Diagnostic and Prognostic Value of Serial Dobutamine Stress Echocardiography for Noninvasive Assessment of Cardiac Allograft Vasculopathy

A Comparison With Coronary Angiography and Intravascular Ultrasound

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Background—Routine methods for surveillance of cardiac allograft vasculopathy (CAV) are coronary angiography and intravascular ultrasound (IVUS). This study analyzed the diagnostic and prognostic value of dobutamine stress echocardiography (DSE) for noninvasive assessment of CAV.

Methods and Results—In 109 heart transplant recipients, 333 DSEs were compared with 285 coronary angiograms and 199 IVUS analyses. Studies were repeated after 1, 2, 3, 4, and 5 years in 88, 74, 37, 18, and 7 patients, respectively. Resting 2D echocardiography detected CAV defined by IVUS and angiography with a sensitivity of 57% (specificity 88%). DSE increased the sensitivity to 72% (P=0.002). M-mode analysis increased the sensitivity of 2D rest and stress analysis (P=0.001, 0.004). Cardiac events occurred after 1.9% of normal stress tests by 2D analysis (combined 2D and M-mode: 0%), compared with 6.3% (3.8%) of normal resting studies. Worsening of serial DSE indicated an increased risk of events compared with no deterioration (relative risk 7.26, P=0.0014). Serial deterioration detected by stress only was associated with a higher risk of events than changes evident from resting studies (relative risk 3.06, P=0.0374).

Conclusions—DSE identifies patients at risk for events and facilitates monitoring of CAV. A normal DSE predicts an uneventful clinical course and justifies postponement of invasive studies. The prognostic value of DSE is comparable to that of IVUS and angiography. (Circulation. 1999;100:509-515.)

Key Words: transplantation ■ coronary disease ■ stress ■ echocardiography

Cardiac allograft vasculopathy (CAV) limits the long-term prognosis after heart transplantation (HTx).1–3 At present, the mainstay of diagnosis consists of invasive methods.1,2 Despite close follow-up intervals, rapid progression of CAV and sudden death may occur.1–5 The incidence of angiographically visible CAV is 40% to 60% 5 years after HTx.1–6 Angiography, however, fails to detect early changes.1–4,6 Intravascular ultrasound (IVUS) is the most sensitive invasive tool to identify CAV in vivo.1–3,7–9 Dobutamine stress echocardiography (DSE) emerged as the most promising of noninvasive tools for detection of CAV.10–17

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This prospective study was designed to analyze the value of DSE to detect CAV, to assess disease progression in serial studies, and to predict clinical events.

Methods

Study Population

Of 117 consecutive patients scheduled for routine angiography after orthotopic HTx, 109 (age 51±11 years, 39±37 (0.5 to 144) months after surgery; 23 women) with adequate echocardiographic image quality at rest were enrolled. Immunosuppression consisted of cyclosporine (n=90), tacrolimus (n=19), prednisone (n=96), and azathioprine (n=65). One hundred three patients received antihypertensive treatment (ACE inhibitors, n=70; diuretics, n=65; calcium channel blockers, n=51; others, n=2). All patients gave informed consent to the study protocol, which was approved by the University of Munich Ethics Committee.

Serial Studies

Serial DSE was performed in 88 patients (2 studies, n=88; 3, n=74; 4, n=37; 5, n=18; ≥6, n=7). The interval between studies was 11.6±3.8 months. Serial angiograms were available in 83 of 88 patients; 5 patients with severely compromised renal function were followed up by DSE only. At least 2 IVUS studies were done in 61 patients.

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Clinical Follow-Up
Clinical outcome was assessed at routine visits or by interviews with referring physicians. Cardiac events were defined as myocardial infarction, heart failure, retransplantation, cardiac death (sudden death without other reason, death from pump failure), or development of angiographic stenosis ≥75% treated by interventional revascularization. The decision to perform interventions was based on angiography, without knowledge of DSE results.

Dobutamine Stress Protocol
Dobutamine infusion was started at 5 μg·kg⁻¹·min⁻¹ and increased every 5 minutes by 5 μg up to 40 μg·kg⁻¹·min⁻¹. DSE was terminated according to standard criteria.15,18

