Stress Echocardiography After Cardiac Transplantation

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35.1 Background

Cardiac transplantation is an increasingly important treatment for end-stage cardiac disease, but rejection continues to be a major complication [1]. Rejection can be either acute or chronic (Table 35.1). Acute rejection is a major problem in the first year following cardiac transplantation. It is characterized by normal epicardial coronary arteries, with a concomitant restriction in coronary flow reserve [2], a pathophysiological hallmark of microvascular disease, as has been described in other situations such as syndrome X or hypertension with normal coronary arteries [3, 4]. In particular, during acute cardiac rejection, the reversible reduction of coronary reserve could be the result of the limitation of vasodilation due to functional abnormalities such as metabolically or immunologically related decreased responsiveness of vascular wall to vasodilator stimuli or to structural abnormalities, for example, interstitial edema or cellular infiltration [2]. Immunosuppressive treatment can resolve structural and functional abnormalities and restore the normal coronary flow reserve [2].

Cardiac allograft vasculopathy (CAV) is a major factor limiting long-term prognosis after heart transplantation [1]. In several respects, the disease differs from atherosclerotic coronary artery disease. The mechanism is thought to be immune-mediated. An early manifestation of CAV is thickening of the vessel wall, with progression to diffuse involvement of the vessel in the longitudinal direction or development of more focal, localized stenosis [5–7]. Small-vessel disease is also common, and contributes to the reduction in coronary flow reserve [8, 9, 10] and unfavorable outcome [11, 12]. The disease may develop rapidly within months and the clinical diagnosis of CAV is difficult. As the transplanted heart is surgically denervated and remains without functionally relevant reinnervation in most patients, angina pectoris does not usually occur. Several noninvasive tests have proven to be of limited value for the detection of CAV [13–16]. This may be explained by some of the specific features of CAV and by the specific alterations of cardiac physiology in heart transplant recipients. For example, exercise electrocardiography is a priori restricted to a minority of transplant recipients due to the high prevalence of (most commonly right) bundle branch block and

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Table 35.1 Heart transplant rejection

	Acute	Chronic
Pathological changes	Edema, cellular infiltrates, myocyte damage	Diffuse coronary artery wall thickening (with focal stenosis)
Diagnostic gold standard	Endomyocardial biopsy	Intracoronary ultrasound (coronary angiography)
Reversibility upon treatment	Yes	No
Rest echocardiography	Increase wall thickness/ texture/decrease in ejection fraction	Segmental abnormalities, decreased systolic thickening
Stress test	ST depression and no dysfunction	Regional dysfunction
Coronary flow reserve	Reduced	Reduced
Stress echocardiography prognostic value	Possible	Proven

altered repolarization in this population. In addition, the mode of provocation of ischemia is important. Physical exercise may not be adequate, because heart transplant recipients frequently have a reduced exercise capacity due to muscular weakness following long-term deconditioning and corticosteroid immunosuppression. More important, the chronotropic response to physical exercise is limited due to cardiac denervation; the reduced increase in heart rate may therefore not be adequate to reach the ischemic threshold in all heart transplantation patients. The limitations of a physical exercise test in transplantation patients have been shown in combination with various diagnostic techniques such as exercise electrocardiogram, radionuclide angiography, or exercise echocardiography [13–17]. The mainstay of CAV diagnosis is currently still made up of invasive techniques [1]. Coronary angiography only presents a luminogram and may not be able to detect diffuse concentric thickening of the vessel wall. Intravascular ultrasound (IVUS) is the method of choice to detect alterations of the vessel wall and has emerged as the most sensitive invasive method for diagnosing CAV [18]. Although most investigators measure thickness and extension of intimal hyperplasia by IVUS, no commonly accepted cut-off points or standardized IVUS definitions for CAV exist (minimal number of coronary segments and vessels necessary for valid diagnosis, grading by worst affected sites or mean values).

