The Clinical Utility of Radionuclide Ventriculography in Cardiac Transplantation

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To assess ventricular function in patients who have undergone cardiac transplantation, 247 radionuclide ventriculograms were performed on 94 patients. During the first three days after transplantation, 19% demonstrated left ventricular dysfunction and 41% showed isolated right ventricular dysfunction. In 95 cases, radionuclide ventriculography was performed within 24 hr of myocardial biopsy. A reduction in left ventricular ejection fraction to <50% was significantly more common with moderate-severe rejection than with mild rejection. In six instances in which there was discordance between ventriculography and biopsy, radionuclide ventriculography proved particularly useful: three cases showed severe left ventricular dysfunction despite only mild rejection by biopsy, and three cases with ventricular dysfunction from rejection were missed by the initial biopsy. Thus, radionuclide ventriculography can provide functional data in transplant patients that is complementary to myocardial biopsies since biopsy grade is a poor predictor of left ventricular function and biopsy can miss significant rejection.

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The major cause of left ventricular dysfunction in cardiac transplant recipients is acute rejection. Many noninvasive techniques for the diagnosis of rejection have been studied but these have not been accurate enough to replace the endomyocardial biopsy (*1–8*). However, the biopsy has significant limitations for the diagnosis and grading of rejection (*9*, *10*). The additional functional information provided by radionuclide ventriculography may have an important impact on the management of the patient with acute transplant rejection.

Radionuclide ventriculography may identify patients who have abnormal left ventricular function in the immediate post-transplant period due to ischemia from preservation and surgical trauma (*11*). Isolated right ventricular dysfunction, commonly seen in the first postoperative week, may also be detected (*12*). In addition, radionuclide ventriculography has the potential to evaluate the functional effects of graft atherosclerosis which may become manifest as silent ischemia or infarction.

Radionuclide ventriculography, however, usually demonstrates normal left ventricular function in patients with mild rejection (*13–16*), thus, leading to the widespread impression that this scintigraphic test is of little value in transplant patients. Because our clinical impression is that radionuclide ventriculography frequently plays an important role in patient management, we undertook a retrospective evaluation of our experience. The frequency of the various anomalies often seen in the normally functioning orthotopic cardiac graft was determined. We evaluated the incidence of left and right ventricular dysfunction in the first several days after transplantation, and its subsequent course. Serial examinations were correlated with biopsy evidence of rejection to assess associated changes in ventricular function.

MATERIALS AND METHODS

Study Population

We studied 94 patients (96 hearts; 2 patients had retransplantation) who underwent orthotopic cardiac transplantation at Washington University Medical Center from January 1985 to November 1988 (*17*). All patients had endomyocardial biopsies at regular intervals, and each patient had at least one radionuclide ventriculogram (total 247 radionuclide studies). The last 70 consecutive patients had radionuclide ventriculography performed in the first three days after transplantation; these studies were evaluated to determine the frequency of early ventricular dysfunction. In 95 instances, radionuclide ventriculography and endomyocardial biopsy were performed within 24 hr of each other, and these studies were used to assess the relationship of left ventricular function to the biopsy-determined severity of rejection. In 45 of these 95 instances, the biopsy revealed rejection. An additional 39 episodes of biopsy-proven rejection were not included in the analysis since radionuclide ventriculography was not performed within 24 hr of the biopsy. A 24-hr cutoff for the biopsy/ventriculogram interval was chosen because of the

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potential for rapid change in cardiac status due to progressive rejection of interval treatment.

Total ischemic time of the donor heart was recorded for the last 58 consecutive patients and correlated with early left ventricular function. The pulmonary vascular resistance (Wood units) measured before transplantation was calculated in 43 patients and correlated with early right ventricular function. The cause of death was recorded in patients who succumbed in the 1-mo period after an episode or acute rejection.

All patients received an immunosuppressive regimen of cyclosporine (10–12 mg/kg preoperatively and then according to blood levels), azathioprine (2–3 mg/kg to maintain a white blood cell count of 4,000–5,000 cells per cubic millimeter) and prednisone (initiated at 1 mg/kg/day, tapered to a maintenance dose of 5–10 mg/day within 3–6 mo).

