The Demise of the Heart Transplant

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The complexity of the human heart is essential to life, but for some not without flaw. An aging demographic reflects a longer mean life expectancy, naturally increasing the imminence of a myriad of dire cardiac ailments. Heart disease is the leading cause of morbidity and mortality worldwide, reflecting nearly twice the number of deaths caused by all forms of cancer combined. A frequently sequential endpoint of heart disease is heart failure (often called congestive heart failure), most commonly stemming from dilated cardiomyopathy or ischemic heart disease. An estimated 400,000 new cases of heart failure are recognized each year; heart failure is the principal cause of 40,000 deaths and furthermore a contributing cause of 250,000 deaths annually.

Despite this rise in heart disease epidemiology, cardiac transplantation as a viable therapeutic option has declined in recent years due to donor heart scarcity. Alarmingly, the donor shortage limits heart transplants to a mere 2,500 in the United States annually, grimly quantifying 10-40% of eligible transplant patients who die before a heart becomes available. Thus, it is imperative to restrict heart transplantation to critically ill patients who are not only most debilitated by heart failure, but also most likely to procure optimal benefit from such an option.

A selective criteria filters transplant candidates with exclusive indication defined as “end-stage heart disease not remediable by more conservative measures.” Patients who should be considered are those with poor prognosis and severe symptoms of heart failure (possibly precipitating from either left-sided or right-sided) such as critical orthopnea, persistent shortness of breath and diminished mentation; intractable angina or rhythm disturbances are also direly symptomatic. More infrequent cardiac ailments remediable by transplant may also include sarcoidosis, amyloidosis and cardiac tumors. Contraindications to a waiting list candidate are much broader in an effort to prevent any possible predisposition of the patient to adversity with an allograft. Pathologies contraindicative to transplant may include active systemic infection, active malignancy or history of malignancy with probable recurrence, irreversible pulmonary hypertension, severe peripheral or cerebrovascular disease, or even irreversible dysfunction of another organ including diseases that may limit later prognosis. Variability in the clinical course of heart failure does exist, though, thus criteria is ultimately patient-dependent.

Generic heart failure risk factors can also work against a transplant recipient since cardiac allograft failure can possibly be due to the same reasons that originally caused the native heart to fail. Strongly associated risk factors of heart failure include age, male gender, hypertension, diabetes, obesity, and myocardial infarction; lesser clinical correlations involve sleep apnea and impaired pulmonary function. Pathogenesis of heart failure is most often insidious (cumulative chronic work overload or post myocardial infarction) but can appear suddenly (acute valvular dysfunction or fluid overload, namely, cor pulmonale) as well.

Pioneered in South Africa by Dr. Christiaan Barnard in December 1967 (following the single failure of a premature xenograft attempt in 1964 by Dr. James Hardy), the world’s first human-to-human orthotopic heart transplant (Fig. 1) was successfully performed. Although the first allograft recipient expired just eighteen days postoperative, subsequent operations proved marked advances in prognosis. Of Barnard’s first ten heart transplants, four patients survived greater than one year, two of whom lived for 13 and 23 years, respectively.
transplantation is regarded as the treatment of choice for end-stage heart failure of coronary and non-coronary etiology despite donor shortage. Of the allograft recipients, current prognosis at 1- and 5-year increments demonstrates 83% and 72% survival rates, respectively, with 50% survival at 9.4 years or more. 

Cardiac transplantation does not come without complications, however. Historic aggregate pathologic findings include rejection, infection, immunodeficiency, graft failure and lymphoproliferative disease. These five differentials are considerably the more frequent causes of death involving a heart transplant. Furthermore, allograft patients may not experience angina due to denervation from the surgical procedure, inhibitory to a potential vasculopathy diagnosis.

Of the major complications, allograft rejection is the predominant limitation leading to morbidity and mortality. Rejection occurs when the recipient immune system recognizes the transplanted organ as a foreign object, triggering a cascade of molecular and cellular immune responses. Graft rejection can be either acute or chronic, with acute further categorized into humoral (antibody-mediated) or cellular, and transpiring anywhere from days to years following surgical transplantation.

The endomyocardial biopsy (EMB) is the clinical gold standard for screening acute graft rejection, as it provides critical information on the grading of pathologic changes and response to therapy. The histologic classification used to evaluate biopsies is referred to as the ‘Banff schema,’ which provides specific morphological criteria. According to the Banff schema for cardiac allograft rejection, the acute humoral mechanism is associated with vasculitis,
hemorrhage and neutrophilic infiltrate. The cellular mechanism, however, is recognized by an interstitial mononuclear cell infiltrate (Fig. 2) with associated edema and myocyte encroachment; chronic rejection is accompanied by vascular changes and interstitial fibrosis. Recurrent episodes of rejection can lead to tissue damage, myocardial necrosis and eventually graft loss. Thus, precise evaluation of rejection status according to the Banff schema is imperative for proper cardiac graft management.

