Progressive Heterogeneity of Myocardial Perfusion in Heart Transplant Recipients Detected by Thallium-201 Myocardial SPECT

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Progressive graft atherosclerosis is a serious complication in long-term survivors after heart transplantation. Coronary angiography is insensitive with regard to the early and characteristic alterations. We evaluated the progression of these abnormalities and the influence of former rejection episodes. **Methods:** Early after transplantation, 43 patients (34 men, mean age 53.7 ± 10.7 yr) underwent stress and redistribution ^{201}Tl myocardial SPECT after treadmill exercise. Twenty patients were followed-up to the second postoperative year, and 13 patients to the third postoperative year. Thallium-201 distribution and kinetic abnormalities were documented in a scheme enclosing 20 myocardial segments. Additionally, a score was developed that measured the degree of inhomogeneity of ^{201}Tl distribution and the severity of perfusion defects, respectively. **Results:** Regarding scintigraphy, pathologic results could be found in 40% of segments (redistribution, 25%; reverse redistribution, 30%; persistent defects, 49%). Score values in heart transplant recipients differed significantly from normal controls ($p < 0.001$) and were comparable to patients with single vessel disease of their native hearts. Thallium-201 inhomogeneity in recipients after treatable rejection episodes did not differ from results in recipients without any biopsy-proven rejection. The follow-up of cardiac transplant patients revealed a significant increase of score values up to the third year after transplantation ($p < 0.02$), despite reproducible normal angiography. There was no direct correlation between score values and IVUS results, although there was a parallel trend in 10 of 12 follow-ups. **Conclusion:** Despite normal coronary angiography, ^{201}Tl myocardial SPECT frequently revealed pathologic results in heart transplant recipients. Scintigraphic results did not correlate with intimal thickening of epicardial coronary arteries accessible to intravascular ultrasonography in the early phase after transplantation. The presented score of inhomogeneity might reveal progressive disease possibly caused by small vessel alterations.

Key Words: thallium-201; SPECT; heart transplantation; graft atherosclerosis; intravascular ultrasound

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After the first postoperative year, progressive graft atherosclerosis accounts for 36% of deaths and 60% of retransplantation procedures after primarily successful cardiac transplantation (*1*). The pattern in graft vasculopathy is quite different from coronary artery disease of the native heart; diffuse concentric intimal proliferation leads to luminal narrowing throughout the coronary tree with distal obliteration and extensive coronary artery stenosis. Although the influence of cytomegalovirus infection is proven, and the role of severe hypercholesterinemia and rejection is under discussion, the definitive cause of these characteristic alterations remains unclear. Immunological injury to the endothelium has to be considered (*2–4*).

Histologic studies and recently intravascular ultrasonography have revealed intimal thickening and vascular sclerosis despite seemingly normal angiographic findings as early as 1 yr after transplantation in nearly all patients (*1,5–7*). A major problem is the lack of a valid "gold standard" in the early detection of this widespread diffuse disease: coronary angiography is quite insensitive in this setting. Intravascular ultrasonography is a new, sensitive imaging modality that has the potential to depict the vessel wall morphology, but it is limited to the large epicardial vessels.

The role of ^{201}Tl myocardial scintigraphy in the follow-up of heart transplant recipients was repeatedly evaluated (*8–12*). With regard to critical stenosis (comparable to coronary artery disease of the native heart) ^{201}Tl SPECT after treadmill exercise yielded satisfying results: sensitivity ranged between 77% and 100% (*8,10*). In our experience, contrast to the reported small number of false-positive findings, ^{201}Tl SPECT of the transplanted heart often shows inhomogeneous patterns, areas with redistribution or reverse redistribution and persistent defects without any correlation to coronary territories.

To evaluate our observations systematically we developed a score that indicates the degree of inhomogeneity or the severity of regional perfusion defects, respectively. We compared results obtained in 43 consecutive transplant recipients without critical or diffuse stenotic segments to 12 patients with single vessel disease of their native heart and to 13 controls. In a subgroup of 27 heart transplant recipients, we prospectively compared the SPECT findings to results of intracoronary ultrasonography.

