Role of Dobutamine Stress Echocardiography in Heart Transplant Patients*

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The objective of this focused review is to describe the rationale, methods, and potential clinical applications of dobutamine stress echocardiography (DSE) in heart transplant recipients. More than 500 studies in 150 heart transplant patients who underwent this procedure (1991-96) are reviewed. Relevant studies from the medical literature that have assessed the utility of DSE in the diagnosis of transplant coronary artery disease (TCAD) are discussed, the predictive ability of DSE for development of TCAD is determined, and the prognostic value of this test in the heart transplant population is evaluated. The protocol of DSE used in the laboratory for this study is presented and discussed with reference to other major studies that have determined the sensitivity, specificity, and positive and negative predictive accuracies. Since many noninvasive cardiac tests have not been consistently optimal to detect TCAD, a substantial number of patients undergo routine surveillance with coronary angiography to define the presence and magnitude of TCAD. Recent studies with DSE have shown it to be valuable in the noninvasive diagnosis of TCAD and to have an accuracy unmatched by other widely used imaging modalities. Other important evolving indications for DSE in heart transplant patients, such as prediction of prognosis and occurrence of cardiac events, are briefly discussed. Based on this study and the currently available literature, DSE appears to be a highly reproducible noninvasive test which can be serially employed in the routine surveillance of coronary artery disease in heart transplant patients.

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Key words: allograft; coronary disease; diagnosis; prognosis; stress echocardiography

Abbreviations: CAD=coronary artery disease; DSE=dobutamine stress echocardiography; IVUS=intravascular ultrasound; TCAD=transplant coronary artery disease; WMSI=wall motion score index

Heart transplantation has evolved as the most definitive therapy for end-stage heart failure. In the past decade, the number of heart transplant centers has increased with a corresponding increase in the number of patients receiving transplantation.1 Recently, advances in understanding of the immunologic and infectious complications coupled with the widespread use of cyclosporine have resulted in improved outcome early after transplantation.2 However, outcome after the initial year of transplantation is significantly limited by accelerated coronary artery disease (CAD).

CAD in heart transplant patients is pathologically complex and differs from typical atherosclerosis in a variety of ways. Transplant CAD (TCAD) usually starts early and progresses rapidly. The disease usually manifests in the terminal branches and distal vessels.3,4 At this early stage, the disease is beyond the resolution of routine angiography. Focal epicardial lesions observed later may represent advanced disease. Clinically, the disease is silent due to cardiac denervation. When symptoms develop, they are usually atypical and represent late manifestations of advanced disease, such as congestive heart failure, sudden death, myocardial infarction, and complex ventricular dysrhythmias.5,6 Histologically, the TCAD is diffuse and involves myointimal hyperplasia of smooth muscle cells that eventually compromise the arterial lumen.3,4,7-9 Studies using intravascular ultrasonography have shown that the disease is ubiquitous by 2 to 3 years after transplantation.10,11 Taken together, recent studies utilizing intravascular ultrasound,11 intracoronary acetylcholine infusion,12 and coronary flow reserve with exercise suggest that TCAD is physiologically heterogeneous. When ob-
served soon after transplantation, endothelial dysfunction has been shown to predict the development of TCAD at 1 year.\textsuperscript{12,13} Preliminary results from the McGuire VA Medical Center support the view that abnormal dobutamine stress echocardiography (DSE) also has the potential to predict the development of TCAD.\textsuperscript{14}

The exact cause of accelerated CAD in transplant patients is unclear. The relationship of factors, such as chronic rejection,\textsuperscript{15,16} serum cholesterol,\textsuperscript{17} and undetected donor disease,\textsuperscript{18} have been examined, but no definite putative roles have been established. The diagnosis of accelerated CAD in heart transplant patients is difficult\textsuperscript{19} due to the diffuse nature of the disease. Coronary angiography, which is routinely performed in many centers, has been shown to underestimate underlying disease.\textsuperscript{19,20} Most of the currently available noninvasive tests, aside from DSE, have not been found to have sensitivity and accuracy rates high enough to be clinically reliable in detecting TCAD.\textsuperscript{21,22}

Recently, Akosah et al\textsuperscript{23} and others\textsuperscript{24,25} have shown that DSE is a reliable screening test in detecting TCAD. However, a definitive role of DSE in the routine follow-up evaluation of heart transplant patients remains to be established. The goal of this review is to discuss the following about DSE: its utility in heart transplant patients, its diagnostic accuracy, its prognostic potential, and its ability to predict the risk for development of CAD.