Cellular rejection is adequately evaluated with light microscopy, while humoral is best assessed by ancillary immunofluorescence (IF) or immunohistochemistry (IHC). IF conveys frozen sections showing deposits of fibrinogen, immunoglobulin (Ig) G or IgM, or the complement components C1q and C4d). IHC involves formalin-fixed, paraffin-embedded tissue detecting IgG or IgM markers. Literature, however, suggests IHC is not entirely reliable as fixation can precipitate serum proteins in tissue, causing false positives. Even so, strong panel reactive antibody markers are further indicative of humoral rejection.

EMB showing acute rejection can change clinical course in the antemortem diagnosis by altering therapy; cellular rejection is remedied with antirejection medication, but humoral rejection is a dire emergency treated with plasmapheresis and intravenous immunoglobulin. EMB can also change clinical outcome: protocol requires 4-6 pieces of tissue biopsied to achieve a lower false-negative rate proportional to a higher number of fragments biopsied - a flaw surfacing from conservative biopsy sizes and limited sampling. Quilty Effect (Fig. 3) is also a recognized cause of discrepancy in EMB grading, as it can easily be mistaken as cellular rejection.
Sepsis following infection is one of the most common causes of death within 30 days postoperative. It can result from viral, bacterial or fungal pathogens that follow a sequence of infection influenced by epidemiologic exposure and immunosuppression. These infections tend to seed at the sutures fusing the native and donor cardiac tissue, forming a mycotic aneurysm with the risk of rupture. Conventional nosocomial infections are seen within the first month and include Herpes Simplex Virus viremia, the onset of hepatitis B or C, and Candida fungemia. The time span between the first and sixth month postoperative is disposed to bacteremia, as well as heightened susceptibility to unconventional and opportunistic infections. Community-acquired or persistent infections tend to be elicited greater than 6 months after transplantation.

The most important pathogen affecting transplant recipients is Cytomegalovirus (CMV) due to its latency and cell association. Such activation can be induced by the following factors present in transplant recipients: allogeneic reactions (cells or tissue that are immunologically incompatible); antilymphocyte-antibody therapy with cytotoxic drugs; systemic infection or inflammation. CMV tends to cause rejection, and is further associated with an amplified risk of lymphoproliferative disorder by a factor of 7 to 10. Aside from CMV, other infections of particular importance in transplant recipients include Epstein-Barr Virus (EBV) and central nervous system infections.

Immunosuppression is another limitation to cardiac transplantation. Administration of immunosuppressive drugs is imperative for transplant patients' medication regimen, but acquiring that balance is crucial. Dosage increase can be nephrotoxic and can result in immunodeficiency, while opportunistic infections can emerge as a complication from such...
compounded therapy combined with viremia. Conversely, insufficient dosage can lead to cellular or humoral rejection. An immune-compromised transplant recipient will lack the capacity for a normal inflammatory response to pathogens or tissue damage, further jeopardizing the patient to a host of secondary conditions.

Allograft failure is among the most common causes of late death not only within 1 month postoperative, but also extending to 1 year. Graft failure stems from chronic transplant dysfunction (CTD), a gradual deterioration of graft function. The most common presentations of CTD in heart transplant recipients involve acute infarction, arrhythmias, congestive heart failure and sudden death. Over time, cardiac allograft failure can possibly be due to the same reasons that originally caused the native heart to fail. The etiology of CTD, however, remains indistinct aside from two working hypotheses suggesting that CTD is the result of either ischemia or a progressive host alloimmune response. Association with recurrent rejection and ischemic injury may lead to irreversible graft damage and consequent failure.

Lymphoproliferative disease poses as a fifth differential in cardiac transplant recipients. Perhaps one of the strongest factors is that of viremia involving EBV, with documented active replication in greater than 80% of patients receiving antilymphocyte-antibody therapy. EBV plays a critical role in the pathogenesis of lymphoproliferative disease (usually B-cell) due to its reactivation from latency. The degree of disease severity ranges from benign polyclonal to a particularly malignant resistant monoclonal lymphoma. Aside from EBV, additional risk factors to lymphoproliferative disease include preceding CMV infection as well as elevated oropharyngeal viral replication levels.

Pathologic findings, whether gross or microscopic, may indicate a variety of complications arising from cardiac transplantation. Rejection, infection, immunodeficiency, graft failure and lymphoproliferative disease all have the propensity to cause death in the cardiac allograft recipient more frequently than other differentials. Despite the complexity of donor tissue compatibility to that of native coupled with the daunting inverse of donor shortage to heart disease epidemiology, cardiac transplantation remains the present treatment of choice for end-stage heart failure. It is imperative, though, to establish rational yet distinctly selective criteria for the allocation of heart allografts. Nonetheless, such transplantation pathology illustrates consequent demise of a heart transplant.

References:


