Role of Dobutamine Stress Echocardiography for Diagnosis of Cardiac Allograft Vasculopathy


Cardiac allograft vasculopathy (CAV) remains a main factor limiting long-term survival after heart transplantation (HTX). Manifestations of CAV include focal stenoses as well as diffuse longitudinal involvement of vessels and small vessel disease. The clinical diagnosis is difficult, as the heart is denervated and usually remains without functionally relevant reinnervation. Routine coronary angiography is therefore the mainstay of diagnosis of CAV; this technique, however, shows a pure luminogram and is not able to detect early changes of CAV, ie, changes in the thickness of the vessel wall. Intravascular ultrasound (IVUS) has emerged as most sensitive invasive method for diagnosis of CAV. IVUS, however, can only be used to analyze the major epicardial vessels and is not able to investigate the entire coronary artery tree. In addition, both angiography and IVUS are invasive, costly and not free of risk.

Several tests employed for noninvasive detection of CAV have proven unsatisfactory. In some studies, this may be related to the mode of provocation of ischemia: physical exercise may be not adequate after HTX, as the chronotropic response to exercise is blunted due to denervation. Stress tests using vasodilators as dipyridamole, which induces relative differences of perfusion, may be less reliable in diffuse CAV, but appear to be superior to exercise tests. Pharmacologic stress testing using dobutamine can overcome the problems associated with other stress modalities. Indeed, dobutamine stress echocardiography (DSE) has emerged as the most promising noninvasive method for diagnosis of CAV. This article reviews our experience and published data on assessment of CAV by DSE.

DSE VERSUS CORONARY ANGIOGRAPHY AND IVUS

Several studies compared DSE with coronary angiography for diagnosis of CAV. Usually, any angiographic lesion irrespective of the degree of stenosis is regarded as marker of CAV. Two groups of investigators reported a sensitivity of regional wall motion analysis during DSE to detect angiographic CAV of 95% and 86%; the specificity was 55% and 91%, respectively. Our data yielded similar results (Table 1). In contrast, one study found DSE not useful for assessment of CAV; resting wall motion abnormalities (WMA) were seen in 11 of 28 patients (7 of 11 had CAV), but no stress induced WMA. IVUS is the most sensitive invasive test for assessment of CAV. There are, however, also some problems in using IVUS as a reference method. No generally accepted definitions exist, how many coronary vessels and segments should be evaluated by

Table 1. Sensitivity and Specificity of DSE for Diagnosis of CAV

<table>
<thead>
<tr>
<th>DSE Analysis</th>
<th>Reference Methods</th>
<th>No. Studied</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>2DE</td>
<td>Angiography</td>
<td>41</td>
<td>95%</td>
<td>55%</td>
<td>(5)</td>
</tr>
<tr>
<td>2DE</td>
<td>Angiography</td>
<td>37</td>
<td>86%</td>
<td>91%</td>
<td>(6)</td>
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<tr>
<td>2DE</td>
<td>Angiography</td>
<td>28</td>
<td>0%</td>
<td>100%</td>
<td>(8)</td>
</tr>
<tr>
<td>2DE</td>
<td>Angiography</td>
<td>46</td>
<td>83%</td>
<td>56%</td>
<td>(7)</td>
</tr>
<tr>
<td>2DE</td>
<td>IVUS</td>
<td>46</td>
<td>79%</td>
<td>83%</td>
<td>(7)</td>
</tr>
<tr>
<td>2DE</td>
<td>Angiography + IVUS</td>
<td>144</td>
<td>76%</td>
<td>82%</td>
<td>(9)</td>
</tr>
<tr>
<td>2DE + M-mode</td>
<td>Angiography + IVUS</td>
<td>139</td>
<td>85%</td>
<td>71%</td>
<td>(9)</td>
</tr>
</tbody>
</table>