35.2 Pharmacological Stress Echocardiography for Detection of Acute Rejection

The main resting transthoracic echocardiographic variables proposed for diagnosis of acute allograft rejection include increased wall thickness and wall echogenicity, pericardial effusion, left ventricular diastolic dysfunction and regional or global systolic dysfunction [19–21]. In general, the results have not been encouraging and no single echocardiographic variable alone can be used for accurate detection of acute allograft

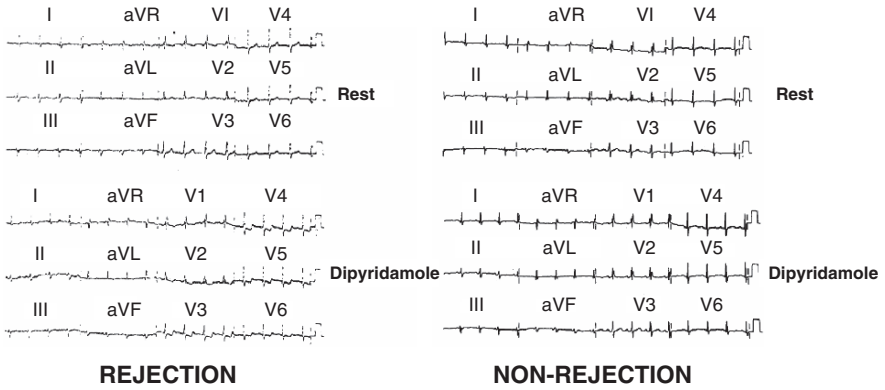

Fig. 35.1 Stress electrocardiogram during acute rejection. The 12-lead electrocardiogram is shown on day 21 after transplantation in resting conditions (*upper panel*) and at peak dipyridamole (*lower panel*). At peak dipyridamole, the electrocardiogram shows a transient ST-segment depression. This patient had bioptic evidence of rejection. (From [14], with permission)

rejection [18]. In acute rejection, coronary flow reserve can be acutely impaired [22] and this is mirrored by transient ST-segment depression during stress, as is typical of microvascular angina [3]. These changes typically occur in the absence of wall motion abnormalities [22] and outline a potential role of coronary flow reserve for the diagnostic evaluation of these patients [23] (Fig. 35.1).

35.3 Pharmacological Stress Echocardiography for Detection of Chronic Rejection

Rest- and stress-induced abnormalities can be detected with pharmacological stress echocardiography using dipyridamole [15, 24, 25] or dobutamine [26–35]. As in native coronary artery disease, both tests have a high feasibility rate and a low incidence of reported limiting side effects [18]. In a series systematically evaluating coronary angiography and intracoronary ultrasound, dobutamine stress echocardiography demonstrated wall motion abnormalities in 40% of patients with an apparently normal angiogram [29]. If angiography is used as a reference method, these findings have to be interpreted as false-positive dobutamine stress tests and would therefore explain the relatively low specificity of the stress tests compared to angiography [28–30]. However, the majority of IVUS studies in patients with a normal angiogram revealed moderate to severe intimal hyperplasia, and two-thirds of normal angiographic studies have an abnormal dobutamine stress test and/or IVUS evidence of CAV [20]. In evaluating noninvasive test results, one should consider that angiography is relatively insensitive in detecting CAV and that a normal angiogram in a heart transplant recipient does not exclude functionally relevant CAV [18, 19], which may be mirrored by functional abnormalities during stress (Figs. 35.2, 35.3). A normal pharmacological stress echocardiography result after heart transplantation has a high predictive value for an uneventful clini-

