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Efficacy of Augmented Immunosuppressive Therapy for Early Vasculopathy in Heart Transplantation

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Objectives. **The present study was undertaken to prospectively and comparatively evaluate the role of serial myocardial perfusion imaging and coronary angiography for the detection of early vasculopathy in a large patient population and also to determine the short- and long-term efficacy of augmented immunosuppressive therapy in the potential reversal of the early vasculopathy.**

Background. **Allograft vasculopathy is the commonest cause of death after the first year of heart transplantation. Anecdotal studies have reported the efficacy of augmented immunosuppressive therapy after early detection of vascular involvement. However, no prospective study has evaluated the feasibility of early detection and treatment of allograft vasculopathy.**

Methods. **In 76 cardiac allograft recipients, 230 coronary angiographic and 376 scintigraphic studies were performed in a follow-up period of 8 years. Angiography was performed at 1 month and every year after transplantation, and thallium-201 scintigraphy at 1, 3, 6 and 12 months after transplantation and twice a year thereafter. Prospective follow-up of 76 patients showed that 18 developed either angiographic or scintigraphic evidence of coronary vasculopathy. All episodes were treated with 3-day methylprednisolone pulse and antithymocyte globulin.**

Results. **Twenty-two episodes of vasculopathy were diagnosed and treated in these 18 patients. Of these 22 episodes, two were detected only by angiography, seven by both angiography and scintigraphy, four by scintigraphy and histologic evidence of vasculitis and nine episodes only by thallium-201 scintigraphy studies. Angiographic and/or scintigraphic resolution was observed in 15 of the 22 episodes (68%) with augmented immunosuppression. The likelihood of regression was higher when treatment was instituted within the first year of transplantation (92%) than after the first year (40%) ($p = 0.033$). Eighty percent of patients who responded to follow-up.**

Conclusions. **The present study suggests that early detection of allograft coronary vasculopathy is feasible with surveillance myocardial perfusion or coronary angiographic studies. When identified early after transplantation, immunosuppressive treatment may result in regression of coronary disease.**

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Transplant-associated vasculopathy is the most important limiting factor in the long-term survival of cardiac allografts (1–5). The incidence of angiographically demonstrable coronary artery disease has been reported in up to 15% of heart transplant recipients at 1 year, 25% at 2 years and 50% at 5 years. Most patients do not complain of chest pain on development of coronary vasculopathy, and the clinical manifestations predominantly include ventricular arrhythmias, silent myocardial infarction, congestive heart failure and sudden death (6,7).

Although the pathogenesis of the allograft vasculopathy has not been clearly elucidated (8), the diffuse pattern of distribution, involvement of both arteries and veins and absence of vasculopathy in vessels outside the graft suggest its relation to rejection (9). The transplant-associated vasculopathy is characterized by diffuse and concentric fibrointimal proliferation of coronary vasculature including small intramyocardial branches (10,11). The chronic fibrotic vascular changes have been reported to evolve over months to years and may have their origin in damage occurring during earlier reversible episodes of rejection (12,13). The acute or subacute episodes of inflammatory changes in the vessel wall have been characterized by the presence of mononuclear cell infiltrates as well as the accumulations of immunoglobulin and complement and have often been referred to as *vascular rejection*. If rejection is the basis of vasculopathy, intervention with immunosuppressive therapy should be able to prevent progression of the disease process (14). We have previously reported 4 patients who developed evidence of diffuse coronary involvement on coro-

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Abbreviation and Acronym
ISHLT = International Society of Heart and Lung Transplantation

nary angiography within 2 months after heart transplantation (15). All patients were treated with methylprednisolone and antithymocyte globulin, and all demonstrated complete angiographic resolution of vascular occlusion.

This prospective study was undertaken in a large patient cohort with the following objectives: i) to evaluate and compare the role of serial myocardial perfusion imaging and coronary angiography in early recognition of coronary vasculopathy; ii) to determine the short-term effects of augmentation of immunosuppressive therapy on early allograft vasculopathy; and iii) to assess the long-term efficacy of early intervention.

