0.6083	0
Peak VO_2	16.2	−0.0546	−0.8845
Serum sodium	132	−0.0470	−6.2040

HFSS is a composite score calculated using seven variables that have been separately identified and validated as prognostic measures. Each of the component variables is assigned a model coefficient based on regression models. It is calculated by taking the absolute value of the sums of the products of each component variable's value and its model coefficient. Patients are stratified into low (≥8.10), medium (7.20–8.09) and high risk (<7.20). Among the patients in the validation sample, 1-year survival rates without transplant for these three strata were 88%, 60%, and 35%, respectively. LVEF: left ventricular ejection fraction; BP: blood pressure; IVCD: intraventricular conduction delay

HEART TRANSPLANTATION

Various survival models have been developed to predict survival in patients with heart failure. The Heart Failure Survival Score (HFSS) (Table 2)[24] and The Seattle Heart Failure Model[25] (an interactive program that helps estimate 1-, 2-, and 5-year survival and the benefit of adding medications and/or devices for an individual patient, available at www.SeattleHeartFailureModel.org) are the most widely used models for predicting survival in ambulatory patients. The Enhanced Feedback for Effective Cardiac Treatment (available at http://www.ccort.ca/CHFriskmodel.asp) and Acute Decompensated Heart Failure National Registry risk tree models were developed to predict 30-day and 1-year mortality in patients hospitalized with acute decompensated heart failure.

Heart transplantation is the treatment of choice for patients with heart failure refractory to medical therapy. Data from the 2008 report from the registry of the International Society for Heart and Lung Transplant (ISHLT) showed that patient survival at 1 and 3 years for patients who received cardiac transplantation was approximately 85% and 79%, respectively.[26] Recent advances in medical and device therapies have also improved the survival of heart failure patients comparable to that for post-heart transplant.[27] More patients need heart transplantation than there are donor hearts available. Heart transplantation is limited to patients who are most likely to benefit with a significant improvement in symptoms and life expectancy. The ISHLT listing criteria guide transplant centers to stratify risk and select patients for heart transplantation, the details of which are beyond the scope of this manuscript. The indications and contraindications for heart transplantation are detailed in Table 3.

Once evaluation is completed, appropriate patients are listed for cardiac transplantation. The donor organ procurement and distribution is regulated by the United Network for Organ Sharing (UNOS) in the

Table 3. Selection Criteria for Heart Transplantation

INDICATIONS

Cardiomyopathy: Patients with cardiac conditions not responding to maximal medical therapy—e.g., ischemic cardiomyopathy (intractable angina in spite of maximal tolerated medical therapy, not amenable to coronary artery bypass grafting/percutaneous transluminal coronary angioplasty), dilated cardiomyopathy, valvular heart disease, hypertensive heart disease, hypertrophic cardiomyopathy (persistant heart failure despite maximal medical therapy, including alcohol ablation, myomectomy, mitral valve replacement, and pacemaker therapy), and congenital heart disease (not amenable to surgical correction and in which fixed pulmonary hypertension is not a complication) should be considered for heart transplantation.

Intractable arrhythmias: Uncontrolled with an implantable cardioverter defibrillator, not amenable to electrophysiologic guided single or combination medical therapy, or not a candidate for ablative therapy.

CONTRAINDICATIONS

Age limit: Patients ≤70 years of age should be considered for cardiac transplantation. Carefully selected patients >70 years of age may be considered for cardiac transplantation. There is an increasing tendency to perform transplantation in older patients. It has been proposed to use an alternate list or strategy of allocating organs from older donors (that would otherwise be unused) to older recepients.

Weight limit: It is recommended that a body mass index (BMI) of <30 kg/m^2 or percent ideal body weight <140% is preferred for listing for cardiac transplantation. Obese patients are at an increased risk for poor wound healing, infection, lower extremity thrombus, and pulmonary complications.

Diabetes: Diabetes with end-organ damage other than nonproliferative retinopathy or poor glycemic control (hemoglobin $A_{1C} > 7.5$) despite optimal effort is a relative contraindication.

Renal dysfunction: Presence of irreversible renal dysfunction (estimated glomular filtration rate <40 mL/min) is a relative contraindication. Combined heart-kidney transplantation may be considered in patients with irreversible renal failure.

Cerebrovascular disease/peripheral vascular disease: Clinically severe symptomatic cerebrovascular disease, which is not amenable to revascularization, may be considered a contraindication. Peripheral vascular disease may be considered as a relative contraindication when its presence limits rehabilitation and revascularization is not a viable option.