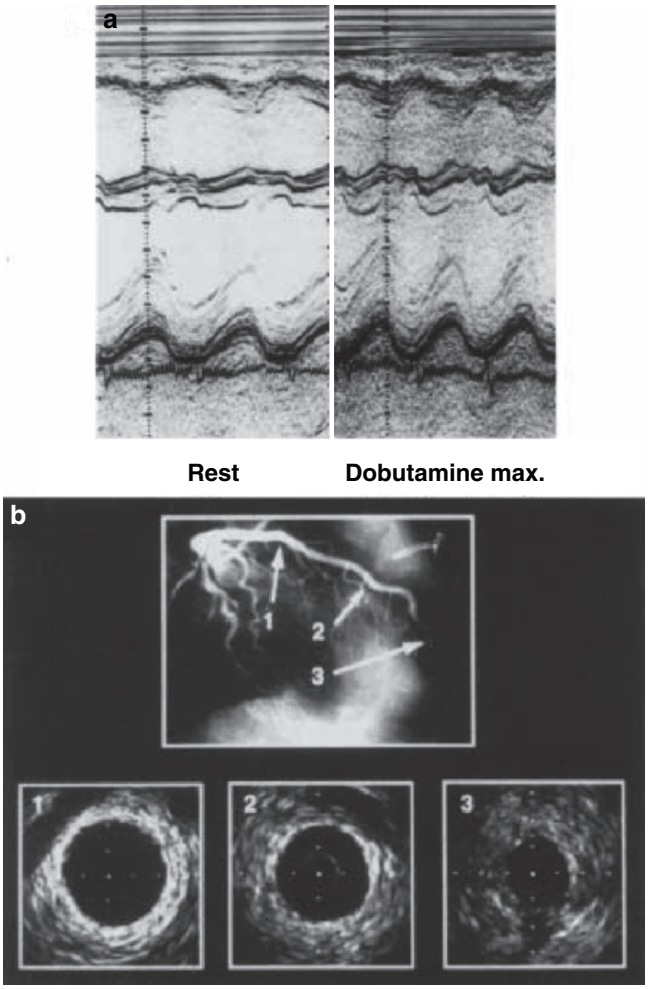

Fig. 35.2 Forty-eight months after transplantation. **a** *M*-mode echocardiogram. Normal systolic wall thickening at rest (*left*) and during maximum dobutamine stress (*right*). **b** Coronary angiogram and intravascular ultrasound (IVUS). Normal left coronary artery by angiography. Absence of significant intimal hyperplasia at three sites (*arrows*) of the left anterior descending artery by IVUS. (From [18], with permission)

cal course [20, 21]. The value of the test seems to be at least comparable to that of a normal angiogram, and a normal pharmacological stress test allows invasive diagnostic procedures to be safely delayed [30–35], especially if coronary flow reserve detectable by transthoracic echocardiography is also above normal (suggested to be 2.7 in these patients) [36]. If the stress test is normal by wall motion and coronary flow reserve criteria, invasive diagnosis is delayed and the next test is scheduled after 12 months [20, 22]: Fig. 35.5. If stress echocardiography shows all motion abnormalities, angiography is performed and, if this test does not yield evidence of CAV, an additional IVUS study might be warranted. This algorithm

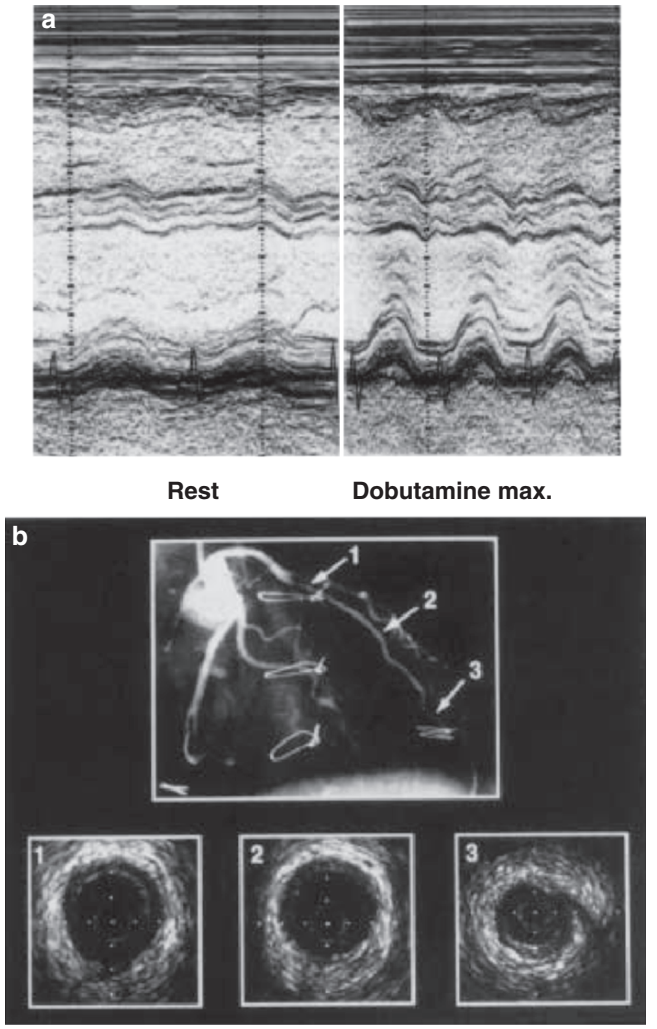

Fig. 35.3 Forty-eight months after transplantation. **a** *M*-mode echocardiogram. Reduced systolic wall thickening at rest (*left*). During maximum dobutamine stress (*right*), septal thickening remains unchanged, whereas posterior wall thickening increases. **b** Coronary angiogram and intravascular ultrasound (IVUS). Contour irregularities without relevant stenosis in left coronary artery by angiography. Severe intimal hyperplasia at three sites (*arrows*) of the left anterior descending artery by IVUS. (From [18], with permission)

helps avoid repeat cardiac catheterization in some patients and leads to a closer surveillance of patients with evidence of functionally relevant and/or progressive CAV [20–22]. This aspect of noninvasive radiation-free follow-up of heart transplant patients is especially important in pediatric patients, in whom dobutamine stress echocardiography was shown to be highly feasible and effective for diagnostic and prognostic purposes [34, 35].