Methods

Study protocol. A total of 76 patients who received orthotopic heart transplantation at the Sant Pau Hospital, Barcelona were prospectively screened for the development of graft vasculopathy from the first month after transplantation. The evaluation included 230 coronary angiography procedures and 376 myocardial perfusion imaging studies over a period of 8 years (March 1986 to February 1994). Coronary angiography was performed at the end of the first month and yearly thereafter. The exercise thallium-201 studies were performed at 1, 3, 6 and 12 months during the first year and biannually thereafter.

Of the 76 patients, 51 have not shown any angiographic or scintigraphic evidence of coronary vasculopathy. Of the remaining 25 patients, 6 developed focal eccentric coronary disease (Stanford, type A classification); 1 patient suffered sudden cardiac death and demonstrated vascular obstruction at necropsy. In the remaining 18 patients (15 men and 3 women; age range, 8 to 58 years; mean age, 42 ± 14 years), coronary artery disease was detected by one or more diagnostic techniques on 22 occasions (Table 1). Included in the present study are all 18 patients who developed vascular involvement during follow-up and were treated with augmented immunosuppression. Patients with angiographic evidence of focal coronary disease were excluded from the study.

Table 1. Diagnosis of Early Allograft Vasculopathy

Diagnostic Criteria	Number of Episodes
I. Abnormal thallium-201 perfusion scan and abnormal coronary angiogram	7
II. Abnormal thallium-201 perfusion scan and vasculitis in EMB (normal coronary angiogram)	4
III. Abnormal thallium-201 perfusion scan only (normal coronary angiogram)	9
IV. Abnormal coronary angiogram only (normal thallium-201 perfusion scan)	2
Total	22

Thallium-201 scintigraphy and myocardial perfusion abnormalities. Symptom-limited (fatigue and dyspnea) exercise test was performed based on Bruce protocol with continuous electrocardiographic monitoring. At peak exercise thallium-201 (111 MBq or 3 mCi) was injected, and exercise was continued for an additional minute. Single-photon emission computed tomography studies were acquired using a rotating gamma camera (Elscint Helix HR) equipped with a low energy, high resolution collimator; 15% windows were centered over both 70 and 167 keV photopeaks. Sixty projections of 20 s each were acquired in step-and-shoot mode over a 180° circular orbit, from the 45° right anterior oblique to the 45° left posterior oblique view, with a 1.4× zoom factor and 64 × 64 word matrix. Each projection image was corrected for intrinsic nonuniformity with a 120 million count image. Series of 6.2-mm thick transverse slices were reconstructed using filtered backprojection with a Ramp filter, and smoothed with a Butterworth filter (cutoff frequency 0.35 cycle per pixel, power 5). A reconstructed transaxial image containing a good-sized cavity was selected, and the long axis in that transaxial plane was manually drawn and overlaid on the image. The image volume was then reformatted along planes perpendicular to the transaxial plane and parallel to the long axis. A sagittal slice was selected, and the long axis projection was drawn. The short-axis images were extracted as the planes perpendicular to the other two axes. No attenuation or scatter correction was applied. The reconstructed tomographic data were displayed in the three planes encompassing the entire left ventricle, normalizing the slice set to the maximum of activity. Polar maps were subsequently generated for display.

Coronary angiography and identification of allograft vasculopathy. All patients underwent catheterization after the first month and first year of transplantation and then yearly. The catheterization was repeated in the interim if the thallium-201 scintigraphy demonstrated perfusion abnormalities. After administration of local anesthesia, a 6-F sheath was inserted in the right femoral artery. Selective angiograms for the left and right coronary arteries in standard orthogonal views were obtained using the Judkins technique. Identical views in serial studies were performed in an individual. Angiograms were interpreted independently by two experienced angiographers. A coronary artery or its branches were considered diseased when at least minor luminal irregularities were seen in more than two orthogonal views. Patients with eccentric and localized abnormality consistent with Stanford type I lesion were excluded (16).