**Rationale for DSE in Transplant Patients**

Factors that favor the role of DSE in the diagnosis of TCAD include the following: First, transplant coronary disease is diffuse and usually involves the entire length of the arterial tree. Such coronary artery morphologic features render the myocardium at risk more vulnerable to demand ischemia. The pharmacologic perfusion imaging tests, depending on vasodilatory impairments, may fail to reveal heterogeneous uptake of radiopharmaceutical perfusion markers, especially when perfusion abnormalities are balanced. Second, TCAD is associated with impaired coronary collateral circulation.\textsuperscript{26} Third, heart transplant patients with cardiac denervation may manifest augmented chronotropic response to dobutamine infusion.\textsuperscript{27} Fourth, since the diastolic BP, an important determinant of coronary perfusion, is reduced by 10 to 15% during dobutamine infusion,\textsuperscript{28} such reduction in coronary perfusion pressure (due to decrease in diastolic blood pressure) in a myocardial territory subserved by an atherosclerotic vessel, especially in the absence of collateral vessels, renders it readily ischemic.

**Assessment of TCAD**

**DSE Protocol**

In general, the various protocols for DSE have been described previously and include the 3- or 5-min stages with or without atropine.\textsuperscript{29-33} Briefly, dobutamine is a synthetic sympathomimetic catecholamine that binds to $\beta_1$- and $\beta_2$-adrenergic receptors and to a lesser extent stimulates $\alpha_1$ receptors.\textsuperscript{34,35} The drug has a half-life of approximately 2 min, and steady state is achieved after 10 min of continuous intravenous infusion.\textsuperscript{35} When administered in lower doses (5 to 10 $\mu$g/kg/min), it causes the force of contraction to increase (positive inotropism). Higher doses result in increases in the rate of contraction (chronotropism). The net result is increase in the myocardial oxygen demand and decrease in the diastolic coronary perfusion time.\textsuperscript{34,35} The increase in myocardial oxygen demand, and the reductions in diastolic coronary perfusion time and pressure result in supply-demand mismatch in myocardial territories subserved by diseased coronary vessels.

We use digital echocardiography to produce cine loop images in the quad-screen format. Complete echocardiographic images, including Doppler, are obtained at baseline. Four standard views are obtained and digitized for off-line analysis. This includes the parasternal long and short axis at the mitral and papillary muscle levels and the apical four- and two-chamber levels, respectively.

Hemodynamic and electrocardiographic monitoring is performed throughout the test. In the laboratory of McGuire VA Medical Center, 5-min infusion stages and a peak dose of 40 $\mu$g/kg/min (5, 10, 20, 30, and 40 $\mu$g/kg/min) are used. End points for early termination include induced angina, symptomatic hypotension, electrocardiographic signs of significant ischemia, and intolerable symptoms. Although used by others, this study did not use attainment of 85% of target heart rate as an end point for early termination of the test. The echocardiographic data are analyzed by side-by-side comparison of digitized images acquired at baseline, 5 $\mu$g/kg/min, peak dose of dobutamine, and recovery. Wall motion score index (WMSI) is derived using the 16-segment model.\textsuperscript{23} By this scheme, a WMSI $>$1.0 is considered abnormal.

**Sensitivity, Specificity, and Accuracy Rates for DSE in Detection of TCAD**

Three major studies\textsuperscript{33-35} have reported the relative accuracy of DSE in the diagnosis of TCAD (Table 1). Akosah et al\textsuperscript{23} reported experience with DSE in 41 asymptomatic heart transplant patients who underwent coronary angiography and DSE within 24 h of...
each other. Patients were excluded if they had clinical instability, had known angiographic disease, or failed to consent. Angiographic disease was considered significant if the luminal percent stenosis was 50% or greater. Twenty-one of the 41 patients had abnormal coronary angiograms. Of these, 20 patients had abnormal results on the stress echocardiograms. Of the 20 patients with normal angiograms, 9 had abnormal stress echocardiograms. The sensitivity was 95% with a specificity of 55%. The positive and negative predictive values were 69 and 92%, respectively.