Rejection, which occurred in the first two to four weeks after transplantation, was treated with bolus methylprednisolone therapy over a 2- to 3-day period with repeat biopsy on Days 5–7. If associated with hemodynamic compromise or if histologically severe, equine antilymphocyte globulin (ALG) was added to the steroid pulse therapy. This agent was administered over 3–5 days at 20 mg/kg/day as a 4–6-hr infusion, and repeat biopsy was performed at an early interval to assess the response to therapy. Rejection occurring more than four weeks following transplantation was treated with increased prednisone to 100 mg/day, a dose that was rapidly tapered to the prerejection level in 7–10 days.

Endomyocardial Biopsy

Biopsies were performed routinely at ~4–8 days after transplantation, weekly for 4–6 wk, and with decreasing frequency thereafter. In addition, a biopsy was performed whenever there was a clinical suspicion of rejection. Three to five pieces of right ventricular myocardium were obtained during each procedure and interpreted by an experienced pathologist. A morphologic grade was determined according to a five-point grading system (*10*); the diagnosis of rejection required the presence of a diffuse lymphocyte infiltrate. The severity was graded according to the intensity of infiltration and the extent of myocyte necrosis. The diagnosis of resolving rejection was based on the presence of active fibrosis, nuclear dust, and a residual infiltrate.

Cardiac Imaging Analysis

Red blood cell labeling was performed by the in-vivo technique with ~25 mCi of technetium-99m-pertechnetate following i.v. stannous pyrophosphate. Seven million count images were obtained in the modified left anterior oblique (LAO) projection giving best separation of right and left ventricle (often displaced to the left in this group of patients). Additional images at 45° to the right and left of this best septal view were also obtained. Images were acquired on a standard field of view scintillation camera equipped with a low-energy all-purpose collimator. Data were stored in a computer in frame mode with 32 frames, each 64×64 pixels.

Analysis performed on the images obtained in the modified LAO projection has been described previously (*18*). The left ventricular time-activity curve was obtained from the unfiltered data with use of a fixed end-diastolic region of interest. The region was manually drawn with reference to a filtered end-diastolic image, a stroke-paradox image (*19*), and a cine display of the filtered images. The mitral valve plane was chosen as the area of lowest counts between the atrium and ventricle on the stroke-paradox image. The cine and stroke paradox images were used to define the aortic valve plane. A background region was assigned 2–3 pixels lateral to the left ventricular free wall. A separate end-systolic region was drawn for ejection fraction determination.

Right ventricular ejection fraction (RVEF) was determined similarly to left ventricular ejection fraction (LVEF), the tricuspid valve plane being chosen as the area of lowest counts between right atrium and right ventricle on the stroke-paradox image. The pulmonary valve plane was defined from the cine and stroke-paradox images. An overall qualitative opinion of right ventricular function (normal, mild, moderate-severe hypokinesis) was determined by visual assessment of right ventricular contraction by two observers with knowledge of the computer-derived RVEF. The qualitative right ventricular functional grade was felt to be more accurate than the computer-derived ejection fraction due to the inherent inaccuracies in the latter technique, especially in this group of patients with enlarged, hypocontractile right atria, in whom separation of the right-sided chambers is often impossible.

Regional wall motion was determined by assessment of three-view radionuclide ventriculography by two experienced observers following processing with a digital filter that has both edge-sharpening and smoothing properties (*20*). The pattern of ventricular contraction was assessed visually and with reference to phase and amplitude studies. Right and left atrial size and contraction patterns were also visually assessed.

Statistics

Correlation between continuous variables (ejection fraction, ischemic time, pulmonary vascular resistance) was assessed using Pearson's correlation coefficient. Correlation involving an ordinal variable (right ventricular grade) was evaluated using Kendall's rank correlation coefficient. The significance of the frequency of left ventricular dysfunction in patients with either mild or moderate to severe rejection was assessed using the chi-squared test (*21*).

RESULTS

Normal Features

The frequency of radionuclide ventriculographic anomalies of normally-functioning orthotopic cardiac transplants and the angle of best ventricular separation are recorded in Table 1.

