Electrocardiographic Changes Suggestive of Myocardial Ischemia Elicited by Dipyridamole Infusion in Acute Rejection Early After Heart Transplantation

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Acute cardiac rejection, syndrome X, and arterial hypertension can induce small vessel damage and, therefore, restriction of coronary reserve in the presence of normal epicardial coronary arteries. A characteristic response pattern to dipyridamole (DIP) infusion has been previously described in syndrome X and arterial hypertension: ST segment depression without any measurable systolic dysfunction. The aim of this study was to establish whether acute cardiac rejection might induce electrocardiographic alterations during DIP infusion. Changes in the 12-lead electrocardiogram and two-dimensional echocardiogram during high-dose DIP infusion (up to 0.84 mg/kg in 10 minutes) were evaluated within 24 hours of endomyocardial biopsy in 14 transplanted patients. A total of 47 biopsy-controlled DIP studies were performed within 5 weeks after cardiac transplantation. For each patient, at least 7 days elapsed between two consecutive studies. Electrocardiographic and echocardiographic tracings were analyzed without prior knowledge of endomyocardial biopsy findings. No remarkable side effects occurred in any case, so that the DIP study could be completed in all patients. A diagnostic (>0.1 mV) ST segment depression was found in 11 studies. The sensitivity and specificity of DIP-induced ST segment depression for the detection of biopsy-proven acute rejection were 72% and 94%, respectively. These data show that DIP stress is feasible and safe in transplanted patients and that acute cardiac rejection can be accompanied by DIP-induced ST segment depression without detectable impairment in systolic function. These changes might provide noninvasive markers for surveillance of rejection. (Circulation 1990;81:72–77)

Cardiac transplantation is an increasingly important treatment for end-stage cardiac disease, but rejection continues to be a major complication. Despite the recent development of several noninvasive parameters, both immunologic and functional,1 for detection of cardiac allograft rejection, serial endomyocardial biopsies are needed for monitoring patients. Biopsy is an invasive and expensive approach to detecting rejection. A noninvasive modality that guides the timing of endomyocardial biopsy and assesses the response to changes in immunosuppressive therapy would be advantageous.

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Acute cardiac rejection can induce a restriction of coronary reserve in the presence of normal epicardial coronary arteries.2–4 A reduction in flow reserve attributed to microvascular damage can also be found in other conditions, such as syndrome X5,6 and arterial hypertension.7,8 A characteristic response pattern to dipyridamole infusion has been previously described in syndrome X3 and arterial hypertension: ST segment depression without any measurable regional or global systolic dysfunction. The aim of this study was to establish whether acute cardiac rejection might induce electrocardiographic alterations during dipyridamole infusion.

Methods

Patients

The patient population consisted of 14 cardiac allograft recipients (11 men and three women), aged 19–64 years (mean, 48.6 years). According to clinical
needs, all were receiving standard immunosuppressive and cardiac medications, which were not discontinued at the time of dipyridamole studies. Cyclosporine A was given at the dosage of 250/360 mg/day from 0–30 days after transplant and at the dosage of 60/180 mg/day after the 30th day. Azathioprine was given at 50–75 mg/day. In case of biopsy-proven acute rejection, prednisone was started at 1 g/day for 3 days; in case of continuing rejection, deltacortene was started at 100 mg/day for 3 days. When rejection persisted, timo-globulins and OKT3 were started with individually adapted dosages.

All patients gave their informed consent before entering the study. Whenever possible, the first dipyridamole study was performed on the seventh day, when all inotropic drugs had been discontinued and patients were hemodynamically and clinically stable. Subsequent serial studies were carried out within 24 hours of myocardial biopsy during the first 5 weeks after transplantation. All patients were studied in the supine position after 15 minutes of rest to achieve basal heart rate and blood pressure. No patient had ST segment depression on resting electrocardiogram.

All patients underwent endomyocardial biopsy at 7, 15, 21, 28, and 45 days after the transplant; for each biopsy, at least three samples adequate for analysis were obtained. Dipyridamole testing was performed within 24 hours of each biopsy.