Derumeaux et al.\textsuperscript{24} reported their experience in 37 patients with DSE using quantitative coronary angiography as the gold standard. The DSE was completed within 1 month of the cardiac catheterization. Patients were categorized into three groups based on the results of the quantitative angiography. Twenty-three patients with normal angiograms comprised group 1. Group 2 (n=7) had insignificant angiographic disease (<50%) and group 3 (n=7) had significant focal disease. The dobutamine stress echocardiograms were abnormal in all 7 patients in group 3, 5 of the 7 patients in group 2, and only 2 of 23 patients in group 1. Taking into account any angiographic disease as significant, the authors derived a sensitivity of 86% and a specificity of 95%. The positive and negative predictive values were 86 and 91%, respectively. Although these results have been interpreted as conflicting to those of Akosah et al.,\textsuperscript{23} they are, in fact, remarkable for their similarities. In their study, Derumeaux et al.\textsuperscript{24} considered any angiographic lesion regardless of severity as significant. Lesions as mild as 15% were considered as true angiographic disease in calculating sensitivity and specificity. Although it has been well documented that angiography underestimates TCAD,\textsuperscript{20} it is not clear if all angiographic abnormalities are associated with functional defects. Assuming coronary angiography as the gold standard and only 50% stenosis as the reference standard for significant disease, the following statistics emerge from their results. The sensitivity, specificity, and positive and negative predictive values are 100, 77, 50, and 100%, respectively.\textsuperscript{37}

Spes and coworkers\textsuperscript{36} correlated DSE in 50 consecutive orthotopic heart transplant recipients with coronary angiography and intravascular ultrasound (IVUS) findings. Four patients were excluded for technically suboptimal echocardiography. The remaining 46 patients were assigned to two groups according to the IVUS or the angiographic data. Group 1 (n=18) had either normal or mild intimal hyperplasia. Group 2 (n=28) comprised those with at least moderate intimal abnormalities (n=23) and 5 without IVUS who had clear angiographic disease. Abnormal DSE correlated well with angiographic disease (10 of 12). Using coronary angiography as the “gold standard,” the sensitivity and specificity were 83 and 56%, respectively; positive and negative predictive value were 40 and 90%, respectively. When compared to IVUS findings of intimal hyperplasia, the following were noted: sensitivity of 79%, specificity of 83%, positive predictive value of 88%, and negative predictive value of 71%.

Spes and coworkers\textsuperscript{37} concluded that DSE appeared to be a feasible noninvasive method for detection of CAD in heart transplant recipients; as a result, use of this method may reduce the need for routine coronary angiography. Furthermore, they argue that by using IVUS as the “gold standard,” their data suggest that wall motion abnormalities in patients with normal coronary angiograms represent false-negative angiographic results and not necessarily false-positive stress echocardiographic findings.

The results of these previously mentioned studies are remarkably similar with respect to the general finding that DSE has high sensitivity and negative predictive value and that this feature makes it ideal as a screening test for coronary disease in heart transplant patients. However, the minor differences in accuracy rates can be explained by differences in the methods employed in each study. First, the presence of any angiographic disease, rather than the conventional ≥50% stenoses, was considered significant in the study by Derumeaux et al.\textsuperscript{24} Second, the peak dose of dobutamine in the study by Spes et al.\textsuperscript{36} was relatively low (mean=20 μg/kg/min) compared with 30 μg/kg/min in the study of Derumeaux et al.\textsuperscript{24} and 37 μg/kg/min in the report of Akosah et al.\textsuperscript{23} In this study reported here, 85% of predicted maximal heart rate was not used as a criterion for early termination of the test. It is unclear if the use of target heart rates derived from the recipient’s age can be considered as valid for heart transplant patients. Third, there is a general problem with the absence of a uniform gold standard in calculating sensitivity and specificity. Although IVUS accurately detects intimal abnormalities in major epicardial vessels, it does not allow investigation of small terminal vessels and the microvasculature. Moreover, the relationship between the observed intimal

### Table 1—Accuracy of DSE in the Detection of TCAD

<table>
<thead>
<tr>
<th>Study</th>
<th>No. Patients</th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
<th>Negative Predictive Accuracy, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Derumeaux et al.\textsuperscript{24}</td>
<td>37</td>
<td>86</td>
<td>95</td>
<td>91</td>
</tr>
<tr>
<td>Akosah et al.\textsuperscript{23}</td>
<td>41</td>
<td>95</td>
<td>55</td>
<td>92</td>
</tr>
<tr>
<td>Spes et al.\textsuperscript{36}</td>
<td>46</td>
<td>79</td>
<td>83</td>
<td>91</td>
</tr>
</tbody>
</table>

CHEST / 113 / 3 / MARCH, 1998 811

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abnormalities and functional abnormalities remains to be determined. The clinical significance of the intimal thickness derived from IVUS studies and the longitudinal extent of intimal abnormalities need to be determined to assess the relative importance of IVUS detected morphologic abnormalities and functional impairment noted by DSE or by intracoronary infusion of endothelial dependent vasoactive substances. The correlation of intimal abnormalities by IVUS with quantitative coronary angiography, endothelial dysfunction, coronary flow reserve abnormalities, and regional contractile dyssynchrony by DSE are likely to provide insights into this complex disease.