Our study should answer the following questions: Does the degree of ^{201}Tl SPECT abnormalities in transplant recipients reach statistical significance in comparison to a control group? Is there any influence of former rejection episodes on ^{201}Tl inhomogeneity? Do ^{201}Tl myocardial SPECT findings reflect progressive disease? Can SPECT findings be explained by sonographically detected wall alterations of epicardial coronary arteries?

MATERIALS AND METHODS

Patients

Forty-three consecutive orthotopic heart recipients (34 men, age range 26–70 yr, mean age 53.7 ± 10.7 yr; body surface area (BSA) 1.90 ± 0.19 (1.51–2.45) m^2; donor age 10–55 yr, mean age 28.9 ± 12.7 yr) have been included in the study if coronary angiography was normal (no stenosis > 50%, no loss of middle sized vessels, absence of pruning effects) and ^{201}Tl SPECT after treadmill exercise was available at the same time. Eighty-one scans have been evaluated. Thirty-three investigations were performed in

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the first, 27 in the second and 21 in the third postoperative years (3.9 ± 2.7, 17.1 ± 3.3 and 30.1 ± 3.7 mo after transplantation, respectively), including 20 who underwent follow-up from the first to the second year and 13 who underwent follow-up from the second to the third year.

Twelve patients with angiographically proven single-vessel disease of the left anterior descending artery (LAD) (10 men, age range 44–71 yr, mean age 61.5 ± 7.6 yr) were evaluated for comparison and validation of the inhomogeneity score. Patients with previous infarction or cardiovascular surgery had been excluded.

Thirteen patients with atypical chest pain and low risk for coronary artery disease (4 men, age range 46–68 yr, mean age 57.5 ± 8.7 yr, BSA 1.80 ± 0.15 (1.59–2.12) m^2) served as control subjects. Angiography and clinical follow-up excluded underlying cardiac disease.

In a subgroup of 27 heart recipients (21 men, age range 24–69 yr, mean age 52.0 ± 11.0 yr), intravascular ultrasonography was performed in the first postoperative year; 12 patients underwent follow-up in the second year.

In transplant recipients, immunosuppression consisted of prednisolone, azathioprine and cyclosporine. In the first year, endomyocardial biopsy was routinely performed once per week during the first month, monthly in the following 5 mo and then at intervals of 6–8 wk up to 1 yr. Patients underwent angiography 3.9 ± 2.7 mo after transplantation and thereafter in yearly intervals. Scintigraphy was performed on the occasion of these routine surveys including endomyocardial biopsy and angiography within 1 wk. Acute rejection episodes at the time of investigation were excluded by endomyocardial biopsy.

Scintigraphy

Vasoactive drugs were withdrawn 24 hr before the study. All patients underwent a maximal symptom-limited bicycle ergometer exercise test in the sitting position in a fasting state. The initial workload of 50 W for 2 min was subsequently increased by 25 W every 2 min. One hundred megabecquerels of ^{201}Tl-chloride was injected intravenously during maximal treadmill exercise and exercise was continued for 1 min. Imaging was started 5–10 min and 3 hr after exercise. Thirty-two views (30 sec) on a 180° rotation (starting in the 45° right anterior oblique position) were acquired in a 64 × 64 matrix. Long and short projections of the heart were obtained using standard SPECT software with filtered backprojection (Butterworth filter of fifth order and 0.5 Nyquist cutoff frequency).

Data Analysis

A target scheme was overlaid on the short axis slices representing best the apical, medial and basal myocardium. Thus, the left ventricular myocardium was divided into 20 segments (Fig. 1). The short-axis slices of the stress and redistribution study of each individual were realigned using the apex of the left ventricle and the anteroseptal insertion of the right ventricle visible on the images without background subtraction. The segment with the maximal uptake was defined for each scan. Segments having less than 40% of the maximal uptake were categorized as Grade 0 (= threshold). Segments with uptake between 40% and 55% were categorized as Grade 1; segments with uptake between 55% and 70% were categorized as Grade 2; segments with uptake of more than 70% were categorized as Grade 3. Thus, intensity of ^{201}Tl accumulation in each segment of the stress and redistribution scan was scored as 0 (no uptake), 1 (severely reduced uptake), 2 (moderately reduced uptake) or 3 (normal uptake) with regard to graduation on the color scale. To avoid the influence of well-known absorption artifacts in ^{201}Tl scintigraphy, the five inferior wall segments were excluded, and the remaining 15 segments were evaluated. Scoring was done by two independent observers. If a discrepancy in scoring was present, score values were averaged.