Radionuclide Ventriculographic Findings 1–3 Days After Cardiac Transplantation

Radionuclide ventriculography was performed within the first three days of cardiac transplantation in 70 patients. Thirteen (19%) patients had demonstrable left ventricular dysfunction in this period with concomitant right ventricular dysfunction in all but one case (Table 2). Left ventricular ejection fraction was mildly to moderately reduced in this group although these studies were generally performed while the patients were receiving inotropic therapy. Each of these patients had repeat radionuclide ventriculography 5–10 days later, which showed a return to normal left ventricular func-

TABLE 1
Frequency of Radionuclide Ventriculogram Findings in 74 Normal Orthotopic Cardiac Transplant Patients

Best septal view (degrees)	≤45°	36%
	46–64°	53%
	≥65°	11%
Paradoxical interventricular septal motion		93%
Right atrium		
akinesis/hypokinesis		95%
enlargement		78%
Left atrium		
akinesis/hypokinesis		34%
enlargement		11%

TABLE 3
Isolated Right Ventricular Dysfunction in the Early Post-Transplant Period

Days post-transplant	Isolated right ventricular dysfunction no. (%)	Return to normal right ventricular function* no. (%)
1	16/31 (52%)	7/11 (64%)
2	7/24 (29%)	4/6 (67%)
3	6/15 (40%)	4/6 (67%)

*23 of the 70 patients had a repeat study.

tion. Correlation to total ischemic time of the donor heart with early LVEF was performed in 58 patients. Only 3 of the 13 patients with early left ventricular dysfunction had an ischemic time of >3 hr, and there was not a significant relationship between ischemic time and early LVEF (r=0.05, p=0.70).

Twenty-nine of the 70 patients (41%) studied in the first three days postoperatively had a normal LVEF with isolated right ventricular dysfunction (see Table 3). In approximately one-third (8/23) of the patients who had a repeat study, abnormal right ventricular function persisted at a mean follow-up time of 7.4 mo (range 10 days–3 yr). In 43 patients, the correlation between pretransplant pulmonary vascular resistance and early RVEF in addition to the qualitative right ventricular functional grade was assessed. All eight patients with a preoperative pulmonary vascular resistance >3.0 Wood units had right ventricular dysfunction. However, pulmonary vascular resistance overall did not correlate well with right ventricular functional grade (r=0.095, p=0.22) or RVEF (r=0.002). Ischemic time was also unrelated to early right ventricular functional grade (t=0.50, p=0.50).

Radionuclide Ventriculographic Findings in Acute Transplant Rejection

Endomyocardial biopsy and radionuclide ventriculography were performed within 24 hr in 95 instances (Table 4). There was overall agreement between the two modalities in 62 cases: in 46 cases the biopsy and LVEF were both normal (i.e., normal biopsy and LVEF≥50%), and in 16 cases both were abnormal. There was disagreement in 33 cases: in 29 cases there was biopsy-proven rejection with normal left ventricular function (27 of these had only mild or resolving rejection), and in the remaining 4 instances left ventricular dysfunction developed but the biopsy was normal.

In three of the four cases in which abnormal left ventricular function developed in the absence of biopsy evidence of rejection, a clinical diagnosis of rejection was made and anti-rejection therapy commenced. Treatment was associated with a recovery of normal left ventricular function and subsequent biopsies showed resolving rejection. Thus, we consider these patients to have had false-negative biopsies initially. The other patient had an abnormal radionuclide ventriculogram at the time of severe sepsis which proved fatal several days later.

Eight of ten cases of moderate-to-severe rejection (80%) were associated with a fall in LVEF to below 50%, while only 8 out of 26 (31%) episodes of rejection graded as mild on biopsy developed left ventricular dysfunction. Importantly, in three patients with mild rejection by biopsy, LVEF fell to 30% (one patient had a LVEF of 19% as shown in Fig. 1), suggesting that rejection may have been worse in these patients than suggested by biopsy.

