Is pre-transplant vascular disease a risk factor for mortality and morbidity after heart transplantation?☆

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Abstract

Background: Severe vascular disease is a relative contraindication to heart transplantation (HTx). We addressed the effect of vascular disease on HTx outcomes. Methods: This is a nonconcurrent cohort study of 402 patients who received HTx at our institution between 1985 and 2004. Pre-transplant vascular evaluation included carotid, lower extremity, and renal artery duplex studies, and CT angiogram when indicated. Patients with severe and nontreatable vascular disease were excluded. Patients were divided into Group 1: those with pre-transplant vasculopathy, and Group 2: those without pre-transplant vasculopathy. Group 1 had 24 patients with 25 vascular lesions: 1 aortic dissection, 2 abdominal aortic aneurysm (AAA)’s, 5 carotid artery stenoses, 1 renal artery stenosis, and 16 peripheral vascular lesions. Interventions were performed to 15 lesions prior to HTx and to 2 lesions after HTx. Results: Median follow-up was 5.5 years. Group 1 had higher incidence of ischemic cardiomyopathy (p < 0.001), hypertension (p = 0.028), chronic obstructive pulmonary disease (COPD) (p = 0.004), and smoking history (p < 0.001). There were no differences in sex, hyperlipidemia, diabetes, stroke, or renal dysfunction. Multivariate analysis revealed odds of post-transplant death in Group 1 was 1.4 (95% CI: 0.48—4.1, p = 0.54) times greater than that in Group 2. Cox proportional hazards model for survival showed a 50% increase in the hazard of death in patients with pre-transplant vasculopathy, but without statistical significance. Group 1 had higher incidence of post-transplant stroke (p = 0.001) but no difference in allograft coronary atherosclerosis. Conclusions: Pre-transplant vascular disease seems to have negative effect on outcomes after HTx. Larger scale study is needed for further evaluation.

Keywords: Heart transplantation; Vascular disease; Mortality; CVA; Allograft coronary artery disease

1. Introduction

In the current environment of limited donor availability, establishing appropriate cardiac recipient selection criteria is very important to identify the transplant candidates with the greatest chance of transplant success [1]. The efforts to define recipient selection criteria were summarized and published in 1995 as ‘A Statement for Health Professionals From the Committee on Heart Failure and Cardiac Transplantation of the Council on Clinical Cardiology’ by the American Heart Association [2]. In the statement, vascular disease was described as one of the contraindications to heart transplantation (HTx). It was, however, also stated that the wide spectrum of vascular disease makes it difficult to establish specific exclusion criteria for HTx in patients with vascular disease. It was recommended that, in such patients, the physician consider (1) the possibility that stress and hemodynamic changes associated with HTx may precipitate an acute thrombotic or embolic event; (2) the need for postoperative intra-aortic balloon support if graft function is poor in the immediate postoperative period; (3) the effect of corticosteroids on progression of atherosclerotic vascular disease; (4) the effects of prior cerebrovascular events on the ability to follow the pharmacologic and rehabilitative regimen after HTx; and (5) the feasibility of revascularization if symptoms due to peripheral or cerebrovascular disease worsen after HTx.

Updated review of selection criteria was recently published by Cimato and Jessup [3] in 2002. This summary described the most common recipient-dependent risk factors for mortality after HTx as PVR >3 Wood units, mechanical circulatory support (either with LVAD or intra-aortic balloon pump), advanced age, female gender, increased serum creatinine...
concentration, ischemic cardiomyopathy, previous sternotomy, and liver failure. The impact of vascular disease on transplant outcome was not mentioned in this review article. However, severe peripheral vascular disease is recognized as a major comorbidity that might preclude eligibility. The basis for this practice stems from the belief that vascular disease impacts negatively on both survival and quality of life, and that the risk factors of vascular disease increase the risk for the development of the allograft coronary artery disease [4]. Given these practices, we set out to further explore the relationship between vascular disease and outcome following HTx.