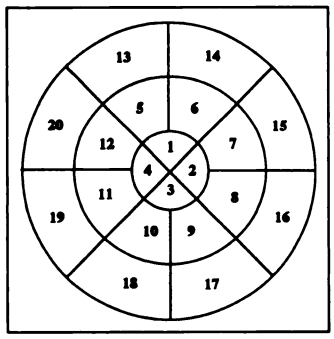

FIGURE 1. Division of left ventricular myocardium in 20 segments. Segments 1–4 = apical myocardium; segments 5–12 = midventricular myocardium; segments 13–20 = basal myocardium.

The score of inhomogeneity was calculated as follows:

$$\text{Score} = 45 - \sum_{i=1}^{15} S_i + \sum_{i=1}^{15} |S_i - R_i| \quad i = 1, \cdots, 15 \qquad \text{Eq. 1}$$

$$\text{Score (\%)} = \frac{\text{Score}}{90} \times 100\% \qquad \text{Eq. 2}$$

$S_1, \ldots, S_{15}$ = grade of ^{201}Tl accumulation in the 15 segments of the stress image. $R_1, \ldots, R_{15}$ = grade of ^{201}Tl accumulation in the 15 segments of the redistribution image. $S_i - R_i$ = difference between grades given in corresponding segments in stress and redistribution image (in positive values).

The first term of Equation 1 results from the stress image: 15 × 3 score points are possible, yielding an ideal value of 45 − 45 = 0. The second term represents the sum of the segmental differences (positive values) comparing stress and redistribution images. With regard to the highest possible score of 90, the score is ultimately expressed in percent (Eq. 2).

Figure 2 gives an example and demonstrates grading of ^{201}Tl accumulation.

Intravascular ultrasonography was confined to one coronary artery (see below). For comparison of scintigraphic results with intravascular ultrasound (IVUS) findings related to the corresponding coronary territory a regional score value was calculated, e.g., including the five anterior segments [1, 5, 6, 13 and 14 (Fig. 1)] in correlation to LAD IVUS findings.

IVUS

During routine coronary angiography using the Judkin's technique by means of the right femoral artery, a guide wire (0.014 inch) was advanced into the midportion of the LAD. Using this guide wire, a 3.5 French sonicath-catheter was advanced using continuous biplane fluoroscopic control. The 30 MHz transducer of the ultrasound catheter (monorail system) was connected to the imaging system Sonos 1000. During withdrawal of the transducer from the midportion of the LAD to the stem, cross-sectional areas of coronary segments were depicted and the vessel morphology including intima-media-boundary was visualized. All intravascular images were stored on VHS videotapes for later analysis.

Data Analysis. Measurement of cross-sectional lumen and plaque was performed off-line. The outer boundaries of plaque areas were determined after the internal elastic lamina. Intimal index (intimal index = plaque area/lumen area) as a parameter of graft atherosclerosis was calculated for each cross-sectional area.

Statistical Analysis

All values are expressed as means ± s.d. Normal distribution of score values in each subgroup was proven by the test of Kolmog-