In this retrospective series, a decline in LVEF to less than 50% had a sensitivity of only 40% (19/48) for detection of rejection diagnosed by biopsy or clinical follow-up. However, this finding was associated with a high specificity of 98% (46/47), provided one excludes focal wall motion abnormalities suggestive of infarction (discussed later) and global abnormalities during the first three days after transplantation that are likely due to preservation injury. In patients with normal left ventricular function at time of biopsy, a fall in ejection fraction from a previous study was not of use in diagnosing rejection (see Table 4). Left ventricular enlargement was sometimes seen (9/16 patients) in conjunction with a fall in LVEF associated with biopsy-proven rejection.

TABLE 2
Left Ventricular Dysfunction (LVEF < 50%) in the Early Post-Transplant Period

Day post-transplant	No. (%)	Mean LVEF (range)	Associated RV dysfunction
1	6/31 (19%)	44% (40–50%)	6/6 (100%)
2	6/24 (25%)	43% (38–50%)	5/6 (83%)
3	1/15 (7%)	44%	1/1 (100%)

LVEF = left ventricular ejection fraction; RV = right ventricular.

TABLE 4
LVEF Within 24 Hr of Endomyocardial Biopsy (n = 95)

Endomyocardial biopsy grade	LVEF < 50% <30%	LVEF < 50% 31%–40%	LVEF < 50% 41%–50%	LVEF ≥ 50%* Fall ≥ 5%	LVEF ≥ 50%* Fall < 4% or no change or increase	LVEF ≥ 50%* No previous study for comparison
1. No rejection (n = 50)	—	1 (sepsis)	3 (biopsy missed rejection)	16	18	12
2. Mild (n = 26)	3	—	5†	5	11	2
3. Moderate (n = 7)	1†	3	2	—	1	—
4. Severe (n = 3)	2†	—	—	—	1	—
5. Resolving (n = 9)	—	—	—	1	5	3

LVEF = left ventricular ejection fraction.
* For those patients with a normal LVEF, when a previous study was available for comparison, the change since the previous study is indicated. (Previous studies demonstrating dysfunction due to preservation injury or prior episodes of rejection were not used for comparison.)
† One patient in each category died within 1 mo due to rejection.

Effect of Treatment of Rejection

There were 16 episodes of biopsy-proven rejection associated with a fall in LVEF to below 50%, as noted in Table 4. In three of these instances, the patient died within 4 wk of the episode, and in the majority of others left ventricular function either improved by at least 10% (2/13) or returned to normal (9/13) with anti-rejection therapy.

Focal Left Ventricular Wall Motion Abnormalities

Two patients developed localized areas of left ventricular hypokinesis or dyskinesis, due to coronary atherosclerosis and subsequent infarction. One of these patients succumbed due to rapidly progressive coronary atherosclerosis confirmed at autopsy; the other patient is still alive and well 13 mo after infarction.

DISCUSSION

Recognition of the normal scintigraphic features in patients with orthotopic cardiac transplants is important in the evaluation of abnormalities and has been incompletely described in the literature. We have shown that an increased angle of ventricular separation due to rotation of the heart to the left is common; 64% of patients have a best septal view of at least 50° and 11% >65°. These findings are in agreement with a recent study of the computed tomographic features of cardiac transplants in which a distinctive leftward orientation of the cardiac mass relative to other thoracic structures was found in 41% of cases (*22*). This finding is presumably related to variability of the size of the retained atria, with the donor heart being placed at a variable angle on a cuff of recipient right and left atria. Increased cardiac mobility and associated paradoxical septal motion ("cardiac rocking") is almost universal in the immediate post-transplant period and related to the post-pericardotomy state and the placement of a normal-sized heart in a large pericardial sac. This phenomenon often becomes less apparent with time, probably due to healing and adhesion formation, but the finding generally does not resolve completely. Although the septum moves paradoxically in early systole, septal thickening can often be seen, thus, aiding in interpretation. Biatrial enlargement is very common in the normal car-