Prognostic Value of DSE in Heart Transplant Patients

The validation of DSE for diagnosis of CAD in this setting in the absence of an ideal “gold standard” is difficult (Table 2). Although the noninvasive prediction of the magnitude of TCAD is important, a more relevant question in the transplant patient population may be to develop a noninvasive test capable of predicting cardiac events and prognosis. Simple noninvasive tests that can identify patients who are at risk for developing cardiac events may allow early intervention with more aggressive and newer investigational treatment modalities. In a study recently reported from the McGuire VA Medical Center,39 a prospective evaluation of 86 heart transplant patients who underwent follow-up cardiac catheterization and endomyocardial biopsy. The mean time since transplant for the group was 51 ± 10 months. Follow-up duration was a mean of 24 months (range, 18 to 28 months) following DSE. Nine patients were excluded, five for acute allograft rejection and four for poor acoustic window. DSE was abnormal in 57 (74%) of the 77 patients. Patients were stratified into two groups. Group 1 comprised 40 patients with normal (n=20) and mild ischemia (n=20). Mild ischemia was defined as WMSI ≤1.5 at peak. In Group 2 there were 37 patients with WMSI of >1.5. During follow-up, no patient in group 1 experienced an event. By contrast, 51% of the patients with WMSI of >1.5 experienced cardiac events. These events included unstable angina in 4; myocardial infarction in 3; congestive heart failure in 7; and cardiac death in 5 patients. Figure 1 is Kaplan Meier survival distribution showing significantly decreased survival in the patients. Multivariate analysis showed only inducible abnormalities and peak systolic blood pressure as independent predictors of outcome. Patients who developed cardiac events had more abnormal WMSI at peak (p<0.001) with attenuated peak BP response (p<0.05). For instance, a peak wall motion score of 1.7 implied a risk ratio of 6 (p<0.001) for cardiac events (confidence interval, 2.3 to 14.4).

This means that among heart transplant patients with abnormal DSE, the extent of myocardium at risk for ischemia (as defined by WMSI) and attenuated BP response to dobutamine are the two most important predictors of patient outcome. Lewis et al39 recently reported results in 63 patients that also suggest the ability of DSE in predicting cardiac events in cardiac transplant recipients even within a short 8-month follow-up period.

The Implications of Angina During DSE in Heart Transplant Patients

Despite the early development and the accelerated progression of TCAD, either spontaneous or stress-induced angina is an uncommon phenomenon. The lack of angina after orthotopic heart transplantation is believed to be due to surgical denervation. During the course of a prospective study, Akosah et al40 observed that a small cohort of transplant patients developed typical angina during dobutamine stress. In order to further characterize this patient group, the correlation between dobutamine-induced angina and the development of wall motion abnormalities was examined and the differences in clinical characteristics between the patients who developed angina and those who did not were assessed.

Eleven patients developed angina during DSE, while 71 did not. The hemodynamic responses including heart rate, BP, and the diastolic pressure at baseline and peak were similar in the two groups.

Table 2—DSE in Predicting Cardiac Events

<table>
<thead>
<tr>
<th>Study</th>
<th>Total Patients, No.</th>
<th>Patients With Abnormal DSE</th>
<th>Mean Follow-Up Period, mo</th>
<th>Patients With Positive DSE</th>
<th>Patients With Negative DSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Akosah et al39</td>
<td>77</td>
<td>57 (74%)</td>
<td>24</td>
<td>22</td>
<td>0</td>
</tr>
<tr>
<td>Akosah et al40</td>
<td>22</td>
<td>11 (50%)</td>
<td>32</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>Lewis et al41</td>
<td>63</td>
<td>21 (33%)</td>
<td>8</td>
<td>5</td>
<td>1</td>
</tr>
</tbody>
</table>

*Serial DSE in new transplants.
The peak dobutamine dose was lower in the group with angina (31±2 vs 37±1 μg/kg/min, p<0.04). The mean time since transplant was much longer in the group that developed angina (80.3±6.2 vs 57.3±3.5 months, p<0.005). Seven of the 11 had resting wall motion abnormalities, and all 11 developed abnormal regional responses at peak. Moreover, patients who developed angina had more severe ischemic response as manifested by higher peak WMSI (1.74±0.01 vs 1.52±0.06; p<0.05). The sensitivity of dobutamine stress-induced angina for predicting angiographic disease was 33% with a specificity of 95%; these values are remarkably similar to those obtained with dobutamine in the general non-transplant population.33 Although sympathetic refferentiation was not directly examined, the clinical characteristics of the patient group with induced angina, the long duration since transplant, and direct demonstration of onset of angina associated with wall motion abnormalities suggest cardiac afferent reinnervation and further imply that in heart transplant patients, occurrence of angina may be a predictor of functional reinnervation.