2. Materials and methods

2.1. Study design

This is a single-centre, retrospective cohort study where the variable of interest is vascular disease and outcomes of interest are mortality, stroke, and allograft coronary artery disease. ‘Vascular disease’ included disease in carotid, lower extremity, renal artery, and aorta.

2.2. Data abstraction

The medical records of subjects undergoing transplantation at the University of Washington over the interval November 1985 to August 2004 were reviewed. We abstracted data pertaining to risk factors for adverse outcomes including age, gender, hypertension, hyperlipidemia, diabetes mellitus, and tobacco use, all of which are commonly cited as predisposing risks for the development of atherosclerosis. In addition, the presence of chronic obstructive pulmonary disease (COPD), renal dysfunction, alcohol abuse, cerebrovascular accident (CVA), and previous cardiac surgery were recorded.

2.3. Pre-transplant surveillance of vascular disease

Routine pre-transplant vascular evaluation included duplex ultrasound of carotid, lower extremity, renal artery, and abdominal aorta. CT angiogram of the aorta was added when clinically indicated. The severity of pre-transplant vasculopathy was scaled into three categories: severe and non-treatable, less severe (severe but treatable, moderate, and mild), and no vascular lesions. Patients were classified into these three categories on the basis of the clinical picture and the results of these surveillance studies. Severe and non-treatable vascular lesions were defined as morbidly symptomatic and anatomically significant lesions, which were not amenable for any endovascular or surgical revascularization therapy. Patients with these vascular lesions were considered to have a contraindication to HTx. Thus, this analysis focuses on a comparison of patients with less severe (severe but treatable, moderate, and mild) vascular disease (Group 1) and those with no vascular lesions (Group 2).

2.4. Follow-up

The subjects in this study were followed up until September 30, 2004. The majority of recipients have received follow-up at the University of Washington, with a relatively small number followed up at institutions with whom a close relationship existed such that both post-transplant care and follow-up are similar.

2.5. Outcomes of interest

The outcome measurements of the current study included death, development of CVA, and/or allograft coronary artery disease after HTx. The diagnosis of post-transplant CVA was established when recipients were found to have neurological deficit and/or radiological evidence of CVA either with ischemic and/or hemorrhagic stroke. No routine surveillance imaging study was performed.

Surveillance of allograft coronary artery disease was performed with dobutamine stress echocardiogram, stress cardiac nuclear perfusion scan, and/or coronary angiogram. A definitive diagnosis was made by coronary angiogram.

Development of new vascular disease after the transplantation was also compared between the groups.

2.6. Statistical methods and multivariate analyses

Means and standard deviations were calculated for continuous variables, and absolute and relative frequencies were measured for discrete variables. Differences between groups were examined for statistical significance by the t-test in the case of continuous variables (age) and by χ² analysis in the case of discrete variables. Poisson regression was used to evaluate differences in outcomes (mortality, development of CVA, and/or allograft coronary artery disease) after adjusting for the confounders. Confounding variables were chosen for inclusion in the model by using a change in estimates approach. Briefly, if the addition of a variable to the model changed the estimate of the main effect by greater than 10%, then the variable was considered an important confounder and was kept in the model [5]. To explore the relationship between risk factors and time to death while accounting for follow-up time, we used a Cox proportional hazards model with a similar approach to the management of potential confounders. The effect of vascular disease on outcomes is presented as either relative rates or relative increases in the risk (or hazard in the case of survival analysis), along with its 95% confidence intervals.

3. Results

3.1. Patient population

A total of 409 HTx’s were performed in 402 recipients over the interval of the study. Patients were followed up for a median of 5.5 years (maximum 18 years).

Group 1 included a total of 24 patients (6.0% of all recipients) with 25 pre-transplant vascular lesions. Fifteen of 25 lesions were treated with interventions prior to HTx. Three patients had aortic disease. One patient with an ascending aortic dissection and another with an abdominal aortic aneurysm (AAA) underwent repair prior to the HTx. Another patient with a 4.9 cm AAA that did not undergo repair ruptured 3 months after HTx. Carotid artery stenosis of
more than 50% was detected in five patients, two of whom underwent carotid endarterectomy prior to HTx. One patient had a renal artery stent placed for renal artery hypertension.

Peripheral vascular disease (PVD), defined as arterial disease in extremities, was detected in 16 patients. Twelve of PVD’s were atherosclerotic peripheral vascular lesions. Seven patients with atherosclerotic PVD underwent bypass surgery and one patient underwent peripheral angioplasty with a stent placement prior to the HTx. One patient had thromboembolism at the femoral artery, which was treated with thrombectomy and fasciotomy. One patient had Berger’s disease and underwent femorofemoral bypass surgery. Two patients suffered from traumatic peripheral vascular complications: one had common femoral artery stenosis from the placement of an intra-aortic balloon pump requiring a patch repair at the time of the HTx, and the other had a blunt trauma compromising vascular system resulting in below knee amputation.

Group 2 consisted of 384 recipients who were found to have no vascular disease in the pre-transplant screening.

3.2. Patient demographics

Table 1 shows the pre-transplant demographics of the two groups. Patients with vascular disease were significantly older, had a higher prevalence of tobacco and alcohol use, and were more likely to have hypertension, COPD, or prior cardiac surgery. Although hyperlipidemia was over-represented in Group 1, the difference in proportions did not achieve statistical significance.

3.3. Effect of vascular disease on mortality

There were 5 (20.8%) deaths in Group 1 compared to 94 (24.5%) in Group 2 ($p = 0.661$). The only potential confounders identified were age, history of smoking, alcohol abuse, hypertension, hyperlipidemia, and previous cardiac operation. After adjustment for these confounders, the odds of death in Group 1 was $1.4$ (95% CI: 0.47—4.1) times greater than Group 2 (Table 2). The median survival of Group 1 patients was 4.9 years, and that of Group 2 was 5.6 years. The Kaplan–Meier survival curve showed no significant difference between the groups. Using Cox proportional hazards regression, the hazard ratio for death was 1.5 (95% CI: 0.59–3.89) times higher in patients in Group 1 compared to those in Group 2 (Fig. 1).

3.4. Effect of vascular disease on post-transplant morbidity

Four patients in Group 1 suffered CVA after HTx in contrast to 12 patients in Group 2 (16.7% vs 3.1%, $p = 0.001$). Three of CVA’s in Group 1 occurred during the same admission as the HTx. To determine the adjusted relative odds of stroke in Group 1 versus Group 2, we adjusted for age, history of smoking, hypertension, and previous cardiac surgery in a logistic regression model. Using this approach, the adjusted odds ratio for stroke in Group 1 versus Group 2 was 6.3 (95% CI: 1.7—28).

The diagnosis of allograft coronary artery disease was made in 6 patients in Group 1 and in 74 patients in Group 2 (25% vs 19%, $p = 0.49$). Using a similar approach, the adjusted odds ratio for allograft cad was 1.5 times greater (95% CI: 0.53—4.08) in Group 1 versus Group 2.

3.5. Development of new vascular disease after heart transplantation

Prevalence of development of a new vascular lesion was compared between the groups. Patients in Group 1 developed...
a total of 8 new lesions (33% of patients: 2 of thoracic aortic disease, 4 of AAA, 1 of renal artery stenosis, and 1 of PVD) as compared to a total of 27 patients in Group 2 (7.0% of patients: 2 of carotid artery stenosis, 2 of thoracic aortic disease, 8 of AAA, 2 of renal artery stenosis, and 13 of PVD). These numbers did not include the two patients in Group 1, who underwent vascular intervention due to progression of pre-transplant vascular disease.

4. Discussion

Presence of severe vascular disease has been repeatedly listed as one of the contraindications to HTx in the published recipient selection criteria. However, there exist very limited reports which addressed the relationship between HTx outcomes and vascular disease. Several studies reported the development of vascular disease following HTx [6,7]. The largest series regarding this subject was a report from Columbia-Presbyterian Hospital by Benvenisty et al. [8]. Among their 520 recipients, 30 patients developed systemic vascular disease following HTx (5.8%). These reports, however, did not provide any information on the selection of HTx recipients with systemic vascular disease.