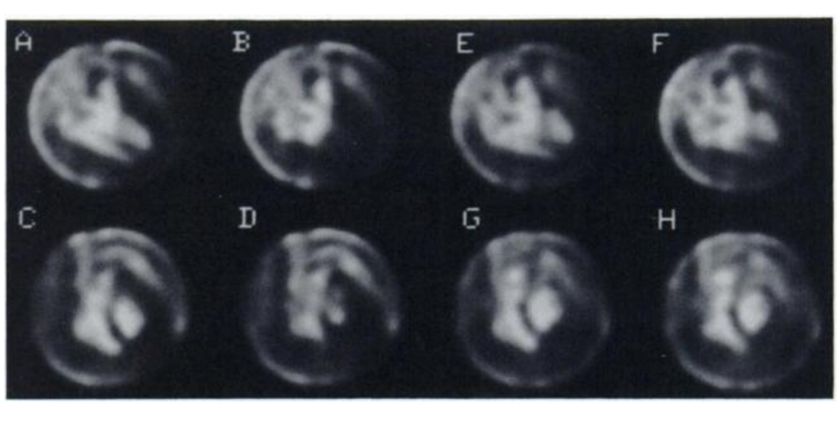

FIGURE 1
Diastolic and systolic frames of radionuclide ventriculograms in a patient with two episodes of mild rejection by biopsy (the top row shows 10° LAO and the bottom 50° LAO views). During the first episode (A-D), the LVEF increased to 82%; during the second episode (E-H), the LVEF dropped to 19% despite similar biopsy findings. Following treatment of rejection, LVEF gradually rose to 45%.

diac graft. Right atrial involvement is often more obvious than that of the left atrium, probably reflecting the difficulty of left atrial visualization by radionuclide ventriculography. Initially, right atrial enlargement may be contributed to by the increased right heart pressures generally seen in the first several weeks after transplantation (*12*). However, some degree of right atrial enlargement often persists indefinitely, probably merely reflecting the sewn together atria; the presence of abnormal intraatrial conduction may contribute.

Endomyocardial biopsy remains the standard technique for the diagnosis and grading of transplant rejection. However, this invasive method has several limitations, including difficulty in interpretation, a false-negative rate for rejection of at least 5% despite study of at least three myocardial samples, and less frequently false-positives due to sampling of an area of inflammation at the site of a recent biopsy (*23*). Various alternate techniques for the noninvasive detection of rejection have been studied but none has been shown to be sufficiently accurate in humans to replace biopsy. These include signal-averaged electrocardiography (*1*), echocardiography (*2*), magnetic resonance imaging (*3*), and various nuclear medicine techniques including thallium-201 scintigraphy (*4*), and technetium-99m-pyrophosphate imaging and gallium-67 scintigraphy (*5*, *6*). Indium-111-antimyosin (Fab) scintigraphy may be useful for the detection of moderate-to-severe rejection but this test relies upon the presence of necrosis (*7*, *8*), which is not present in mild rejection. Recently, indium-111-lymphocytes have been shown at our institution to be a feasible means of detecting rejection in an animal model at stages prior to overt myocardial necrosis (*24*), but confirmation in humans is not yet available.

The non-rejecting, transplanted human left ventricle has been shown to demonstrate normal contractile characteristics and reserve (*25*). Others (*13–15*) have suggested that left ventricular dysfunction is an infrequent concomitant of transplant rejection. However, we have shown that left ventricular hypokinesis is not uncommon even in mild rejection, occurring in 31% of cases in this study. In addition, we have found that radionuclide ventriculography provides clinically useful information in several settings, particularly in cases where there is significant discordance between biopsy and the clinical impression. Clearly, knowledge that a patient with biopsy evidence of only mild rejection has a LVEF of less than 30% (as in three instances in this study) has major therapeutic and prognostic implications. If no other clinical etiology for the depressed left ventricular function is present, such patients likely have more severe rejection than predicted by the biopsy and may need hospitalization, aggressive anti-rejection therapy, and treatment for cardiac failure. This situation contrasts with that of the more common patient with mild rejection and normal left ventricular function who is generally treated only with increased doses of corticosteroids. It seems likely that the biopsy is underestimating the severity of rejection in many of the patients with mild rejection by biopsy who develop significant left ventricular dysfunction. Clearly other causes of declining LVEF such as arrhythmias, suboptimal loading conditions, and myocardial infarction need to be excluded before such inferences can be made. Radionuclide ventriculography also provides clinically useful information in patients with symptoms suspicious for rejection such as fatigue, fever, and dyspnea who have a negative biopsy. If left ventricular function is normal in such patients, depending upon clinical suspicion, they may remain on routine immunosuppression under close surveillance, or undergo repeat biopsy. In contrast, when left ventricular dysfunction develops in these patients a decision to repeat the biopsy or treat as rejection missed by the initial biopsy should be considered in the context of other clinical data.