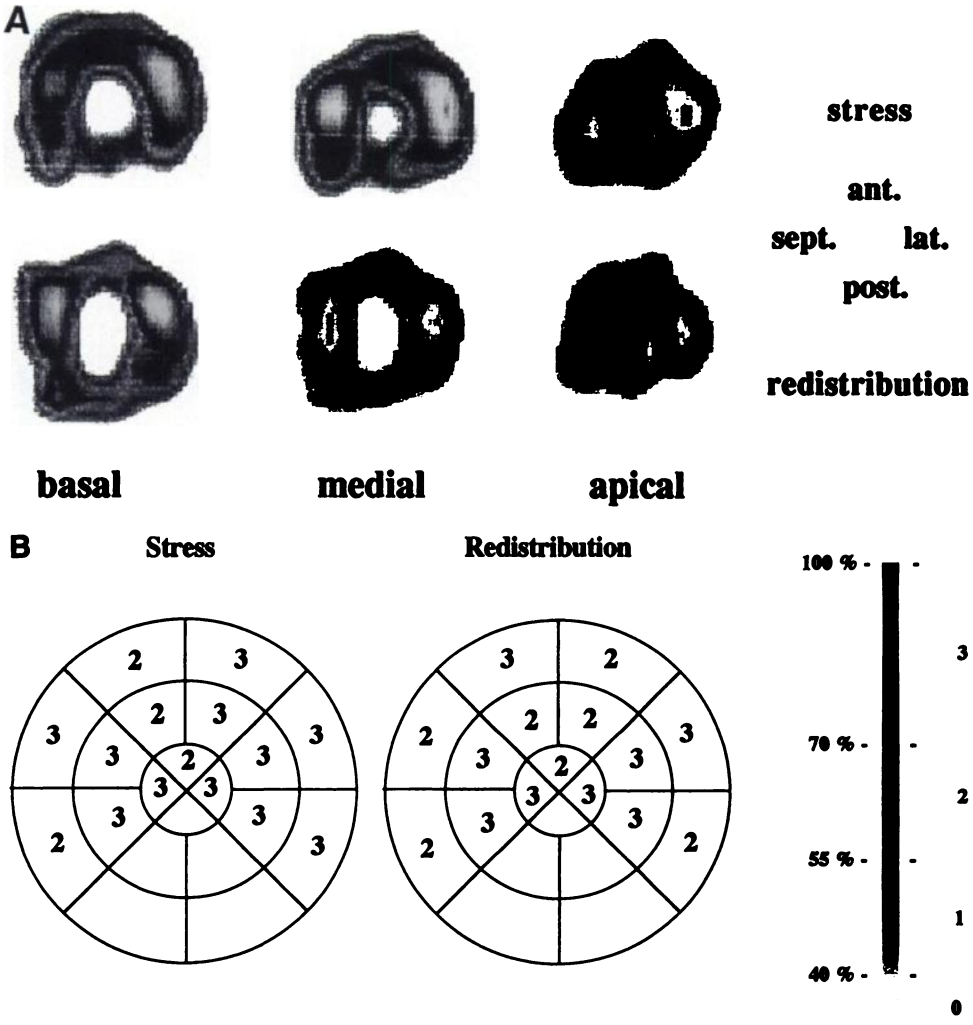

FIGURE 2. (A) Thallium-201 SPECT of a 62-yr-old man 18 mo after heart transplantation (age of donor heart was 35 yr) with normal coronary angiography. (B) Thallium-201 accumulation in 15 segments (posterior wall excluded) in the stress and redistribution image. Calculation of the inhomogeneity score results in a value of 10%.

orov and Smirnov. Two-tailed paired and unpaired Student's t-tests were used to compare group means. Because of the possible influence of former rejection episodes on angiopathy, transplant recipients were divided into one group without any rejection and one group after at least one treated rejection episode. One-way analysis of variance with repeated measures was used for simultaneous comparison of more than two mean values in follow-up analysis. Bonferroni's correction was subsequently applied to localize the source of the difference. Regression analysis was performed to detect correlation between inhomogeneity score and intimal indices obtained from IVUS investigations. For testing agreement between independent observers the κ test was performed and differences were analyzed according to a Bland–Altman form of statistic. A p value below 0.05 was considered to indicate statistical significance.

RESULTS

Transplant Recipients

Results of Thallium-201 Scintigraphy. Eighty-one ^{201}Tl SPECT studies of 43 recipients were evaluated (33 investigations in the first year, 27 in the second year and 21 in the third year after transplantation). Double product (systolic pressure × heart frequency) during maximal treadmill exercise was 19.190 ± 3.630 (10.800–29.400) in the first year, 22.970 ± 4.960 (14.300–31.900) in the second year (significant increase: $p < 0.03$) and 23.290 ± 4.200 (12.800–31.200) in the third year, respectively. In all recipients coronary angiography did not reveal any pathologic findings.

