Cardiac transplant or rotary blood pump: Contemporary evidence

Stephen Westaby, MS, PhD, FRCS, FECTS, FESC, FACC

Congestive heart failure affects 23 million people worldwide including 7.5 million in North America (670,000 new cases per year) and 7 million in Europe.[1] Inasmuch as systolic left ventricular dysfunction develops in 10% of the population over 65 years, the number of patients with heart failure will double during the next 2 decades. At any time, 10% of patients are categorized as having stage D disease—advanced structural heart disease and symptoms at rest, despite detailed medical and cardiac resynchronization therapy. Twenty percent are younger than 65 years of age, comprising between 100,000 to 150,000 patients for both the United States and Europe.[2]

The population with chronic preterminal heart failure has short wretched lives. In the Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) study, only 8% of the medically treated patients were alive at 2 years and remained housebound with severe breathlessness and fatigue in the interim.[3] A recurrent sentiment is that they would sacrifice some duration of survival for periods of symptomatic relief.[4] With the cardiologist as gatekeeper, cardiac resynchronization therapy is widely used at substantial cost but cannot be regarded as effective in severely debilitated patients (Figure 1). A meta-analysis of 14 trials that randomized resynchronization against medical treatment showed only 59% of the patients in New York Heart Association (NYHA) class IV supported with a device to have borderline symptomatic improvement to NHYA class III with no survival benefit.[5] Boyle and associates[6] compared functional outcomes for patients in NYHA class IV after resynchronization or implantation of a pulsatile left ventricular assist device (LVAD). By 6 months, resynchronized patients achieved only an additional 6 m in the 6-minute walk test and remained in NHYA class III/IV. In contrast, patients with an LVAD improved by 341 m, achieving NYHA class I or II. Notably, the study could not be randomized because 90% of LVAD candidates were bedbound on intravenous inotropes and were unable to walk beforehand. Thus the potential options for those who exhaust maximum medical therapy are palliative care, a lifetime LVAD, or cardiac transplantation. Even in affluent health care systems the vast majority receive only palliative care irrespective of age.[7]

Cardiac transplantation is repeatedly described as the gold standard treatment for severe heart failure. In epidemiologic terms, this is similar to describing a lottery win as the preferred method to gain wealth. On a more optimistic note, recent data from the Fourth INTERMACs Annual Report demonstrate 1- and 2-year rotary LVAD survivals of 80% and 70% in predominantly non–transplant-eligible patients.[8] Particularly favorable survival of 85% at 2 years was recorded for patients up to 70 years without diabetes, renal impairment, or cardiogenic shock. This considerable achievement is placed into context by the much less satisfactory 56% and 33% survivals with the pulsatile HeartMate XVE device (Thoratec Corporation, Pleasanton, Calif) only 5 years before.[9] With improvements in technology, the survival curves for transplantation and mechanical circulatory support are converging. Carefully selected and electively implanted patients can anticipate 5 years of event-free survival as far as out to 7.5 years.[10-12] This situation now calls for prospective randomized trials of cardiac transplantation versus mechanical circulatory support in specific patient groups.[13] In the meantime, the aim of this review is to rationalize the evidence base and indications for these complementary therapies.

WHAT DO WE KNOW ABOUT CARDIAC TRANSPLANTATION?

Essentially restricted to patients less than 65 years without significant comorbidity, fewer than 2200 donor hearts per year are made available in the United States and around 100 in the United Kingdom. The early experience at Stanford University Medical Center between January 1968 and August 1976 demonstrated overall 1- and 2-year survivals of 52% and 43%, together with a 90% return to NYHA class I.[14] In this era, 95% of patients selected but not receiving a transplant died within 6 months of evaluation. Because of these original observations, transplantation has never been tested against alternative treatments in a prospective randomized model. During the past 20 years, substantially improved outcomes have been achieved with drugs and nontransplant heart failure surgery.[15] This has reduced the comparative survival benefit gained by transplantation in some categories of patient.

From Oxford University Hospitals, Oxford, and Institute of Life Sciences, University of Swansea, United Kingdom.

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Address for reprints: Stephen Westaby, MS, PhD, FRCS, FECTS, FESC, FACC, Oxford Heart Center, John Radcliffe Hospital, Department of Cardiothoracic Surgery, Headley Way, Headington, Oxford, Oxfordshire OX3 9DU, United Kingdom (E-mail: Stephen.Westaby@orh.nhs.uk).