**Dipyridamole Testing**

Two-dimensional echocardiographic monitoring was performed in combination with dipyridamole infusion\textsuperscript{12,13} (0.56 mg/kg for 4 minutes, 4 minutes of no dose, and then 0.28 mg/kg in 2 minutes). The cumulative dose was 0.84 mg/kg over 10 minutes. During the procedure, the blood pressure (by cuff sphygmomanometer) and the 12-lead electrocardiogram were recorded by the minute. Two-dimensional echocardiograms were continuously performed, and intermittently recorded, during and up to 10 minutes after dipyridamole administration. A commercially available wide-angle phased-array imaging system with 2.25 and 3.5 MHz transducers (model 77020, Hewlett-Packard, Palo Alto, California) was used. All patients received intravenous aminophylline (70 mg for 1 minute) at the end of the test to abate side effects.

**Data Analysis**

All electrocardiographic and echocardiographic studies were analyzed without prior knowledge of the biopsy findings. Electrocardiographic changes were visually analyzed by two independent and experienced observers (J.A.S. and A.D.) and considered diagnostic when there was an ST segment depression of at least 0.1 mV 0.08 seconds after the J point, as compared with baseline. A unanimous decision was reached in 45 cases; in the remaining two cases, there was a consensus decision.

The videotapes with echocardiographic images were analyzed by two independent observers (G.D.P. and E.P.). The criterion for a positive echocardiographic study was the development of a transient regional dyssynergia, absent in resting conditions.\textsuperscript{12,13} In all cases there was a unanimous decision regarding positivity or negativity. Segmental anatomy and wall motion were assessed in a qualitative manner as previously reported.\textsuperscript{12,13} In all studies, the percent ejection fraction and the end-systolic volume of the left ventricle were measured with the single-plane “area-length” method from the apical four-chamber view in resting conditions and at 1 minute after the end of the full dipyridamole infusion.

Biopsy findings were interpreted by two experienced and independent pathologists (E.A. and A.P.) who were unaware of the electrocardiographic and echocardiographic results. The findings were assigned to one of three categories: 1) normal (no evidence of rejection), 2) mild cell infiltration with myocyte necrosis, or 3) severe myocyte necrosis with interstitial edema and hemorrhage.\textsuperscript{14} A unanimous decision was reached in 45 cases; in the remaining two cases, there was a consensus decision.

**Statistical Analysis**

For each variable, the mean value and the SD were reported. Intergroup differences were tested for significance by Student’s t test for unpaired values.

**Results**

**Histologic Findings**

Eleven biopsies showed evidence of acute rejection; nine showed mild rejection; and two showed moderate rejection. In eight patients, all biopsy studies were negative for rejection; in six patients, at least one study had evidence of rejection (Table 1).

**Feasibility of Dipyridamole Studies**

Electrocardiographic and two-dimensional echo images were adequate for analysis in all patients. Side effects due to dipyridamole were always of mild severity and well tolerated by the patients so that the test could be completed in all patients. Headaches occurred in eight patients (17%) undergoing dipyridamole studies; mild transient facial flushing occurred in 17 (36%); and dizziness occurred in one (2%). Patients who experienced a side effect during the first study usually had this effect in the repeat studies. In all patients, aminophylline promptly abated side effects at the end of the study. No patient had severe (>40 mm Hg) hypotension during the study; the detailed hemodynamic findings are reported in Table 2.

**Two-dimensional Echocardiographic Findings**

In resting conditions, all patients showed a normal regional and global contraction; none had increase in thickness or abnormal echo texture.

No patient showed a regional dyssynergia during dipyridamole infusion. The end-systolic volume showed similar values for the 11 patients with rejection and the 36 patients without rejection in resting conditions (41.6±3.2 vs. 36±3.4 ml/m²,
TABLE 1. Dipyridamole Studies

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ECG, ST segment depression assessed by 12-lead electrocardiogram during dipyridamole infusion; H, rejection determined by endomyocardial biopsy; +, presence; −, absence; ···, no test performed.

*p=NS) and at peak dipyridamole (38.8±2.6 vs. 32.4±3 ml/m²). The percent ejection fraction also showed similar values between the patients with and without rejection in resting conditions (38.2±3.7 vs. 42.5±4.3%, p=NS) and at peak dipyridamole (42.2±3.6 vs. 46.8±4.9%, p=NS).