Echocardiography
2D Echocardiography
At each step, cardiac cycles of 4 imaging planes (parasternal long- and short-axis, apical 2- and 4-chamber views) were digitized. Data were evaluated, with the researcher blinded to invasive results, by use of a side-by-side display of 4 stages (rest, 5 to 10 μg·kg⁻¹·min⁻¹, 10 to 15 μg·kg⁻¹·min⁻¹, and maximum dobutamine dose) of the same view. Discrepancies were resolved by a third expert. In a 16-segment model,19 wall motion in each segment was graded as normal/hyperkinetic, hypokinetic, akinetic, or dyskinetic (scores 1 to 4). Postoperatively altered septal motion with preserved systolic thickening was classified as normal.15,20 A wall motion score index (sum of scores divided by number of segments) of 1.0 at rest and 2.4* 1.27 vs 1.47 ± 0.22* 1.18 ± 0.18 vs 1.14 ± 0.18 vs 1.09 ± 0.15*

TABLE 1. Wall Motion Patterns (Index Study)

<table>
<thead>
<tr>
<th>Type of Response</th>
<th>Number of Studies</th>
<th>WMAs: No. of Segments</th>
<th>Wall Motion Score Index</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>Rest</td>
</tr>
<tr>
<td>Normal</td>
<td>54</td>
<td>49.5</td>
<td>0</td>
</tr>
<tr>
<td>Abnormal</td>
<td>55</td>
<td>50.5</td>
<td>0</td>
</tr>
<tr>
<td>Type A</td>
<td>10</td>
<td>18.2</td>
<td>0</td>
</tr>
<tr>
<td>Type B</td>
<td>25</td>
<td>45.4</td>
<td>5.2±2.6</td>
</tr>
<tr>
<td>Type C</td>
<td>10</td>
<td>18.2</td>
<td>2.8±2.0</td>
</tr>
<tr>
<td>Type D</td>
<td>10</td>
<td>18.2</td>
<td>3.5±1.6</td>
</tr>
</tbody>
</table>

Stress indicates maximum dobutamine dosage. *P<0.001 vs rest.

Coronary Angiography
Cardiac catheterization and right ventricular biopsies were obtained within 24 hours of DSE. Data were analyzed by at least 2 experts using a qualitative grading system: grade I, normal angiogram; grade II, luminal irregularities, diameter reduction <30%; grade III, diameter reduction <50%; grade IV, diameter reduction ≥50% and/or diffuse narrowing of small vessels.8

Intravascular Ultrasound
IVUS image acquisition and analysis at our institution were described in detail previously.6 Images were obtained from several coronary artery segments (5.0±1.6 segments per patient, range 3 to 11) by use of a mechanical 30-MHz system and a motorized pullback device (CVIS). The site with the most severe disease in each segment was graded according to the degree and circumferential extent of intimal hyperplasia on a 6-grade scale.8,15 A mean IVUS grade and

TABLE 2. Diagnostic Value of Echocardiography (Index Study)

<table>
<thead>
<tr>
<th>Echocardiography</th>
<th>No. of Studies</th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
<th>Positive Predictive Value, %</th>
<th>Negative Predictive Value, %</th>
<th>P, χ²</th>
<th>2D vs Stress</th>
<th>2D + M* vs Stress</th>
<th>Rest vs Stress</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resting echocardiogram</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2D analysis</td>
<td>98</td>
<td>57</td>
<td>88</td>
<td>90</td>
<td>51</td>
<td>0.0001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M-mode analysis</td>
<td>95</td>
<td>41</td>
<td>90</td>
<td>90</td>
<td>42</td>
<td>0.0021</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Combined 2D/M-mode analysis</td>
<td>98</td>
<td>72</td>
<td>85</td>
<td>90</td>
<td>61</td>
<td>0.0001</td>
<td>0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dobutamine stress echocardiogram</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2D analysis</td>
<td>98</td>
<td>72</td>
<td>88</td>
<td>92</td>
<td>62</td>
<td>0.0001</td>
<td>0.002</td>
<td></td>
<td></td>
</tr>
<tr>
<td>M-mode analysis</td>
<td>95</td>
<td>57</td>
<td>87</td>
<td>90</td>
<td>49</td>
<td>0.0001</td>
<td>0.041</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Combined 2D/M-mode analysis</td>
<td>98</td>
<td>85</td>
<td>82</td>
<td>90</td>
<td>73</td>
<td>0.0001</td>
<td>0.004</td>
<td>0.021</td>
<td></td>
</tr>
</tbody>
</table>

Reference methods: combined IVUS and angiography. *, †1- and 2-tailed McNemar test to compare sensitivity.
intimal index (intimal area/vessel cross-sectional area) were calculated from all segments analyzed in each patient.

