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Donor left ventricular hypertrophy increases risk for early graft failure

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Abstract A review of factors contributing to early mortality after cardiac transplantation revealed that up to 25 % of deaths were due to primary graft dysfunction unrelated to rejection or infection. In light of this finding, evaluation of a donor heart with regard to its suitability for transplantation takes on added importance. In an effort to screen the suitability of donor hearts in the region covered by the Northwest Organ Procurement Agency (USA), all donors are evaluated by two-dimensional transthoracic echocardiography as part of the initial evaluation. A total of 110 donor echocardiograms were reviewed and an attempt was made to correlate the 30-day outcome with the parameters measured. An unexpected finding was that the presence of left ventricular hypertrophy in the donor heart was associated with an increase in the incidence of donor heart dysfunction compared with donors with normal echocardiographic profiles (33 % vs 3 %, $P = 0.007$).

Key words Left ventricular hypertrophy, heart transplantation · Heart transplanation, left ventricular hypertrophy · Graft failure, left ventricular hypertrophy · Ultrasound, left ventricular hypertrophy, heart transplantation

Introduction

The importance of donor and recipient characteristics in determining the successful outcome of cardiac transplantation was soon recognized following the initiation of the procedure in 1967. As a result, strict donor and recipient selection criteria were established to minimize morbidity and mortality post-transplantation [1, 14]. As more clinical experience has been obtained, myocardial preservation has improved [6], and new pharmacologic alternatives are now possible (i.e., immunosuppressive and vasoactive drugs). A liberalization of recipient selection criteria has ensued such that recipients who previously would have been deemed unsuitable can now often be successfully transplanted [10].

The limiting factor to increasing the number of transplants annually remains the chronic shortage of donor organs. It has been estimated that approximately 20000–40000 recipients would benefit annually from cardiac transplantation, but only 2000 suitable donors are presently available [8]. Because of this donor shortage, every effort must be made to utilize all referred donor hearts without jeopardizing recipient outcome. In an effort to decrease this imbalance, a liberalization of donor selection criteria [19, 20, 25] has been used (e.g., older donors, donors with coronary artery disease, donors with a history of cardiopulmonary resuscitation, donor hearts with longer cold ischemic times, etc.).

The importance of donor heart function for the successful outcome of cardiac transplantation is becoming more and more evident. An ever-increasing number of centers have begun to use echocardiography as part of routine screening measures to evaluate donor hearts [12, 15]. In our region, served by the Northwest Organ Procurement Agency, all prospective cardiac donors (irrespective of age) have a two-dimensional transthoracic echocardiogram performed as part of the donor workup to evaluate ventricular function, global and regional wall motion, and valvular abnormalities. If patients are on high-dose inotropes at the time of initial evaluation, the echocardiogram is repeated after inotropes have been weaned to a safe range (dopamine or dobutamine to less than 5 μg/kg per minute). The present study is a retrospective study that attempts to correlate 30-day recipient outcome with findings on donor echocardiography.

Material and methods

A total of 110 transthoracic two-dimensional echocardiograms of donors who subsequently underwent cardiac transplantation in the region covered by the Northwest Organ Procurement Agency from January 1990 to September 1992 were reviewed. An attempt was made to correlate findings on donor echocardiography with 30-day recipient mortality. This study does not include the echocardiographic results of donors who were not eventually transplanted.

Each echocardiogram was performed at the center where the donor was being evaluated. The findings were reviewed by a cardiologist at that hospital and discussed in all cases with the cardiologist at the recipient hospital before any decision was made as to whether to proceed further with procurement. Parameters evaluated included chamber size (atrial and ventricular), left and right ventricular wall thickness, valvular abnormalities (function and structure), and wall motion abnormalities (localized and generalized). A written record of the echocardiographic data was used to generate the analysis we present.

Left ventricular hypertrophy (LVH) was said to be present if the left ventricular wall during diastole measured more than 11 mm [9, 18]. Thirty-day recipient outcome was correlated with donor echocardiographic findings.

Fischer's exact test was used to calculate significance. A P value below 0.05 was considered significant.

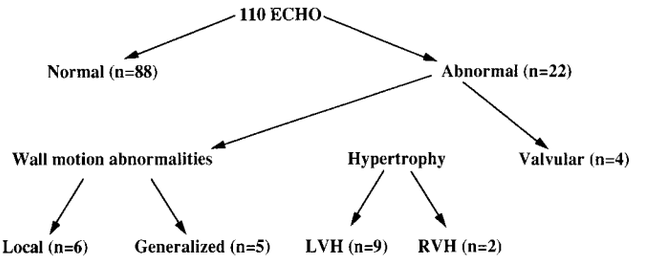

Fig. 1 Summary of donor echocardiographic findings for all 110 patients

Table 1 Results (*LVH* left ventricular hypertrophy, *RVH* right ventricular hypertrophy)

ECHO findings	Total (n = 110)	30-Day failure	Significance (Fischer's exact test)
Normal	88	3 (3%)	
Local wall motion abnormalities	6	1 (17%)	P = 0.20
Generalized wall motion abnormalities	5	0	
Myxomatous valve	4	0	
LVH	9	3 (33%)	P = 0.0007
RVH	2	0	

Results

The overall findings are summarized in Fig. 1. Eighty-eight donor hearts had no echocardiographic abnormalities. There were 11 donors who had echocardiographic evidence of wall motion abnormalities, 6 localized and 5 generalized. The presence of such abnormalities in this study did not correlate with a poor outcome (P = 0.20, Table 1). However, the numbers are small and, hence, a type II error cannot be excluded. Furthermore, the number of donors who had such severe wall motion abnormalities that they were not even considered as potential candidates for transplantation were not included. Nine patients had echocardiographic evidence of LVH. Recipients of three of these hearts had severe early graft dysfunction, resulting in death in two patients on postoperative days 6 and 16. The third patient could not be weaned off cardiopulmonary bypass and required intraoperative placement on biventricular (centrifugal) support. He was successfully retransplanted the following day (Table 2). Analysis of all echocardiographic characteristics revealed that the presence of LVH in the donor was associated with a higher incidence of early (within 30 days) graft dysfunction (P = 0.007; Table 1). Table 3 outlines the characteristics of the nine donors who had evidence of LVH on echocardiography. The six patients who survived did not re-

Table 2 30-Day graft failure (*LVH* left ventricular hypertrophy)

Patient	ECHO	Time of failure	Outcome	Cause of death/re-tx	Cold ischemic time (min)	Cause of donor death/age
1	LVH	16 days	Death	Low CO	220	Gunshot wound to the head
2	LVH & Hypokinesis	6 days	Death	Low CO	445	
3	LVH	Intra-operative	Re-tx	Low CO	90	

Table 3 LVH Patient data

Date/Place	Age/ gender	Race	Donor inotropes	Cause of death	Recipient outcome	Method of procurement
4/90 Oregon	44/F	Caucasian	Dopa 6 mg/kg per minute	Cerebral hemorrhage	Alive and well	Crystalloid cardioplegia
10/90 California	32/M	Caucasian	Dopa 8–13 mg/kg per minute	Gunshot wound to head	Died	Crystalloid cardioplegia
12/91 Washington	50/F	Caucasian	Dopa 4 mg/kg per minute	Subarachnoid hemorrhage	Alive and well	Crystalloid cardioplegia
4/92 Washington	44/M	Caucasian	Dopa 10 mg/kg per minute	Intracerebral bleed	"Stone heart" re-tx	Crystalloid cardioplegia
5/92 Utah	45/F	Caucasian	Dopa 15 mg/kg per minute	Closed head injury	Alive and well	Crystalloid cardioplegia
5/92	43/F	Caucasian	Dopa 10 mg/kg per minute	Gunshot wound to head	Alive and well	Crystalloid cardioplegia
7/90 Oregon	30/M	Caucasian	Dopa 4 mg/kg per minute	Gunshot wound	Alive and well	Crystalloid cardioplegia
4/90 Washington	40/F	Caucasian	Dopa 2 mg/kg per minute	Subarachnoid hemorrhage	Alive and well	Crystalloid cardioplegia
12/91 Washington	55/M	Caucasian	Dopa 5 min/kg per minute	Subarachnoid hemorrhage	Died	Crystalloid cardioplegia

quire high doses of inotropic support before they could be weaned from bypass.

The initial pre-procurement echocardiogram of the donor heart obtained for patient number 3 is shown in Fig. 2. Because of the inability to wean the recipient off cardiopulmonary bypass, biventricular support devices were placed. A transesophageal echocardiogram done postoperatively showed severe systolic dysfunction with severe LVH increasing from 15 mm (Fig. 2) preoperatively to 20 mm post-transplantation (Fig. 3). Histological evaluation of the failed original allograft, removed at the time of retransplantation, demonstrated the presence of edema and extensive left ventricular subendocardial necrosis.

Discussion

With improvements in immunosuppression and the development of newer antiviral agents, the incidence of, and morbidity and mortality from, acute rejection and infectious complications has decreased. However, there is still approximately 10% hospital mortality associated with cardiac transplantation, with up to 25% of these deaths being due to primary graft dysfunction [5, 11]. A number of nonimmunological, recipient-related factors (e.g., pulmonary hypertension) and donor-related factors (e.g., prolonged cold ischemic times) are felt to play a contributing role [3, 23].

Our study suggests that the presence of LVH in the donor heart increases the incidence of early graft dysfunction. What reasons could there be for this? It is known that the region of the heart most susceptible to ischemic injury is the subendocardium [24]. This is particularly so in the presence of LVH. Failure to adequately protect the hypertrophied left ventricle is known to result in extensive subendocardial hemorrhage, as was noted in the early days of aortic valve replacement for aortic stenosis.

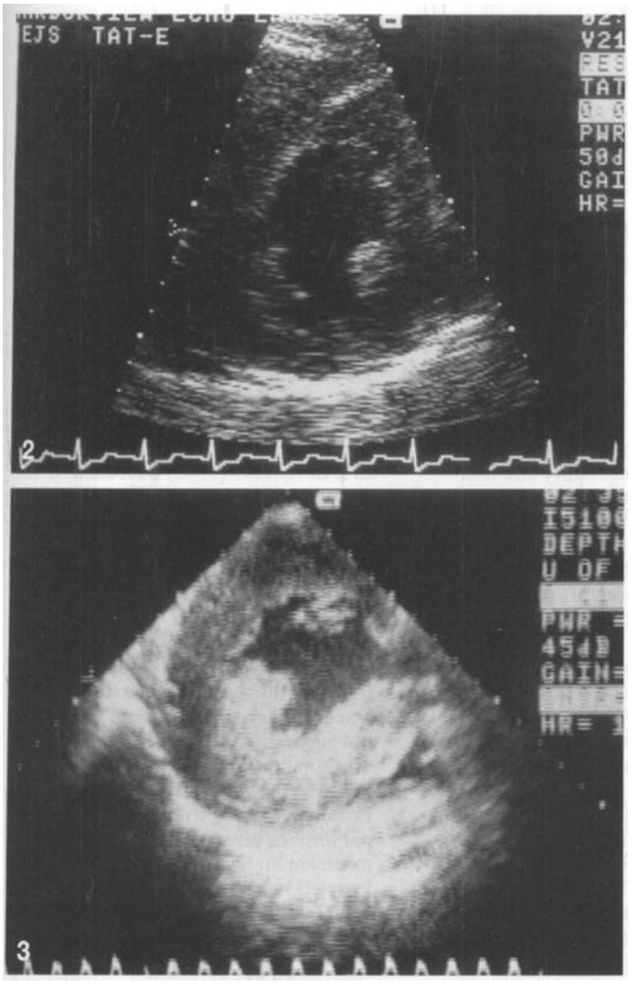

Fig. 2 Parasternal short axis view of the donor left ventricle taken prior to explantation. There is concentric left ventricular hypertrophy (15 mm)