Pathologic scintigraphic findings were shown in 648 of 1620 (40%) of the segments. Abnormal segments were localized as follows: septum 15%, anterior wall 29%, lateral wall 7%, posterior wall 49%. Persistent defects made up 49%, redistribution 21% and reverse redistribution 30% of all pathologic results. To avoid absorption artifacts the inferior wall segments were not considered for the calculation of score values resulting in a number of 328/1215 abnormal segments (27%). Figure 2 shows representative short-axis slices of a recipient 18 mo after transplantation and demonstrates the calculation of the inhomogeneity score.

Scoring of the two independent observers showed very good agreement with a κ value of 0.89 (chance corrected proportional agreement). Analysis of differences according to a Bland–Altman form of statistic (*13,14*) revealed a mean difference of 0.25 score-points and an s.d. of a difference of 0.85 score-points leading to limits of agreement (mean ± 2 s.d.) of −1.45 and 1.95 score-points.

Twenty-two patients (34 investigations) developed at least one rejection episode in the past. Twenty-one patients (47 investigations) were free of rejection. There was no influence of former rejection episodes on the scintigraphic results: the inhomogeneity score did not show significant differences in the two subgroups of patients (Table 1). Therefore, the two groups were composed for further evaluation.

Figure 3 illustrates the findings in control subjects, in patients with single vessel disease and in transplant recipients. Score values of both patient groups and control subjects differed

TABLE 1
Thallium-201 Inhomogeneity in Heart Recipients With and Without Rejection Episodes

Year after transplantation	Score of inhomogeneity (%) Mean ± s.d.	Range	No. of investigations and significance of differences (* vs.†)	
First	5.3 ± 2.8	1.1–9.9	n* = 19	ns
	5.8 ± 2.3	3.0–11.0	n† = 14	(p = 0.4)
Second	6.5 ± 3.9	2.2–15.4	n* = 11	ns
	7.1 ± 3.7	1.1–14.3	n† = 16	(p = 0.5)
Third	5.8 ± 3.6	3.3–11.0	n* = 4	ns
	6.9 ± 4.2	1.1–15.6	n† = 17	(p = 0.5)

*Without rejection.
†After treatable rejection.
ns = not significant.

significantly ($p < 0.001$). The degree of abnormality in patients with single vessel disease and transplant recipients was on the same level, given the fact that score values do not depend on distribution of pathologic segments. The score values of patients covered a wide range (mean values and s.d. in year 1, 2 and 3: 5.5% ± 2.6%, 6.6% ± 3.7% and 6.8% ± 4.6%, respectively).

Follow-up studies in 20 patients from the first to the second year and in 13 patients from the second to the third year could be obtained. Results are listed in Table 2. Analysis of variance with repeated measures showed significantly increasing score values in course of time ($p < 0.05$). Bonferroni corrected paired t-test revealed a significant increase from the first to the second year and from the first to the third year ($p < 0.04$).

In the subgroup of the 27 patients with 39 IVUS investigations a mean inhomogeneity score of 5.8% ± 2.6% in the first year and of 7.8% ± 4.3% in the second year was calculated. In the 12 patients who underwent follow-up, paired t-test revealed a significant increase of score values ($p < 0.03$).

Results of IVUS. In 39 IVUS investigations (including 12 patients who underwent follow-up), a three-layer appearance of the vessel wall indicating significant intimal thickening was demonstrated in 112/283 (39%) of all cross-sectional areas. At first investigation (n = 27), mean intimal index of all cross-sectional areas was 0.08 ± 0.1 (range: 0.0–0.314). At second investigation (n = 12), mean intimal index was 0.09 ± 0.1 (range: 0.0–0.346). The increase was not significant.

Comparison Between Thallium-201 SPECT Results and IVUS Findings. There was no correlation either between the inhomogeneity score values, including 15 myocardial segments and the intimal indices ($r = 0.06$, $p = 0.72$), or between regional inhomogeneity score and corresponding intimal indices ($r = 0.143$, $p = 0.49$).