Definition of CAV
CAV was defined by angiographic changes of grade II or greater and/or a mean IVUS grade >3.0.15

Definition of Disease Progression
An increase in the number of segments with WMAs or in the wall motion score by ≥1.0 was defined as progression of CAV by echocardiography, as was any visible deterioration by angiography or an increase in the intimal index by 5% by IVUS.21

Statistics
Data are given as mean±1 SD. Differences between groups were analyzed with unpaired Student’s t test or Mann-Whitney U test and differences between stress stages with a Wilcoxon test. Dichotomous variables were compared by a χ² test. The diagnostic value of 2D and combined 2D/M-mode echocardiography and corresponding rest/stress data were compared by a McNemar test. Probability values <0.05 were considered significant. One index study (the first study or the first study using all different methods) in each patient was selected for statistical assessment of the diagnostic and prognostic value. The index study and the following study were chosen for analysis of serial changes and subsequent events. This approach was used because serial studies in the same patient may not be independent. Nevertheless, all studies are described.

Results
Coronary Angiography
Angiograms were not obtained in 48 cases: patients with renal dysfunction (n=21), normal findings in 2 preceding studies (n=14), massive weight gain (n=2), and patient denial/other reasons (n=11). Of 285 angiograms, 158 (55.4%) were normal; grade II, III, and IV lesions were observed in 68 (23.9%), 14 (4.9%), and 45 studies (15.8%), respectively. Acute rejection >grade 1B (International Society for Heart and Lung Transplantation) was not observed.

Intravascular Ultrasound
IVUS was not performed in patients monitored without catheterization (n=48), in those with abnormal (n=52) or normal (n=9) angiography and IVUS at 2 preceding occasions, and for technical/other reasons (n=16). In 199 IVUS studies, 995 coronary segments in 316 major epicardial vessels were analyzed. The mean IVUS grade was >3.0 in 136 of 199 studies (68.3%).

Clinical and Hemodynamic Response to Dobutamine Stress
No patient developed angina. Heart rate (rest, 92±12 versus 88±16 bpm; maximum stress, 140±13 versus 139±17 bpm) and maximum dobutamine dosage (19.8±5.6 versus 18.8±6.4 μg·kg⁻¹·min⁻¹) were not different with and without CAV. Patients with CAV had a higher rate-pressure product at rest (11.6±2.2×10⁵ versus 10.6±2.2×10⁵ mm Hg/min, P<0.01) and maximum stress (19.5±4.6×10⁵ versus 17.9±3.3×10⁵ mm Hg/min, P<0.05). Hemodynamic parameters in serial studies were not different. Reasons to
terminate DSE were target heart rate \((220 - \text{age}) \times 0.85\) reached (77%); no increase in heart rate over \(>1\) stage (9%); patient discomfort (4%); symptom-associated blood pressure decrease (3%); WMA suggesting severe ischemia (3%); ventricular premature beats (1%); maximum dobutamine dosage (1%); and other reasons (2%). No severe adverse events occurred.

**Echocardiography**

Six 2D studies (technical reasons, \(n=1\); inadequate stress image quality, \(n=5\)) and 27 M-mode echocardiograms (technical reasons, \(n=6\); inadequate quality, \(n=21\)) could not be analyzed. Among 2D studies, 159 of 327 (48.6%) were normal. Stress-induced WMA occurred in 106 of 168 abnormal studies (63.1%; type A, \(n=20\); type B, \(n=86\)). Type C (D) reactions occurred in 29 (33) studies. Table 1 shows the index study data.

**Diagnostic Value**

WMA in any left ventricular area at rest had a sensitivity of 57% to detect CAV. Combined 2D and M-mode analysis at rest was superior to 2D analysis \((P=0.001; \text{Table 2})\). Stress testing increased the sensitivity of 2D and combined 2D and M-mode analysis \((P=0.002 \text{ and } 0.021; \text{Table 2})\).

Table 3 describes invasive findings within the main epicardial arteries and corresponding echocardiograms. Rest echocardiography had a poor sensitivity to identify regional disease, particularly in the left circumflex and right coronary arteries. Stress and, for left circumflex disease, also M-mode analysis improved the identification of regional CAV. Of 126 diseased vessels, 17 (13.5%) were detected by DSE only.

**Serial Studies: Detection of Changes**

Serial angiography and DSE were concordant in 55 of 81 studies (first serial pairs; 68%; no progression, \(n=40\); progression, \(n=15\)). Sensitivity of serial echocardiography to predict angiographic progression was 60%, specificity 71%, positive predictive value 48%, and negative predictive value 80% \((P=0.0072)\). All pairs of serial angiographic-echocardiographic studies showed concordant results in 130 of 181 comparisons (72%) (Figure 1A). Serial resting echocardiograms identified 67 of 89 changes (75%); in 22 cases (25%), changes were detected by stress testing only.