Note: 2DE denotes regional wall motion analysis of two-dimensional echocardiograms. M-mode denotes quantitative analysis of systolic wall thickening by M-mode echocardiography. No. studied: number of tests performed. Further explanation: see text.
IVUS, or if the worst affected site or a mean value of several sites should be used for definition of CAV. We analyze in each coronary segment intimal thickness and circumferential extent of intimal hyperplasia according to a 6-grade scale; a mean grade of all segments investigated in a individual patient is calculated to reflect the total burden of intimal hyperplasia. A mean IVUS grade >3.0 is regarded as marker of moderate-to-severe intimal changes; this threshold has been shown to be clearly abnormal. Using this IVUS definition of CAV, regional wall motion analysis by DSE had a sensitivity of 79% and a specificity of 83%. The specificity of DSE in comparison with IVUS is clearly better than in comparison with angiography. This is explained by the fact, that over one third of patients with a normal appearing coronary angiogram have WMA at DSE, the majority of these patients have CAV when investigated by IVUS. Thus, WMA at DSE in patients with a normal angiogram may represent a false negative angiogram rather than a false positive DSE. Based on this findings, a combined angiographic and IVUS definition of CAV was used: either angiographic changes or, if the angiogram was normal, a mean IVUS grade >3.0 were regarded as indicators of CAV. With this definition of CAV, analysis by 2D-DSE in 144 studies had a sensitivity of 76%, while specificity was 82% (Table 1).

In addition to regional wall motion analysis, quantitative measurement of systolic wall thickening during DSE has been employed. In patients with CAV by angiography and/or IVUS, systolic thickening of septum and posterior wall was significantly lower than in patients without CAV. In a subgroup of patients without CAV, acute rejection, LV hypertrophy or other cardiac complications, normal values were calculated. The cut-off values (mean – 2SD) for systolic thickening were: septum, rest, >17.2%; septum, maximum stress, >45.9%; LV posterior wall, rest, >41.6%; LV posterior wall, maximum stress, >67.6%. When data below these values was regarded as abnormal, the M-mode analysis improved the sensitivity of the 2D-DSE from 76% to 85% (Table 1).

PROGNOSTIC RELEVANCE OF DSE

The impact of DSE findings on cardiac events (heart failure, unstable angina, myocardial infarction, revascularization, retransplantation, cardiac death) during follow-up has been investigated in three studies. In all studies, a negative DSE test was associated with an uneventful clinical course; none of 20 normal DSE, 1 of 42 normal DSE, and 1 of 87 normal DSE were followed by an event at follow up during mean observation periods of 8 to 24 months in the respective studies. On the other hand, 22 of abnormal 57 DSE, 5 of 21 abnormal DSE and 14 of 80 abnormal DSE were followed by an event. Newly developed WMA and a higher number of segments with WMA at DSE were indicators of subsequent cardiac events. These findings suggest, that DSE may help to identify patients with functionally relevant CAV at risk for future events.

CLINICAL IMPACT OF DSE AFTER HTX

As a noninvasive technique with a reasonable sensitivity and specificity, DSE may replace some of the commonly performed routine angiograms in HTX patients. Based on our experience and the prognostic outcome observed also by others, we propose to postpone angiography in patients with a normal DSE. Patients with WMA, but no relevant changes in serial DSE studies are now also followed non-invasively in intervals of 6 to 12 months, with invasive testing every 24 months. Tests showing new WMA indicate a high risk and require invasive diagnosis and eventually therapy (revascularization, retransplantation); these patients are followed by control DSE at shorter intervals of 4 to 6 months. The value of this new monitoring schedule at our institution in comparison to nonflexible routine annual angiography remains to be confirmed in larger numbers of patients.

LIMITATIONS

The main limitation of DSE is the restriction to patients, in whom adequate echocardiographic images can be obtained. About 10% of patients cannot be monitored by DSE. All published studies interpreted WMA as indicator of CAV. There are, however, no data to confirm, whether WMA are caused by perfusion abnormalities or by an altered myocardial contractile reserve. Nevertheless, both vascular and myocardial alterations might be caused by the same chronic immunologic process, which was previously termed chronic rejection and is the supposed underlying mechanism of CAV.

CONCLUSION

DSE is a useful noninvasive method for detection of functionally relevant CAV and for prediction of prognosis after HTX. With help of DSE, the indication for invasive diagnosis may be planned individually, and unnecessary procedures may be avoided.

REFERENCES