The Clinical Implications of DSE Early After Transplantation

In the preceding paragraphs, the relevant medical literature has been discussed. Studies have been noted that define the role of DSE in the detection of TCAD and in providing prognosis. Most of the studies were performed in patients with a mean duration since transplant of 3 to 5 years. By this time, the disease is rather extensive, and the treatment options may be limited. A longitudinal study was undertaken with serial DSE in 22 asymptomatic heart transplant patients soon after transplantation to determine the ability of DSE to predict future events. These new heart transplant patients were enrolled soon after transplantation.14 DSE was performed within 24 h of scheduled endomyocardial biopsy or diagnostic coronary angiography. Patients were followed up for a period of 32±11 months (range, 5 to 50 months) for development of angiographic coronary disease, myocardial infarction, or death. There were a total of 86 serial stress echocardiograms and 41 cardiac catheterizations in the 22 patients. Patients were categorized by group according to the pattern of results in serial DSE. In group 1, there were 7 (32%) patients whose serial DSE remained normal on all tests. Four patients (group 2) developed intermittent abnormalities (18%). Although the patients in this group developed wall motion abnormalities in some tests during the course of the study, the abnormalities resolved on subsequent testing. The remaining 11 patients (group 3) had inducible wall motion abnormalities that remained persistent on serial testing. In most cases, the extent of inducible abnormalities worsened during the course of the study, the threshold for inducible regional dysfunction decreased, and some patients eventually developed resting abnormalities. During follow-up, no patient in either group 1 or 2 developed angiographic disease or suffered a cardiac event. By contrast, 8 of the 11 patients (73%) in group 3 experienced cardiac events. Seven (64%) of these patients eventually developed angiographic CAD. One patient suffered nonfatal myocardial infarction in spite of two documented normal coronary anatomy by angiography. Three patients with angiographic disease died (27%). Figures 2 and 3 demonstrate the event rates by group. One may interpret these results to suggest that persistent inducible wall motion abnormalities on serial DSE done soon after heart transplantation are predictive of the eventual development of angiographic disease and subsequent cardiac events. Since the number of patients in this study is relatively small, further studies are needed to confirm these important observations.

Future Direction

Currently, the use of DSE in heart transplant patients is becoming increasingly popular. The ultimate question is if DSE should be a part of the routine battery of cardiac tests in posttransplant evaluation. The following considerations support that assertion. First, the high sensitivity and negative predictive value make DSE an ideal test for screen-
DSE and coronary angiography: All transplant patients should undergo early baseline (<1 year) coronary angiography for reference. Asymptomatic patients should undergo serial screening with DSE during their annual posttransplant evaluation. Patients with negative DSE may be spared from subsequent cardiac catheterization. Patients with inducible wall motion abnormalities (persistent on serial testing) need further evaluation with coronary angiography. Intracoronary ultrasound studies can be performed where available to study coronary morphologic features. Patients with severe inducible abnormalities (WMSI, ≥1.7) represent a group at high risk for subsequent cardiac events. These patients need close follow-up and aggressive therapy including percutaneous revascularization and consideration for retransplant where applicable.

**SUMMARY AND CONCLUSION**

DSE has been shown to be a reliable test for the screening for CAD in heart transplant patients. It has a high sensitivity and negative predictive value with a diagnostic accuracy that compares favorably with invasive methods such as coronary angiography and intracoronary ultrasound imaging. In addition, DSE results have been shown to have important prognostic implications in that they predict the development of angiographic disease and identify patients at risk for development of cardiac events and poor outcome. Patients with greater ischemic burden as manifested by WMSI ≥1.7 need close follow-up and treatment strategy directed toward early intervention and atherosclerotic regression. Based on these observations, it is justified to propose that DSE be implemented as part of the routine evaluation of patients after heart transplantation. After initial baseline angiography, subsequent diagnostic cardiac catheterization should be reserved for those patients with abnormal DSE demonstrated in two consecutive dobutamine stress tests. This strategy may be safer, more cost-effective, and may provide a range of clinical information critical to the successful management of heart transplant patients.

**REFERENCES**