Combined serial IVUS-angiographic changes were concordant with 2D echocardiography in 56% (first paired studies). Serial DSE had a low sensitivity (47%) to detect changes defined by combined IVUS angiography (specificity 72%; positive predictive value 74%; negative predictive value 44%). Figure 1B shows the results of all paired studies.

**Clinical Outcome**

During follow-up over 3500 patient-months, 29 events occurred (interventional revascularization, \(n=15\); heart failure, \(n=5\); retransplantation, \(n=3\); death, \(n=6\)). One patient had an event after exclusion at follow-up DSE because of worsening image quality.

**Prognostic Value**

Normal findings at rest and even more at DSE indicated a lower risk for events than abnormal tests (Table 4). Patients with stress-induced WMA (type A and B) had a significantly higher risk of events than patients without stress-induced worsening (type C and D, normal DSE; risk ratio 9.16, \(P<0.0001\)). Wall motion score indices (rest, 1.19±0.16 versus 1.07±0.13, \(P<0.007\); stress, 1.33±0.24 versus 1.11±0.21, \(P<0.002\)) were higher in patients with abnormal DSE and subsequent events than in those without events. Considering all studies, 3.4% of normal and 14.9% of abnormal resting 2D echocardiograms were followed by changes. Four of 28 studies (14.3%) with events were identified by stress testing only. Figure 2 shows DSE patterns in relation to subsequent events. Two of 159 normal 2D DSEs (1.3%) were followed by events (death from humoral rejection; interventional revascularization of a 75% left marginal branch stenosis).

**Prognostic Value of Serial Studies**

Patients with worsening DSE had a higher risk of subsequent events than those without (Table 5). Deterioration detected by stress only indicated a higher risk than changes evident from resting studies (Figure 3; risk ratio 3.06, \(P=0.0374\)).
DSE changes identified subsequent events with a sensitivity comparable to that of angiography (Table 5). Both methods discriminate between patients at very low and at moderate risk. Combined IVUS-angiography did not improve the value of serial angiography (Table 5).

Discussion

This study is the first to compare serial DSE with angiography, IVUS, and clinical outcome. In addition to 2D analysis, wall thickening was quantified by M-mode analysis. The dobutamine dose was increased in smaller steps and kept constant longer than in other protocols.18,19 Although the peak dobutamine dose seems relatively low, the mean cumulative dose is comparable to that in these protocols.18,19 Recently, a 5-minute dobutamine protocol produced a greater hemodynamic benefit at lower doses than usual 3-minute protocols. 22

Diagnostic Value: Noninvasive Versus Invasive Findings

Although high-grade stenoses were present in only 45 of 285 angiograms, 2D DSE detected CAV with a sensitivity of 72%. This is compatible with previous studies after HTx.13–16 Systolic wall thickening was reduced in patients with morphological evidence of CAV, even if 2D echocardiography appeared normal. Our findings suggest that quantifying systolic thickening helps to detect CAV, particularly in the left circumflex artery. There, and in the right coronary artery, DSE had a lower sensitivity to detect CAV than in the left anterior descending artery. This is also known from coronary artery disease.23,24

Of patients with abnormal DSE, 90% had CAV by IVUS, but only 49% by angiography. This confirms that angiography is relatively insensitive in detecting CAV, even if 2D echocardiography appeared normal. Our findings suggest that quantifying systolic thickening helps to detect CAV, particularly in the left circumflex artery. There, and in the right coronary artery, DSE had a lower sensitivity to detect CAV than in the left anterior descending artery. This is also known from coronary artery disease.23,24

Assessment of Disease Progression

In a smaller study, DSE had a sensitivity of 84% to detect angiographic CAV progression.16 Our data show only a modest sensitivity (60%). Nevertheless, serial angiography and DSE were comparable in detecting CAV progression leading to events. Combined serial IVUS-angiography showed no close relation to DSE changes. Therefore, DSE may not be sensitive enough to detect an increase of intimal index of >5%, or such changes may be not relevant functionally. The threshold of 5% was based on a previous report.21 There is, however, no consensus on the number of sites to be analyzed or cutoff values of IVUS parameters in serial studies.21,28
Prognostic Impact

Resting echocardiography, particularly combined 2D/M-mode analysis, had an important prognostic impact, which was further improved by stress testing. A normal DSE had a high predictive value for an uneventful clinical course. These results confirm other studies after HTx and in patients with coronary artery disease. Stress-induced WMAs had the highest predictive value of subsequent events: 37% of type A/B DSE had events, compared with 10% in type C/D and with 1.8% in normal tests. Similarly, in coronary artery disease, stress-inducible WMAs indicated the highest risk of events.