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Abbreviations and Acronyms

COMPANION = Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (Investigators)
COPERNICUS = Carvedilol Prospective Randomized Cumulative Survival (Study Group)
CUBS = Clinical Utility Baseline Study (Group)
ESSENTIAL = Studies of Oral Enoximone Therapy in Advanced Heart Failure (Trial)
INTERMACS = Interagency Registry for Mechanically Assisted Circulatory Support
INTrEPID = Investigation of Nontransplant-Eligible Patients Who Are Inotrope Dependent (trial)
LVAD = left ventricular assist device
NYHA = New York Heart Association
REMATCH = Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure
REVIVE-IT = Randomized Evaluation of VAD Intervention before Inotropic Therapy (study)
UNOS = United Network for Organ Sharing

Currently the median posttransplant longevity is 12.2 years with a 1-year survival of around 85%.[16] However, there are twice as many patients listed for transplantation annually as there are donor hearts and approximately 8% die while waiting. Equally, more than 20% of those receiving transplants die within 3 years.[17] Data from the United Network for Organ Sharing (UNOS) currently suggest benefit for hospitalized patients on inotropic and intra-aortic balloon pump or LVAD support (UNOS status I) but question the value of transplantation for ambulatory patients whose condition has yet to deteriorate into critically low cardiac output (UNOS status II).[18] At 89%, the 1-year survival of status II candidates who have not had surgery is equivalent to or exceeds the outcome of transplantation. In 2005, 48% of heart transplant candidates had spent more than 2 years on the waiting list and survival of status I patients approached 70%.[19] These data echo the findings of Deng and coworkers,[20] who showed that status II wait-listed patients who did not receive a donor heart had 3- and 4-year survivals similar to those of patients receiving a transplant. Around 30% of status II patients improve symptomatically and prognostically when managed by a specialist heart failure team. Patients are then considered too well for transplantation if they demonstrate a sustained improvement in peak oxygen uptake of more than 2 mL · kg^{-1} · min^{-1}. Furthermore, Shah and colleagues[21] showed that 1- and 3-year survivals for status II patients removed from the waiting list were 100% and 92%, respectively. Idiopathic dilated cardiomyopathy, the most frequent diagnosis in transplant patients, often showed spontaneous improvement and better prognosis than ischemic cardiomyopathy. In addition, some patients with idiopathic dilated cardiomyopathy respond to mechanical ventricular unloading with reverse remodeling and sustained improvement in left ventricular function.[22]

For status I candidates, predictors of early death (within 2 months) are the need for mechanical ventilation, valvular cardiomyopathy, UNOS status Ia, serum creatinine greater than 1.5 mg/dL, presence of an intra-aortic balloon pump, age greater than 60 years, use of intravenous inotropic drugs, body weight less than 70 kg, and pulmonary capillary wedge pressure less than 20 mm Hg.[23] Without treatment, these patients have a projected mortality varying from imminent to more than 50% at 6 months, whereas transplant survival exceeds 80% at 1 year and is almost 50% at 10 years. Eligibility for transplantation remains dependent on age and comorbidity with direct sequelae of chronic heart failure (pulmonary hypertension and renal impairment) mitigating against suitability.[24]

In the absence of randomized trials, recent comprehensive registry data from UNOS help to define who should and should not receive a transplant. In an analysis of 22,385 patients undergoing transplantation, Kilic and associates[25] found that 42% survived for 10 years or more, but for those who did not reach 10 years, mean survival was 3.7 ± 3.3 years. Clear predictors of transplant longevity were age less than 55 years, white race, younger donor age, and shorter donor heart ischemic time. Diabetes, renal impairment, and the need for preoperative ventilation militated against long-term survival. In a separate report, the same authors reviewed data from 15,960 patients who had received transplants (1998-2008), observing the influence of metabolic risk factors on survival.[26] Preoperative hypertension was found in 40% of patients, obesity in 25%, and diabetes in 21%. Only 40% had none of the 3, whereas 18% had 2 and 4% had all 3 risk factors. Those with all 3 were older (mean age, 55 vs 50 years), more likely to be male, and had significantly higher serum creatinine levels. They were more likely to have ischemic than idiopathic dilated cardiomyopathy and to receive an LVAD (20%) as bridge to transplantation. From multivariate analysis incorporating 22 covariates, each of the 3 factors was found to be a significant predictor for reduced survival.