Cases of left ventricular dysfunction with a false-negative biopsy or biopsy underestimation of the severity of rejection are relatively uncommon, comprising 6 of 45 cases of rejection in this study. It should be noted that 39 cases of rejection were excluded from analysis because radionuclide ventriculography was not performed within 24 hr of the biopsy. In many of these 39 instances, radionuclide ventriculography was performed but not included in the study as the radionuclide study was performed more than 24 hr after the biopsy. There could have been a bias towards obtaining blood-pool studies more promptly in the most symptomatic patients, thus leading to possible overestimation of the frequency of discordance.

Depression of left ventricular contraction in the immediate post-transplant period has been demonstrated experimentally and appears to be the result of ischemia from preservation and sugical trauma (*11*). Recently, hormonal deficiencies, especially of plasma-free triiodothyronine, depletion of which occurs rapidly after brain death, have been implicated in the development of abnormal myocardial metabolism and dysfunction in donor hearts (*16*). In this study, almost one-quarter of patients studied in the first 48 hr after transplantation had abnormal biventricular function with LVEF in the range 38%–50% despite inotropic therapy. In all patients who were followed, left ventricular function returned to normal within the next week. We found no correlation between early post-transplant LVEF and total ischemic time of the donor heart. Indeed, the majority of patients with early left ventricular dysfunction did not have prolonged ischemic times. Knowledge of such early biventricular dysfunction in these often hemodynamically unstable patients can be a valuable adjunct to management. Our findings also suggest that if radionuclide ventriculography is to be used to monitor rejection then a baseline study should probably be performed on approximately the fourth day post-transplantation because at this time the incidence of both preservation injury and early acute rejection is very low.

Isolated right ventricular dysfunction was a common finding early after transplantation in our study and was shown to resolve spontaneously in the majority of patients. In some instances, this phenomenon may be a result of preoperative pulmonary hypertension, which would explain the universal right ventricular dysfunction in patients with pretransplant pulmonary vascular resistance >3.0 Wood units, as seen in this study. The improvement in right ventricular function with time is probably due to the ability of the newly-transplanted right ventricle to adapt to a mild elevation of pulmonary vascular resistance. However, the lack of a significant relationship between pulmonary vascular resistance and early post-transplant right ventricular function overall suggests that other factors are also involved. An insight into possible alternate mechanisms is provided by a previously reported hemodynamic study, which demonstrated high right atrial, right ventricular end-diastolic, pulmonary arterial, and pulmonary artery wedge pressures with restrictive features in the 24–48-hr period after successful transplantation (*12*). These pressures gradually returned to normal over 3 mo but an occult restrictive process could be uncovered by volume loading. A combination of factors have been implicated, including ischemia from preservation, small perciardial effusions, atrial misshaping resulting from the implantation procedure, volume overload, pulmonary hypertension, and later myocardial infiltration related to rejection.

As more cardiac transplant recipients survive for longer periods, graft coronary atherosclerosis will become an increasingly common and important problem. Detection of such patients is made difficult by the painless nature of their ischemia and infarctions and the presence of diffuse and small vessel coronary disease (*26*). Thallium scintigraphy may have reduced specificity for the detection of ischemia in these cases as rejection and myocardial fibrosis may also cause perfusion defects (*26–28*). In patients several years after cardiac transplantation, radionuclide ventriculography may be the first test to detect myocardial infarction and, thus, careful assessment for focal ventricular wall motion abnormaliies should be made.

In conclusion, our general experience is that radionuclide ventriculography provides important data which complements the biopsy findings in transplant rejection. Knowledge of left ventricular function in acute rejection provides an additional parameter of severity and, in patients with left ventricular dysfunction, another objective method by which the response to treatment can be monitored. We recommend that radionuclide ventriculography be performed immediately following biopsy diagnosis of rejection, particularly in the first month following transplantation when rejection can be more precipitous, and also when there is a high clinical suspicion of rejection but a negative biopsy.

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