Neoplasms: Active neoplasms from origins other than skin are an absolute contraindication to cardiac transplantation. Depending on tumor type and response to therapy, if tumor recurrence is low and metastatic work-up is negative, then cardiac transplantation can be considered. Cancers that have been in remission for 5 years or more may be acceptable for transplant evaluation. All patients should be screened as per American Cancer Society guidelines for malignancies.

Other comorbidities: Comorbidities such as amyloidosis; any active infections, including human immunodeficiency virus infection; and sarcoidosis are exclusions for cardiac transplantation.

Psychosocial conditions: All patients being considered for transplantation should be assessed for ability to give informed consent, comply with instructions, and have support systems. Mental retardation or dementia is a relative contraindication.

Tobacco and substance abuse: Active tobacco smoking is a relative contraindication. Active tobacco smoking during the previous 6 months is a risk factor for poor outcomes after transplantation. Patients who remain active substance abusers (including alcohol) should not receive heart transplantation.

United States.[22] There are typically four UNOS listing categories based on the severity of cardiac illness:

UNOS Status 1A: This is the highest priority category. Patients on mechanical ventilation (for no more than 30 days) or mechanical cardiac support such as IABP or VADs, high-dose inotropic agents, and continuous hemodynamic monitoring are included in this category.

UNOS Status 1B: Patients with VADs implanted for >30 days, inpatient or outpatient continuous inotropic agent infusion at a low dose.

UNOS Status 2: All others active on transplant list.

UNOS Status 7: Temporarily inactive.

All listed patients should be re-evaluated at 3- to 6-month intervals for improvement or deterioration, and their statuses should be adjusted accordingly.

Usually, patients <50 years of age who are brain dead are potential cardiac donors. Contraindications for heart donation include significant heart dysfunction, congenital heart disease, malignancies (except basal cell and squamous cell carcinomas of skin, primary tumors of the central nervous system with low metastatic potential), or transmissible diseases. Once brain death is declared, the organ procurement organization should be involved for further donor management with the main focus to maintain the function of the organs to be transplanted. The most suitable recipient is identified and matched to receive the heart based on ABO compatibility, body size compatibility (within 20% difference of height and weight), and location (within 2–4 hrs of the hospital where the donor is available).

Patients require chronic post-transplant immunosuppression to prevent allograft rejection. Immunosuppressants, while decreasing the incidence of rejection, are associated with increased risk of opportunistic infections. Cytomegalovirus, *Pneumocystis carinii*, and fungal infections are common in post-solid organ transplant patients. Hence, prophylactic agents to prevent these infections should be considered and initiated in all patients post-transplant. Hypertension, diabetes, and osteoporosis are common, attributable to the long-term use of steroids and some immunosuppressants. Chronic immunosuppression also increases the risk of malignancies (most commonly lymphoproliferative disorders).

END-OF-LIFE CARE

All patients with heart failure should be approached regarding wishes for resuscitative care, and their wishes should be documented in a living will or other advanced medical directives. Palliative measures, including inotropes, should be considered and offered to patients with advanced heart failure who do not qualify for heart transplantation and are unresponsive to medical therapy. Hospice care at home, hospital, or at specialized centers may be considered for patients with NYHA Class IV symptoms, life expectancy of 6 months or less, and refractory heart failure after all the options of standard of care are exhausted. Hospices generally provide oral medications and symptomatic management. Some hospices may provide complex treatments such as intravenous inotropes, continuous positive airway pressure (CPAP), etc. Continued participation of the clinician and meticulous management of fluid status are essential to maximize quality of life even after the patient enrolls in hospice.[28]

CONCLUSION

In spite of remarkable advances in understanding the pathophysiology and treatment of heart failure, it continues to be a major global health concern. Heart transplantation is the treatment of choice for carefully selected patients for whom medical therapy is unsuccessful. However, in view of limited availability of organ donors and ever increasing number of patients with advanced heart failure, other advanced therapies such as VADs and inotrope infusions should be explored as bridges to transplantation and offered to patients. Palliative measures, including intermittent or continuous inotropes and referral to hospice care, should be considered in patients with advanced heart failure who do not qualify for heart transplantation and are unresponsive to medical therapy. Most clinical trials in heart failure have focused on symptomatic and refractory heart failure. Further research focusing on understanding the complexity of the onset and progression of heart failure and prevention is essential.

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