The prognostic value of a single DSE study compared favorably with angiography, as was observed by other authors. IVUS, mean intimal thickness >0.3 mm was associated with an inferior clinical outcome.

Changes between serial tests yielded important prognostic information. Serial normal DSE indicated a very low risk of events. Similar findings were observed early after HTx. Serial DSE deterioration indicated a higher risk of subsequent events than no change. The relative risk for events after DSE worsening was slightly lower than with angiographic deterioration but higher than in IVUS-defined CAV progression.

Resting Versus Stress Echocardiography

Stress testing significantly improved the diagnostic and prognostic value of resting echocardiography. DSE improves stratification in patients with WMAs at rest: patients with additional stress-induced abnormalities have more events than those without. Serial changes detectable only by stress had a higher predictive value than those evident at rest. The incremental value of DSE justifies potential disadvantages: the additional cost is outweighed by the fact that invasive—and expensive—procedures may be avoided. DSE is safe, whereas invasive procedures carry some risks, which also include potential impairment of renal function by contrast agents.

Clinical Implications

According to interim results of our study, we implement DSE for routine monitoring of CAV. Beyond 1 year after HTx, invasive diagnosis is postponed if DSE is normal. If DSE is abnormal (particularly type A/B), angiography is recommended and patients are followed up by DSE in 4- to 6-month intervals.

Limitations

In 20 cases, the last DSE was not accompanied by angiography. The only events we may have missed, however, are stenoses leading to revascularization.

IVUS was not performed in all patients. Serial changes may therefore be underestimated in patients with normal angiograms.

WMAs and reduced wall thickening were interpreted as markers of CAV. Both findings, however, may be caused by decreased myocardial perfusion, impaired myocardial function, or a combination. Immune system-mediated processes may affect vessels and myocardium in cardiac allografts. Although study of vessel morphology identifies CAV in the strict sense, DSE may be superior in that it analyzes myocardial function and thus not only vascular but also myocardial sequelae of this immune system-mediated process.

The diagnostic value of DSE may have been underestimated in patients with submaximal heart rate response. All 7 events in this subgroup occurred in patients with type A/B DSE patterns. Both normal DSEs followed by events achieved the target heart rate.

The prognostic value is limited by the fact that many events were coronary interventions. The number of hard events was low, as in other studies; nevertheless, our data represent the largest echocardiographic study after HTx reported to date.

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**TABLE 5. Changes Between Serial Tests and Subsequent Events**

<table>
<thead>
<tr>
<th>Serial Test</th>
<th>No Progression, Events/Patients (Events/All Studies)</th>
<th>Progression, Events/Patients (Events/All Studies)</th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
<th>Positive Predictive Value, %</th>
<th>Negative Predictive Value, %</th>
<th>Relative Risk, Events/Patients (Events/All Studies)</th>
<th>P, Events/Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stress echocardiography (2D analysis)</td>
<td>2/50 (3/118)</td>
<td>9/31 (11/63)</td>
<td>82</td>
<td>69</td>
<td>29</td>
<td>96</td>
<td>7.26 (6.87)</td>
<td>0.0014</td>
</tr>
<tr>
<td>Angiography</td>
<td>2/56 (2/122)</td>
<td>10/27 (13/63)</td>
<td>83</td>
<td>76</td>
<td>37</td>
<td>96</td>
<td>10.37 (12.39)</td>
<td>0.0001</td>
</tr>
<tr>
<td>IVUS/angiography</td>
<td>2/22 (2/53)</td>
<td>9/44 (11/89)</td>
<td>82</td>
<td>36</td>
<td>20</td>
<td>91</td>
<td>2.25 (3.28)</td>
<td>0.2429</td>
</tr>
</tbody>
</table>

P, χ² test, progression vs nonprogression between index study and subsequent study (events/patients). Data on all serial pairs of studies (events/all studies) in parentheses.

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**Figure 3. Events after serial changes detected by resting echocardiography and by stress testing only.**
DSE depends on image quality and cannot be used in all patients. Furthermore, DSE requires more experience than resting echocardiography. If performed and read by experienced echocardiographers, however, DSE appears to be valuable to assess CAV.

Conclusions
Noninvasive DSE provides useful diagnostic and prognostic information in HTx patients. By serial DSE, the surveillance intensity for high- and low-risk patients may be modified. Normal DSE has a high predictive value for an uneventful midterm for high- and low-risk patients may be modified. Noninvasive DSE provides useful diagnostic and prognostic information in HTx patients. Furthermore, DSE requires more experience than experienced echocardiographers, however, DSE appears to be valuable to assess CAV.

References
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