Endomyocardial biopsy, criteria for cellular rejection and vasculitis. During the first year after heart transplantation sequential endomyocardial biopsies were performed in every patient for surveillance of cellular allograft rejection. Biopsy interpretation was made according to the Working Formulation of the International Society of Heart and Lung Transplantation (ISHLT) (17). Acute rejection was treated when evidence of myocardial cell damage was detected in the biopsy

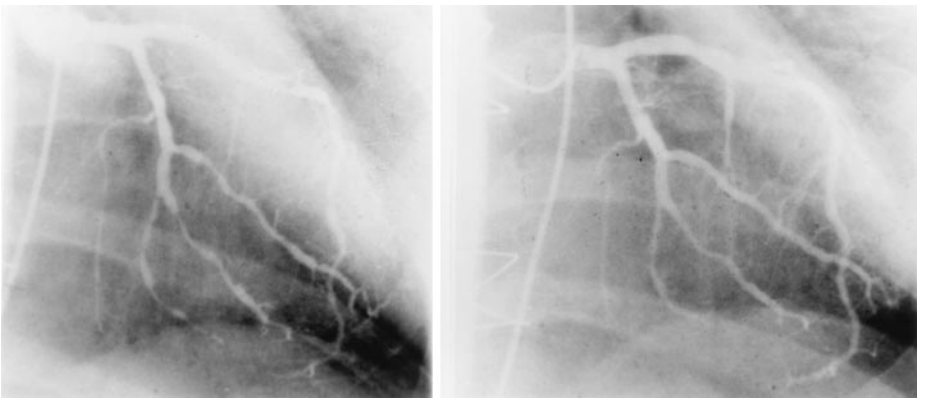

Figure 1. Angiographic evidence of early graft vasculopathy that responded to increased immunosuppressive therapy. Coronary angiography in left anterior oblique view in patient #1 demonstrated diffuse coronary artery disease 2 months after transplantation (**A**). The angiographic evidence of vasculopathy was also accompanied by anterior myocardial perfusion defect. The angiographic abnormality showed resolution with augmented immunosuppression. There was a complete resolution of scintigraphic perfusion abnormality. The patient continues to show angiographically normal coronary arteries 126 months after operation.

specimens (ISHLT grade 2 or more). In the event of cellular rejection, a repeat endomyocardial biopsy was performed 5 to 7 days after the treatment for rejection.

A special effort was made to identify arterioles for the diagnosis of vasculitis. Arterioles with clearly definable internal and external elastic laminae were evaluated for the presence of endothelial swelling, intimal monocellular infiltration, intimal proliferation or fibrinoid necrosis of the medial muscular layer (Fig. 2). No immunohistochemical studies were performed for detection of vascular deposition of immunoglobulins or complement.

Immunosuppressive therapy and management of allograft rejection. Immediately after transplantation antithymocyte globulin was administered to all patients for 7 to 10 days. Corticosteroids were given in the form of methylprednisolone bolus of 1 g, 500 mg and 500 mg for the first 3 days following transplantation. Subsequently, patients have been managed with triple immunosuppressive treatment of oral cyclosporine, azathioprine and prednisone. Cyclosporine doses were adjusted to whole blood levels of 400–800 ng/ml using polyclonal and 100–200 ng/ml with monoclonal antibody kits. Azathioprine was started as a 1–2 mg/kg dose and was adjusted to the total white blood cell count. Prednisone was maintained at 0.1–0.2 mg/kg/day.

Treatment of acute cellular rejection comprised a 3-day course of intravenous methylprednisolone (1,000–500–500 mg or 500–250–250 mg, respectively) and antithymocyte globulin (5 mg/kg/day with adjustment to T-cell level between 100 and 200 mm^3). Two patients required OKT3 therapy for refractory rejection.