In 10 of 12 follow-ups, there was a parallel change in both intimal index and inhomogeneity score. In six patients, both parameters increased, in four patients both parameters decreased, in two patients there were discordant developments.

Patients with CAD (Single-Vessel Disease of the LAD)

In each patient, scintigraphy showed persistent perfusion defects or redistribution in accordance with angiographic results (more than 70% luminal narrowing of the LAD). Score values ranged from 3.3%–9.9% (mean 6.5% ± 2.2%).

Control Subjects

In 13 normal control subjects, score values ranged from 0%–3.3% (mean 1.1% ± 1.4%). The difference between score values of control subjects and heart recipients proved to be highly significant ($p < 0.001$).

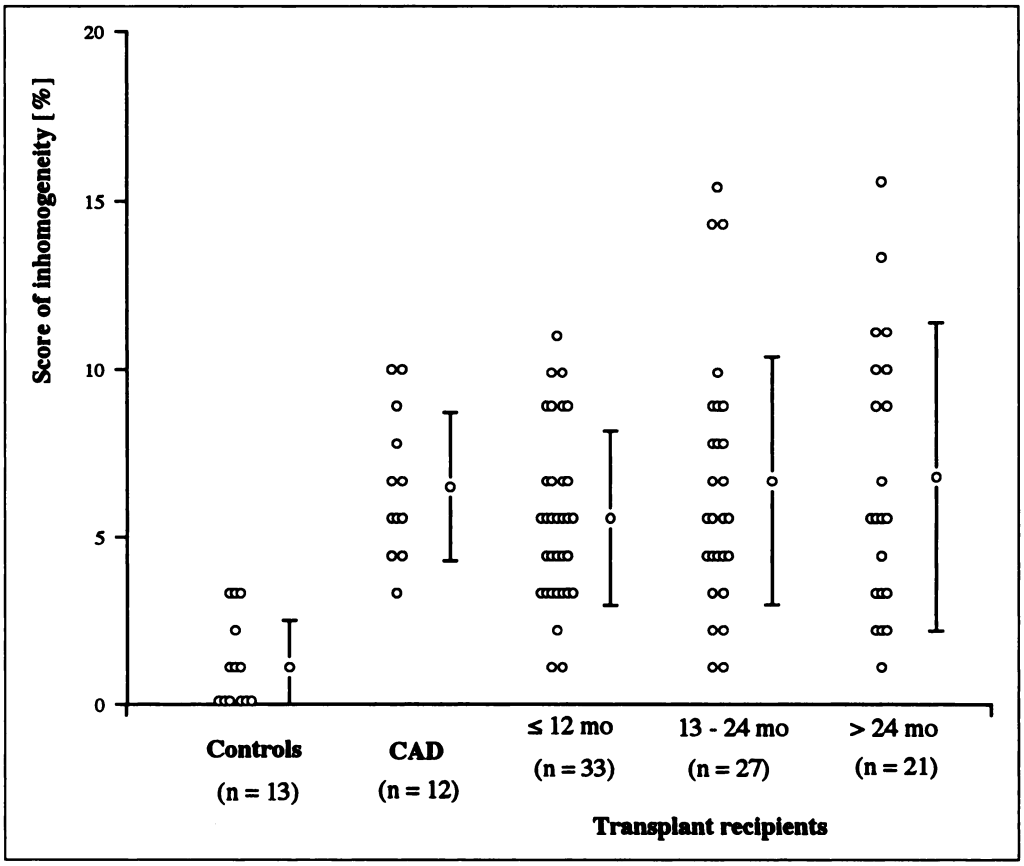

FIGURE 3. Distribution of score values in controls, in patients with single vessel disease (CAD) and heart transplant recipients. Posterior segments were excluded.