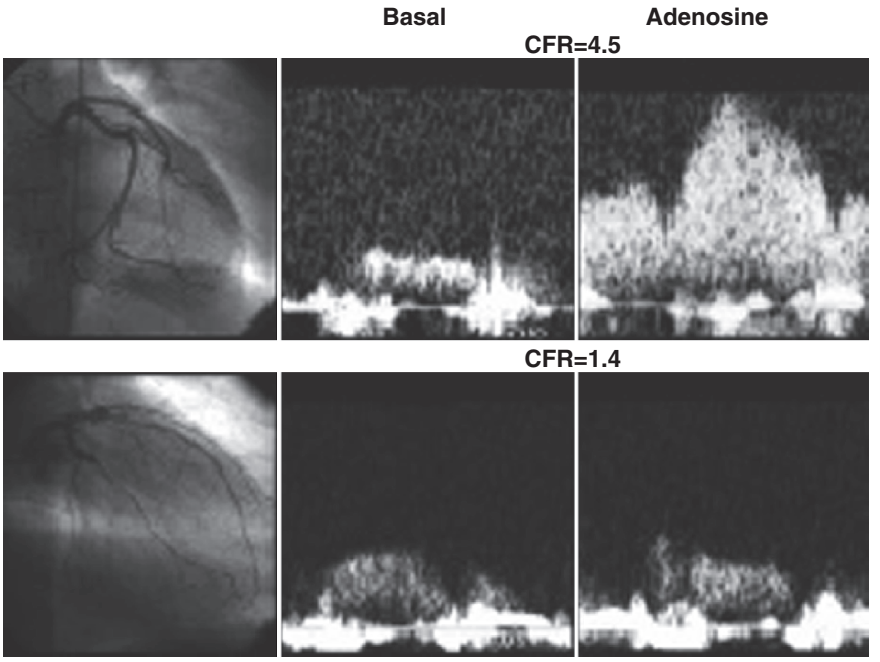

Fig. 35.4 Coronary angiography and coronary flow reserve findings in a patient without (upper panels) and with (lower panels) rejection, which severely reduces coronary flow reserve. (From ref. [23]).

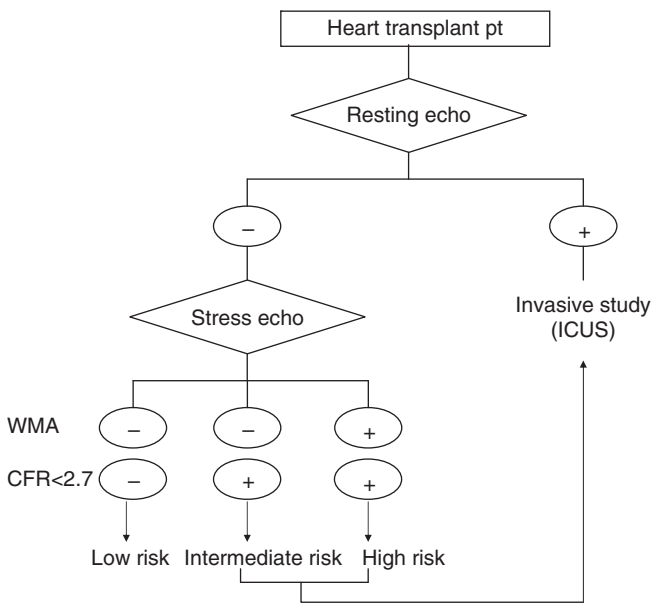

Fig. 35.5 A proposed diagnostic flow-chart in the surveillance of posttransplantation patient. Yearly testing with pharmacological stress echocardiography may help to reduce the need for invasive studies. The reliability of pharmacological stress echocardiography is stronger when the test response shows no wall motion abnormalities and normal coronary flow reserve on left anterior descending artery during transthoracic vasodilation stress echocardiography. CFR, coronary flow reserve; ICUS, intracoronary ultrasound; WMA, wall motion abnormalities