Fig. 3 Short axis view of the donor left ventricle from a transesophageal echocardiographic study obtained 1 day post-transplantation. The donor heart now has severe left ventricular hypertrophy (20 mm) with a marked decrease in the end diastolic diameter. At autopsy, the severe left ventricular hypertrophy was due to interstitial edema and subendocardial hemorrhage

In the present study, the presence of extensive left ventricular subendocardial necrosis was clearly evident at autopsy in patient number 3 (Fig. 3) and supports the concept of ischemia/reperfusion injury of the thickened ventricle as playing a role in the etiology of early graft dysfunction in donors with LVH. The principles of myocardial protection are of particular importance in the arena of cardiac transplantation [23]. Most centers utilize hypothermic, crystalloid hyperkalemic solutions administered antegrade via the ascending aorta to rapidly arrest and cool the donor heart, followed by immersion in cold crystalloid solutions for the duration of transport. Increasing reports suggest that University of Wisconsin solution may have a beneficial role to play in cardiac transplantation, particularly when prolonged ischemic times in excess of 4 h are required [3, 9] for transportation.

In donors with known LVH, it is presently not known whether additional measures to further enhance myocardial protection (e.g., antegrade plus retrograde administration of cardioplegia) should be used to ensure that all layers of the heart are rapidly cooled. Furthermore, consideration should be given to implement measures to decrease the extent of reperfusion injury, which is known to exacerbate any underlying preservation-related injury, e.g., use of free radical scavengers and the administration of terminal warm blood cardioplegia prior to releasing the aortic crossclamp [17, 24].

Another potential cause of early allograft dysfunction includes neurologically mediated myocardial injury in the donor prior to procurement. The association between cardiac dysfunction and intracranial hemorrhage is well established. A number of studies have reported the association between subarachnoid hemorrhage and subendocardial necrosis [2, 4, 7]. In this study, the incidence of early graft dysfunction did not correlate with the etiology of death of the donor.

Immunological mechanisms could also be responsible for allograft dysfunction following implantation. In the present study, the T-cell crossmatches were negative for all patients transplanted with LVH hearts. Furthermore, there was no histological evidence of rejection in the allografts examined upon removal.

Should all donors with evidence of LVH on echocardiography be excluded from consideration as potential donors? This absolute recommendation cannot be made until a larger number of donor echocardiograms are analyzed to determine if there is a degree of hypertrophy that markedly increases the risk of early graft failure. It is known that in healthy, young athletes the upper limit of physiologic hypertrophy is 16 mm [21]. Thus, using a donor heart from a young athlete with physiologic LVH may not have the same prognostic importance as a heart from a 45-year-old with an intracranial bleed and a history of hypertension and pathological LVH. Clearly, not every recipient who receives a heart with evidence of LVH fares poorly. Indeed, there is evidence that regression of LVH in a transplanted heart can occur [16]. However, until we are able to identify donor hearts that have a high chance of early dysfunction, caution needs to be exercised in accepting such hearts for routine transplantation.

The limitations of this study include the facts that: (1) it is a retrospective study, (2) not all echocardiograms were reviewed by a single cardiologist, and (3) this data does not allow us to differentiate whether physiologic

hypertrophy (i. e., athletic hearts) has the same prognostic significance as pathological hypertrophy.

In sum, this retrospective study suggests that donor hearts with echocardiographic evidence of LVH have a markedly higher risk of early graft failure than those without. We encourage other centers to review their own results regarding the outcome of implantation of donor hearts with echocardiographic evidence of LVH to see if these results can be generalized. Until further collaborating evidence is available, we advise caution in the acceptance of such donor hearts for transplantation.

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