TABLE 2
Thallium-201 Inhomogeneity in Follow-up Patients

Year after transplantation	Score of inhomogeneity (%)		Significance of difference	
	Mean ± s.d.	Range	1st to 2nd year; 2nd to 3rd year	1st to 3rd year
First	6.0 ± 3.0	1.1–11.0		
			n = 20; $p < 0.05$	
Second	7.0 ± 3.3	2.4–15.4		n = 10; $p < 0.04$
			n = 13; $p = 0.066$	
Third	7.4 ± 3.7	1.1–13.2		

DISCUSSION

Progressive graft atherosclerosis has a strong impact on the long-term survival of heart transplant recipients. Coronary angiography reveals atherosclerotic lesions in 20%–40% of patients 3 yr after transplantation (*8*). After 5 yr, about 50% of transplant recipients are concerned, whereas 20% have critical stenosis of more than 75% (*15*). However, transplant vasculopathy is different from coronary atherosclerosis of the native heart because its diffuse nature of concentric narrowing affecting the small endocardial vessels as well as the large epicardial arteries. Therefore, sensitivity of coronary angiography is low with regard to the early characteristic alterations of graft vessels. Histologic studies and intravascular ultrasonography have revealed a high percentage of patients with at least diffuse intimal thickening as early as 1 yr after transplantation (*1,6,7*).

The evaluation of ^{201}Tl myocardial scintigraphy in the follow-up of heart transplant recipients has focused on the detection of circumscribed coronary artery stenoses comparable to CAD of the native heart. The reported sensitivity of exercise ^{201}Tl scintigraphy ranged from 77% (*10*) to 100% (*8*), whereby the particular investigations were based on small numbers of patients. Oral application of dipyridamole is a questionable method of pharmacological stressing and resulted in a low sensitivity of 21% (*11*). The degree of resorption of dipyridamole is probably a poor controlled factor in this protocol and kinetics of ^{201}Tl are different from exercise studies (*16*).

Thallium-201 distribution does not only depend on patency of coronary arteries and their branches. It rather reflects perfusion throughout the coronary tree up to the capillary bed. McKillop et al. (*17*) reported on four patients without coronary artery stenoses of their transplants and fixed defects in planar ^{201}Tl scintigraphy. The authors discussed small vessel disease as a possible cause. Apart from that, the reported small number of false-positive results in the working groups of Ciliberto, Rodney and Ambrosi is surprising (*8,10,12*). In contrast to these findings, we frequently observed pathologic ^{201}Tl SPECT results in patients with normal angiography after heart transplantation. The distribution of abnormalities was arbitrary and did not correlate to coronary territories as in CAD of the native heart. One possible explanation for this contradiction could be the criteria for a pathologic scan used by other investigators: most authors focused on the typical scintigraphic equivalent of ischemic myocardium, i.e., redistribution or persistent defects. However, the diffuse nature of graft vasculopathy may not result in scintigraphic abnormalities depicting coronary territories (*18*).

To objectify our visual impression, we analyzed 81 scans of 43 transplant recipients semiquantitatively in a 20-segment scheme. The evaluation by two independent observers demonstrated high reproducibility. We observed abnormalities in 40% of all segments of the angiographically normal hearts.

To measure the degree of ^{201}Tl inhomogeneity and severity of regional perfusion defects, a score was developed based on ^{201}Tl accumulation in 15 left ventricular myocardial segments. The loss of information about the localization of defects was accepted because of the diffuse nature of graft atherosclerosis. Even if the posterior wall was excluded, score values of transplant recipients without significant angiographic findings differed significantly from normal control subjects. The degree of abnormality in terms of inhomogeneity score was comparable to patients with angiographically proven-single vessel disease (Fig. 3). It is difficult to exclude soft-tissue artifacts possibly caused by breast absorption. It has to be considered that 9 women in the group of 13 control subjects may at most raise the mean score value and increase variability in inhomogeneity scores, respectively. Nevertheless, the difference between controls and recipients reached a high grade of significancy. On the other hand, the longitudinal study evaluating intraindividual changes is not influenced by breast absorption. Therefore, we did not exclude women from our investigation.

The degree of exercise in transplant recipients was comparable to those reported by other authors (*19*). The group around Schelbert demonstrated that the absolute myocardial flow under stress in heart transplant recipients is not significantly different from normal control subjects, although the level of exercise was lower in patients (*20,21*). The exercise protocol used in that quantitative PET study was identical to that used in our study. Therefore, ^{201}Tl SPECT abnormalities in our patients cannot be explained by suboptimal exercise levels.