Augmented immunosuppressive treatment for vasculopathy. The episodes of early vasculopathy were treated with augmented immunosuppressive therapy with methylprednisolone and antithymocyte serum for 3 days identical to the treatment of acute cellular rejection. After 7 to 10 days of treatment for the vascular obstruction, coronary angiography and thallium-201 scintigraphy were repeated for comparison with the pretreatment investigations.

Statistical analysis. The differences between the proportion of episodes of vascular occlusion resolved by augmented immunosuppression before the first year and after that period was assessed by a chi-square test. The freedom from episodes of vascular occlusion was determined by the Kaplan–Meier method.

Results

Myocardial perfusion abnormalities in early graft vasculopathy. In the 8-year interval, 22 episodes of early vasculopathy were diagnosed in 18 patients and treated with augmented immunosuppression. One patient suffered three episodes, and 2 other patients demonstrated two episodes of vasculopathy each. The cumulative percentage of being free of vasculopathy at 1, 3 and 5 years was 87%, 82% and 68%, respectively.

Scintigraphic evidence of perfusion abnormality was observed in 20 episodes (Table 1). Of these, seven were accompanied by angiographic coronary disease (Fig. 1) and four by pathologic evidence of vasculitis (Fig. 2); nine of the 20 episodes were solely detected by thallium-201 perfusion scan. The remaining two of the 22 episodes not evident on perfusion scintigraphy were detected by coronary angiography.

The scintigraphic appearance of the vasculopathy was usually confined to one coronary territory (Table 2). The anterior, anteroseptal or apical involvement was observed on 11 occasions, and inferior or posterior involvement was observed in the remaining nine. In the patient with three episodes of vasculopathy (patient #3), the first involved the anterior myocardial region, the second the anteroseptal region and the third episode detected at coronary angiography was not discernible on thallium-201 imaging. In the other 2 patients with two episodes of vasculopathy each (patients #8 and #15), the primary and recurrent episodes involved the same coronary territory as identified by thallium scintigraphy.

Effect of augmented immunosuppression on early graft vasculopathy. Of 22 episodes of early graft vasculopathy treated with increased immunosuppression, 15 demonstrated resolution of the myocardial perfusion and/or angiographic abnormalities (68%) (Table 2, Fig. 1). Of the seven remaining unresolved episodes, two were recurrent episodes. The episodes treated within the first year after transplantation had a higher probability of resolution (11 out of 12, 92%) compared with those treated thereafter (4 out of 10, 40%) ($p = 0.033$)