12-Lead Electrocardiographic Findings

During dipyridamole infusion, ST segment depression appeared in 11 patients (Figure 1) in the absence of any detectable impairment in systolic function. The leads showing diagnostic changes were usually the precordial ones (mostly V₆–V₆); in four patients, ST segment depression was also detectable in limb leads.

Correlation Between Histologic Findings and Electrocardiographic Findings During Dipyridamole

Of the 11 patients with biopsy-proven rejection, eight had ST segment depression during dipyridamole; in the three patients without ST segment depression, rejection was of mild severity. The overall sensitivity of dipyridamole-induced ST segment depression for biopsy-proven acute rejection was 72%; the specificity was 94% (Figures 1 and 2). In the three patients with a false-positive dipyridamole test (i.e., ST segment depression in the absence of rejection), the subsequent dipyridamole study was again positive, and the biopsy response became positive (patients 8 and 9 in Table 1).

Discussion

These data show that dipyridamole echocardiography is feasible and safe in transplanted patients and that acute cardiac rejection in the early posttransplant period is often accompanied by dipyridamole-induced ST segment depression without any measurable impairment in systolic function.

Pathophysiologic Meaning of Dipyridamole-Induced ST Segment Depression

The transient dipyridamole-induced ST segment depression during an episode of acute rejection might indicate a subendocardial underperfusion. The dissociation between ST segment changes and left ventricular systolic function may appear surprising, since the regional mechanical dysfunction is usually considered an earlier and more sensitive marker of myocardial ischemia. However, such a response pattern to dipyridamole stress is frequently found in other situations, such as syndrome X⁹ and essential hypertension with chest pain and normal epicardial coronary arteries. In all these conditions, and in acute cardiac rejection as well, a small vessel disease of the coronary tree has been hypothesized with the pathophysiologic hallmark of a reduced coronary reserve and normal epicardial coronary arteries. In particular, during acute 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, such as

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Values are mean±SD.
*p<0.05 vs. basal.
interstitial edema or cellular infiltration. The administration of cyclosporine might also contribute to coronary small-vessel damage; it has already been shown that cyclosporine can alter blood flow of renal transplants by stimulation of the renin-angiotensin system, inhibition of prostaglandin-mediated vasodilation, the action of cyclosporine α-agonists on sympathetic receptors, or arteriopathy. In the presence of a reduced coronary flow reserve, the infusion of a coronary arteriolar dilator such as dipyridamole might shunt blood to the subepicardium away from the subendocardium, where the increase in resistances due to the interstitial and perivascular infiltration of inflammatory cells and edema can be more pronounced. The process of subendocardial underperfusion can be extensive enough, in a horizontal or circumferential sense, to determine ST segment changes. However, the vertical or "transmural" extent of underperfusion is not sufficient to provoke a regional mechanical dysfunction, which only occurs when more than 30–40% of the ventricular wall is rendered ischemic. However, it is interesting to notice that, although not significant, there was a trend toward lower values of percent ejection fraction in the rejection group in resting conditions and at peak dipyridamole.

**Clinical Implications**

It has been previously shown that dipyridamole echocardiography is a useful tool for the diagnosis of angiographically assessed coronary artery disease. Major advantages of this test are high feasibility, safety, and low cost. The present study shows that the test is feasible, well tolerated, and safe also in transplanted patients. The findings of this study document the paramount importance, in this particular setting, of the electrocardiographic monitoring and the little additive information pro-
FIGURE 2. Electrocardiogram showing no rejection. The 12-lead electrocardiogram of patient 8 (same patient as in Figure 1) is shown on day 45 after transplant in resting conditions (upper panel) and at peak dipyridamole (lower panel). The resting electrocardiogram is similar to that recorded on day 21 (upper panel of Figure 1). However, at peak dipyridamole, no significant ST segment changes are observed. The patient had no biopic evidence of rejection.

References

KEY WORDS • transplantation • electrocardiography • dipyridamole • ST segments
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