An influence of acute rejection episodes on ^{201}Tl uptake has been repeatedly demonstrated in experimental and clinical studies (*22–24*). Apart from impaired myocardial perfusion, the alteration of membrane integrity by immunological processes seems to be of importance. Therefore, acute rejection was excluded by biopsy in our study.

Effects of former rejection episodes on graft artherosclerosis are under controversial discussion. We compared one subgroup of patients without any rejection episode in the history with a subgroup with at least one treatable rejection crisis. Score values did not differ significantly in both groups. This result is in accordance with the studies of Nitenberg and Richter who found a rapid normalization of coronary flow reserve and ^{201}Tl scintigraphy after recovery from acute rejections (*25,26*). Gao et al. (*27*) did not find any correlation between frequency and severity of rejection episodes and accelerated graft atherosclerosis. However, chronic rejection that is not proven by biopsy could not be excluded in our study.

In the course of time, transplant recipients showed significantly increasing inhomogeneity scores ($p < 0.04$), despite reproducible normal angiographic findings. The observed abnormalities in the ^{201}Tl SPECT studies do obviously indicate a progressive course.

For interpretation of these results, morphology and distribution of the disease may be important: histologic studies dem-

onstrated graft vasculopathy as an accelerated, diffuse process of intimal hyperplasia of the whole coronary tree (*18*). Johnson et al. (*6*) found intimal alterations in all explanted hearts as early as 1 yr after transplantation. Billingham et al. (*28*) showed early occlusion of small distal vessels without sufficient collateralization leading to microinfarction of the myocardium. Mason et al. (*29*) reported the case of a patient who died shortly after a normal coronary angiography because of multiple microinfarctions. Autopsy showed normal epicardial vessels, but intimal proliferation and occlusion of the small distal vessels. Therefore, the progressive abnormalities demonstrated in our study may well be early signs of accelerated graft vasculopathy of the small vessels. This would be in line with findings of a PET study of coronary flow in transplant recipients with angiographically proven graft atherosclerosis (*30*). Coronary resistance was homogeneously increased not only in the coronary territory of the narrowed vessel. Wolpers et al. (*30*) explain this discrepancy between morphological and functional findings by microvascular obliterations.

Another factor contributing to inhomogeneity of ^{201}Tl uptake may be endothelial dysfunction leading to altered microvascular circulation. Angiography demonstrated a high percentage of patients with abnormal endothelial reaction on intracoronary acetylcholine in the first year after transplantation (*7*).

Contrary to expectation, there was no direct correlation between intimal indices calculated from IVUS images and the inhomogeneity scores from ^{201}Tl SPECT. There are some explanations for this discrepancy: the mean extent of intimal hyperplasia measured by IVUS in the LAD was discrete. In addition to this, the findings in the proximal and mid-portion of the LAD do not necessarily represent the extent of vasculopathy throughout the coronary tree. Klauss et al. (*31*) demonstrated the differences in degree and extent of the disease between different coronary segments and arteries by intravascular ultrasonography. However, there was a parallel change (predominantly deterioration) of 10 of 12 follow-up patients. Long-term follow-up studies should focus on this trend.

CONCLUSION

One problem in the evaluation of follow-up procedures in heart transplant recipients is the lack of a valid gold standard for the early state of graft vasculopathy. Sensitivity of coronary angiography is low with regard to early, diffuse changes in vessel morphology. IVUS is certainly an accurate imaging technique of vessel morphology, but it is limited to the large epicardial arteries. Biopsy does normally not depict relevant vessels. Possibly the observed progressive scintigraphic abnormalities may be early signs of beginning graft vasculopathy, i.e., angiographically silent small vessel disease that is not necessarily correlated to IVUS findings in epicardial coronary arteries. However, possible influences of chronic rejection or endothelial dysfunction could not be excluded. The prognostic relevance of ^{201}Tl SPECT findings, the possibility of identifying "high risk patients," has to be evaluated in a further long-term follow-up study.

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