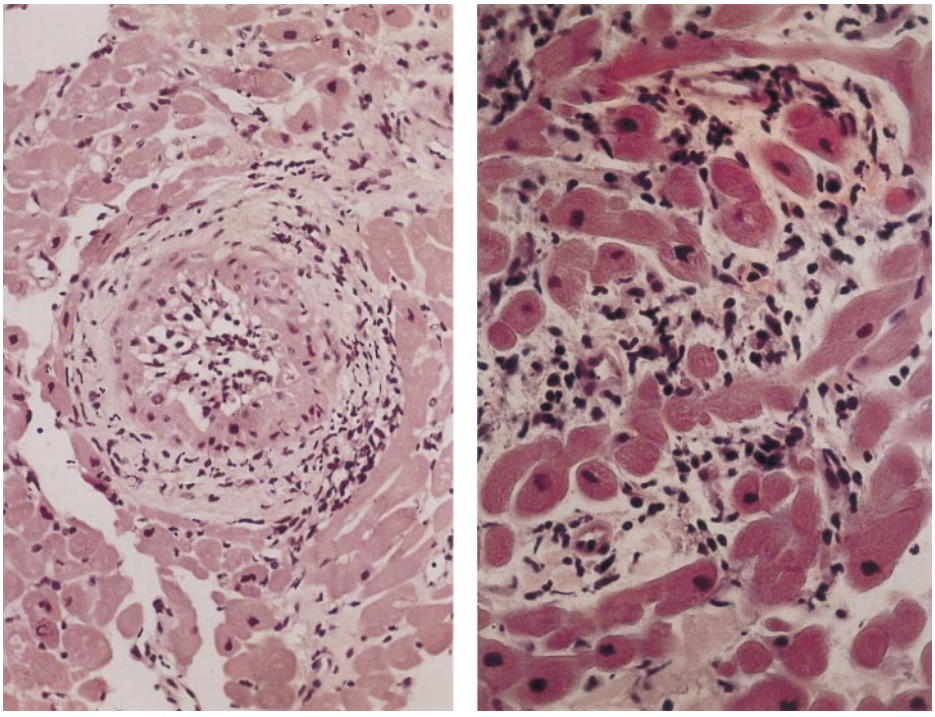

Figure 2. Histologic evidence of vasculitis. Endomyocardial biopsy specimen 1 month after heart transplantation in patient #10. A myocardial arteriole demonstrates evidence of vasculitis with intimal proliferation and edema almost obliterating the lumen (hematoxylin and eosin, ×200). In addition to vasculitis, there was an evidence of ISHLT grade 3A parenchymal rejection (**B**). This patient demonstrated anterior myocardial perfusion abnormality in thallium perfusion scan. He was treated with increased immunosuppressive therapy with complete resolution of perfusion defect. This patient demonstrated normal coronary arteries at 34 months, when he died of a cerebrovascular accident.

(Table 3). The resolution of early graft vasculopathy was observed in all four episodes that were associated with pathologic evidence of vasculitis and seven of nine episodes (78%) detected by myocardial perfusion scan alone. When the evidence of vasculopathy was detected by angiography, only four of the nine episodes showed resolution with treatment.

Long-term effects of resolution of early graft vasculopathy. Of the 18 patients with 22 episodes, 10 patients demonstrated resolution of their early graft vasculopathy, and 5 patients did not show any benefit. The remaining 3 patients sustained recurrent episodes of vasculopathy. These 18 patients were followed for 61 ± 32 months (median, 64 months).

Of the 10 patients who had demonstrated resolution and did not develop recurrent vasculopathy, 6 showed normal coronary angiograms and normal perfusion scans up to 124 months of follow-up (patients #1, 2, 7, 11, 12 and 17), and 2 died of acute cardiac rejection (patient #9) and cerebrovascular accident (patient #10) at 64 and 35 months with normal coronary arteries. The remaining 2 of the 10 patients have demonstrated an eventful course; 1 has developed diffuse coronary disease 32 months after treatment of vasculopathy (patient #13), and another patient presented with acute myocardial infarction and congestive heart failure 32 months after treatment and underwent retransplantation (patient #14).

Five of the 18 patients had failed to respond to augmented immunosuppressive therapy. While 1 of them showed late resolution (patient #16), the remaining 4 patients died with diffuse coronary artery disease and congestive heart failure and acute myocardial infarction within 11 to 33 months of treatment (patients #4, 5, 6 and 18).

The remaining 3 of the 18 patients developed recurrent vasculopathy. The first of the 3 patients showed recurrences of vasculopathy at 27 and 44 months (patient #3), developed congestive heart failure 1 year after the last episode and was retransplanted. The second patient showed two episodes of vasculopathy; both resolved with increased immunosuppression, but the patient has developed diffuse coronary artery disease at 10 years of follow-up (patient #8). The third patient showed complete resolution of his primary episode but developed a recurrence 22 months later (patient #15). The recurrent episode did not respond to immunosuppression. However, the subsequent set of studies performed in this patient revealed normal arteries; he is free of epicardial coronary disease at 72 months of follow-up. Eight of the 13 initial responders (62%) and only 1 of the 5 nonresponders (20%) were free of coronary occlusion at the end of follow-up.