Julia et al. [9] reviewed patients who underwent HTx in their unit between 1984 and 1991, and found 17 patients (8.5%), who were diagnosed prior to HTx, to have systemic vascular disease. Their pre-transplant vascular workup consisted of duplex scanning of the cervical vessels, the aorta, and the lower limb arteries. This was one of the earliest studies addressing pre-transplant vascular disease and HTx, but it was only to advocate elevated cholesterol level as a risk factor for presence of vascular lesions in HTx recipients without assessing the effect of vascular disease on HTx outcomes. Ganesh et al. [10] recently reported risk factors for post-transplant mortality from the United Kingdom Cardiac Transplant Audit database. The database included 1254 adult recipients, and Cox analysis identified recipient’s PVD (definition not provided), along with donor age, organ ischemia time, recipient creatinine clearance, recipient diagnosis, ventilation, diabetes, and donor—recipient size mismatch, as a risk factor for early, late, or overall mortality \((p < 0.10)\). Hazard ratios of PVD for early, late, and overall mortality were 3.30 (95% CI: 1.50—7.27, \(p = 0.03\)), 0.53 (95% CI: 0.07—3.81, \(p = 0.5\)), and 1.93 (95% CI: 0.94—3.95, \(p = NA\)) respectively. The focus of this study was, however, to address the effect of donor cause of death on post-transplant survival, and therefore, the detailed information on PVD was not reported.

The present study was one of the first studies that addressed the direct impact of recipient vascular disease on HTx outcomes. In our series, 6% of our recipients had vascular disease diagnosed prior to the HTx, and 60% of the vascular lesions were treated with intervention before the HTx. The demographics of the recipients who had systemic vascular disease were significantly different from those without. They were older, had ischemic cardiomyopathy as a cause of heart failure more commonly, and had more frequent history of smoking, hypertension, COPD, and prior heart operations. These findings support the existing concern that vasculo-pathic recipients are more likely to fail post-HTx. More importantly, we found that the recipient systemic vascular disease was a significant risk factor for post-transplant CVA. This was still significant after adjusting the confounding variables suggesting that vascular disease itself was an independent risk factor for CVA. Its presence was also associated with somewhat higher risk of mortality and allograft coronary artery disease, although this was not statistically significant.

The strong relationship between development of AAA and HTx has been well described in the literature [11,12]. It is also well known that patients with PVD have a higher incidence of AAA [13,14]. In our series, six recipients in the cohort group developed AAA including two cases diagnosed before HTx (25% of the cohort patients). The incidence of AAA in nonvasculopathic recipients was 2.1% (eight cases in Group 2). The combination of HTx and pre-transplant vascular disease might have exacerbated the predisposing risk of development of post-transplant AAA.

Our study has several limitations. First, the number of the cohort was small. Our series included a total of only 23 recipients with vascular disease among 402 recipients. The actual number of outcomes of interest in the cohort group was small. This might explain the reason why the detrimental effect of pre-transplant vascular disease on HTx did not reach statistical significance in our study.

Second, our current practice does not have objective algorism to classify the severity of the vascular disease of the transplant candidates. We determined the severity based on the results of the vascular studies as well as on patient’s clinical picture. The severe vascular lesions not amenable to interventional treatment were considered contraindication to the HTx, and transplant candidates with these lesions were excluded from the transplant waiting list. The lack of precise definition of the severity makes the interpretation of the current study more difficult and confusing.

In conclusion, this study was a first attempt to evaluate the effect of vascular disease on HTx. It showed that recipient vascular disease was associated with higher incidence of risk factors, and appeared to result in worse outcomes. These results provide clinical information, and support the current practice of recipient selection based on the severity of the vascular disease. It is, however, too premature to retrieve a solid conclusion from the study due to small number of patients as well as lack of objective definition of the severity of vascular disease. A larger scale study using multicenter or nationwide database is necessary to further evaluate this important subject.

References