35.4 Pharmacological Stress Echocardiography for Recruitment of Donor Hearts

The heart transplantation is a treatment of heart failure, which is not responding to medications, and its efficiency is already proved: unfortunately, organ donation is a limiting step of this life-saving procedure. Heart donor shortage is a society problem [37]. Patients on the heart transplant waiting list have a 7.3% death rate, and the average waiting time is 2–3 years. As an example, in Italy, approximately 650 patients are on the transplant list and only about 300 transplantations are performed each year. An effective way to solve the current shortage would be to accept an upward shift of the age cutoff limit (from current 45 to 70 years) but age-related high prevalence of asymptomatic coronary artery disease and occult cardiomyopathy severely limit the feasibility of this approach. Recently, Bombardini and coworkers have proposed an alternative approach based on pharmacological stress echocardiography performed at bedside in marginal donors (aged>55 years) [38]. When resting and stress echocardiography results are negative, a prognostically meaningful underlying coronary artery disease or cardiomyopathy can be ruled out and the heart can be rescued and transplanted (Fig. 35.6). Although certainly more data are needed at this point, the appeal of this stress echocardiography-driven way to select hearts "too good

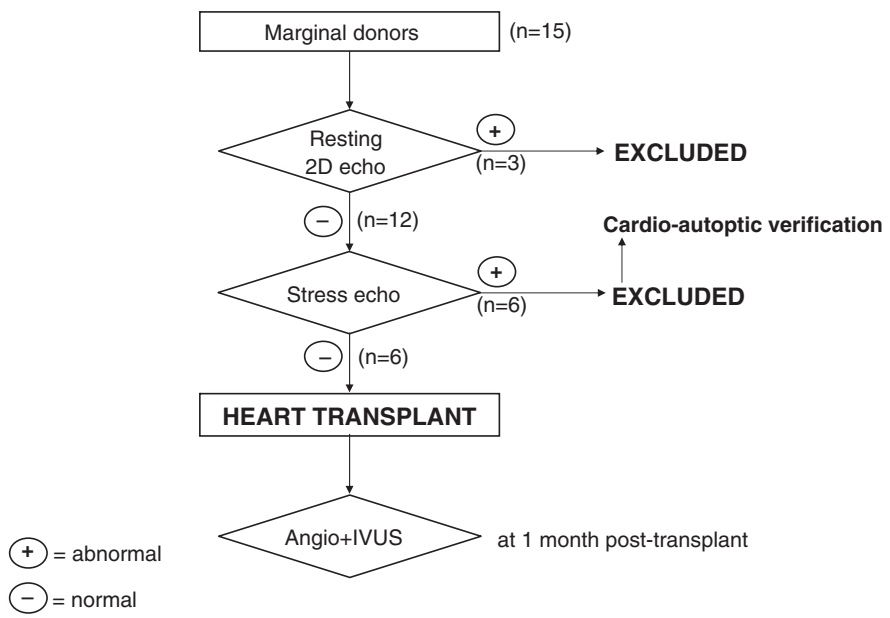

Fig. 35.6 The initial experience with pharmacological-stress echocardiography in recruiting hearts from marginal donors (>55 years). A negative stress echocardiography result deems hearts otherwise lost to donation eligible for donorship. IVUS, intravascular ultrasound (From [39])

Table 35.2 Clinical applications of stress echocardiography in heart transplantation

	Acute rejection	Chronic rejection	Donor recruitment
Unproven	√		
Established		√	
Investigational			√

to die" is exciting for its potential to drastically solve the current mismatch between donor need and supply, with a very favorable cost–benefit profile. The cost of a donor heart is estimated around €200,000 on the "transplant black market." We can recruit otherwise ineligible hearts at the cost of one stress echocardiography (around 500 at the average cost in Europe), with obvious downstream economic benefits.

35.5 Conclusions

Stress echocardiography in cardiac transplantation has three main potential applications: the detection of acute rejection in the first year after cardiac transplantation; the detection of chronic rejection later after cardiac transplantation; and the recruitment of marginal donor hearts as a way to solve the current donor heart shortage (Table 35.2). The three applications have different clinical roles today. Despite the ongoing efforts of old and innovative resting and stress echocardiographic techniques in predicting biopsy-proven acute rejection, endomyocardial biopsies are still regarded as the gold standard for the detection of acute allograft rejection, which is often associated with an acute reduction in coronary flow reserve of potential diagnostic value. Conversely, stress echocardiography is able to identify cardiac graft vasculopathy accurately and has a recognized prognostic value in this clinical setting, where a normal stress echocardiography by wall motion criteria justifies avoiding or delaying invasive studies. In the setting of cardiac allograft vasculopathy, the integration of coronary flow reserve to transthoracic stress echocardiography might further improve the value of the method. Finally, the use of bedside stress echocardiography is still purely investigational, although promising, to select appropriately marginal heart donors with brain death to solve the current shortage of donor heart supply.

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