Discussion

The present study indicates that detection of early allograft vasculopathy is feasible by serial myocardial perfusion scans. Twenty episodes of vasculopathy were detected by thallium-201 scintigraphy in a prospective follow-up of 76 patients. Of the 20 episodes, 13 were not apparent on coronary angiograms, suggesting that perfusion abnormalities may precede angiographic evidence of the disease. These results differ from previous reports of myocardial perfusion scans that failed to confirm the clinical utility of the procedure (18–23). The perfusion scans in the referred studies were performed late after transplantation, after diffuse and chronic involvement of the coronary arteries had probably occurred; at this time,

Table 2. Clinical, Angiographic and Scintigraphic Features of 22 Episodes of Vascular Occlusions Detected in 18 Patients and the Response to Augmentation of Immunosuppressive Treatment

Patient	Age (years) and gender	Posttransplant interval	Tl-201 (pre)	Tl-201 (post)	Angiogram (pre)	Angiogram (post)	EMB* ISHLT ≥2	Response†	Follow-up
Abnormal thallium-201 and abnormal coronary angiogram									
1.	24M	2 mo	Anterior	Normalization	Diffuse	Normalization		+	126 mo normal coronaries
2.	58M	4 mo	Apical	Normalization	Diffuse	Normalization		+	48 mo normal coronaries
3-1.‡	39F	12 mo	Anterior	Normalization	Diffuse	Normalization		+	39 mo new episode + CHF
3-2.‡	42F	39 mo	Anteroseptal	Persistent	Diffuse	Persistent			58 mo new episode + CHF
4.	30M	42 mo	Inferior	Persistent	Diffuse	Persistent			24 mo diffuse coronary + CHF, died 80 mo CAD
5.	50M	42 mo	Septal	Persistent	Diffuse	Persistent			51 mo diffuse coronary + CHF, died 70 mo CAD
6.	51M	48 mo	Anterior + apicolateral	Persistent	Diffuse	Persistent			15 mo coronary diffuse + CHF, died 70 mo CAD
Abnormal thallium-201 and vasculitis at EMB									
7.	53M	1 mo	Posterior	Normalization	Normal	Normal	+	+	36 mo normal coronaries
8-1.‡	42F	1 mo	Anterior	Normalization	Normal	Normal		+	53 mo new episode
9.	8M	1 mo	Posterior	Normalization	Normal	Normal	+	+	64 mo died acute rejection, normal coronaries
10.	57M	1 mo	Anterior	Normalization	Normal	Normal	+	+	35 mo died CVA, normal coronaries
Abnormal thallium-201 and normal coronary angiogram									
11.	56M	3 mo	Inferior	Normalization	Normal	Normal	+	+	64 mo normal coronaries
12.	52M	4 mo	Anteroseptal	Normalization	Normal	Normal		+	96 mo normal coronaries
13.	47M	4 mo	Anterior + apicolateral	Normalization	Normal	Normal	+	+	36 mo diffuse coronary disease
14.	39M	7 mo	Inferior	Normalization	Normal	Normal		+	39 mo AMI + CHF, 70 mo retransplantation
15-1.‡	28M	23 mo	Inferoapical	Normalization	Normal	Normal		+	35 mo new episode
15-2.‡	29M	35 mo	Inferior	Persistent	Normal	Normal			72 mo normal coronaries
16.	55M	30 mo	Inferolateral	Persistent	Normal	Normal			60 mo normal coronaries
8-2.‡	48F	53 mo	Anterior	Normalization	Normal	Normal		+	120 mo diffuse coronary disease
17.	50M	54 mo	Inferior	Normalization	Normal	Normal		+	78 mo normal coronaries
Normal thallium-201 abnormal coronary angiogram									
18.	27M	11 mo	Normal		Diffuse	Persistent			Diabetes, 22 mo died AMI
3-3.‡	44F	58 mo	Normal		Diffuse	Normalization		+	87 mo CHF + retransplantation

pre, investigation at the time of diagnosis of vascular occlusion before treatment; post, investigation after immunosuppressive treatment; CAD, coronary artery disease; CVA, cardiovascular accident; AMI, acute myocardial infarction. *ISHLT rejection of grade ≥2. †Response to immunosuppressive treatment: (+), complete resolution. ‡Patients #3, 8 and 15 have demonstrated more that one episode of diffuse vasculopathy. Vasculitis in EMB was observed only in patients #7–10.

regional perfusion defects are not likely to be detected due to balanced ischemia in various coronary territories (18,23). In fact, 2 of the 76 patients in our cohort also did not demonstrate perfusion abnormalities despite angiographic evidence of the disease. These 2 patients with false negative scans had severe diffuse triple vessel disease; 1 died and the other needed retransplantation.

The process of early vasculopathy may be reversible by augmentation of immunosuppressive therapy. In the present study, two thirds of the episodes of vascular occlusion were successfully treated. Vasculopathy treated within the first year of transplantation demonstrated a 90% probability of resolution, whereas the results dropped to 40% when the vascular process was detected after 1 year. The reason for this finding could be that early vasculopathy is likely to be associated with inflammatory process (24), and therefore more susceptible to immunosuppression, whereas after the first year, the likelihood of benefit is reduced due to the development of chronic obliterative changes of intimal proliferation and fibrosis. This would also explain the higher success rate seen in patients with either histologic (100%) or scintigraphic evidence (78%) of vascular involvement compared to those who had angiographic evidence (45%) of vasculopathy. It is likely that angiographically discernible disease represents a later phase of the vasculopathic change less amenable to medical treatment.

Treatment of vasculopathy detected early after transplan-

Table 3. Clinical Response According to Diagnostic Criteria and the Time of Treatment After Transplantation

	Episodes treated	Positive response	Success rate
Diagnostic criteria			
Abnormal Tl-201, abnormal coronary angiogram	7	3	43%
Abnormal Tl-201, vasculitis on EMB	4	4	100%
Abnormal Tl-201, normal coronary angiogram	9	7	78%
Normal Tl-201, abnormal coronary angiogram	2	1	50%
Total	22	15	68%
Interval after transplantation (months)			
<12 months	12	11	90%
>12 months	10	4	40%
Total	22	15	68%

tation should prevent development of chronic occlusive vascular disease. In the present study, 80% of patients who were successfully treated and did not develop recurrent disease remained free of coronary disease up to 3 to 10 years of follow-up. On the other hand, 80% of the patients who failed therapy died of acute myocardial infarction or congestive heart failure due to chronic diffuse coronary artery disease. Although our results suggest long-term benefit of early treatment, a controlled randomized study will be required to substantiate these findings.

The strategies of the detection and treatment of early stages of rejection-related vasculopathy need to be reconsidered. The first coronary angiography is performed in most centers after the first year of transplantation (25–27). This approach may fail to detect potentially treatable episodes of early vasculopathy. On the other hand, even if vascular involvement is detected by coronary angiography, by myocardial perfusion scintigraphy or by intravascular ultrasound, medical treatment is not considered (18–23,25–30). The findings of the present study suggest that more frequent scintigraphic or angiographic studies should be performed during the first year of transplantation in order to detect the early vasculopathic changes. If detected, an aggressive immunosuppressive treatment—similar to that employed in the setting of an acute cellular rejection—should be considered. Although the likelihood of reversibility is greater at the early stages of transplantation, our findings indicate that treatment should probably be attempted when the vasculopathy is detected after the first year of the operation.

Limitations of the study. In patients included in group III (abnormal perfusion studies with normal coronary artery anatomy) the possibility of false positive results should be considered. Due to the lack of an adequate gold standard, this issue is difficult to address.

This is primarily an observational, uncontrolled study not subjected to blinding or randomization. Therefore, the conclusions reached herein must be considered with care and contrasted with future studies designed to confirm the reported findings.

Conclusions. The present study demonstrates the feasibility of detection of *early* vasculopathy after heart transplantation by serial myocardial perfusion studies and early coronary angiography. The augmented immunosuppressive therapy results in resolution of the vascular involvement especially if detected in the first year after transplantation. The treatment could result in long-term prevention of late vascular disease.

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