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Reduced Myocardial Perfusion Reserve and Transmural Perfusion Gradient in Heart Transplant Arteriopathy Assessed by Magnetic Resonance Imaging

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OBJECTIVES The goal of this study was to detect transplant arteriopathy (Tx-CHD) by a reduced myocardial perfusion reserve (MPR) and resting endomyocardial/epimyocardial perfusion ratio (Endo/Epi ratio).

BACKGROUND Transplant arteriopathy often lacks clinical symptoms and is the reason for frequent surveillance angiography in heart transplant (Tx) recipients. Magnetic resonance perfusion imaging (MRPI) allows noninvasive assessment of transmural and selective endomyocardial and epimyocardial perfusion.

METHODS Fifteen healthy volunteers (controls) and three groups (A, B, C) of Tx recipients were included. In controls and patients, MPR (hyperemic/resting perfusion) and Endo/Epi ratio were determined with MRPI after injection of gadolinium-diethylenetriamine pentaacetic acid at rest and during hyperemia (intravenous adenosine). Group A (n = 10) had no left ventricular (LV) hypertrophy and/or prior rejection, while patients in group B (n = 10) had at least one of these characteristics. Patients in group A and B had a normal coronary angiogram and a coronary flow reserve (CFR) of ≥2.5 (CFR = hyperemic/resting blood flow). Group C (n = 7) had Tx-CHD diagnosed by angiography and a reduced CFR (<2.5).

RESULTS In group C, MPR (1.7 ± 0.5) and Endo/Epi ratio (1.1 ± 0.2) were significantly reduced compared with controls (4.2 ± 0.7 and 1.6 ± 0.3; both $p < 0.0001$), group A (3.6 ± 0.7 and 1.6 ± 0.2; both $p < 0.0001$) and B (2.7 ± 0.9, $p < 0.01$ and 1.4 ± 0.1, $p < 0.04$). Transplant arteriopathy can be excluded by an MPR of >2.3 with sensitivity and specificity of 100% and 85%. If LV hypertrophy and prior rejection are excluded, Tx-CHD can be excluded by an Endo/Epi ratio of >1.3 with 100% and 80%.

CONCLUSIONS Magnetic resonance perfusion imaging detects Tx-CHD by a decreased MPR. After exclusion of LV hypertrophy and prior rejection, resting Endo/Epi ratio alone might be sufficient to indicate Tx-CHD. (J Am Coll Cardiol 2003;42:1054–60) © 2003 by the American College of Cardiology Foundation

With improved treatment for rejection, heart transplant arteriopathy (Tx-CHD) has become the most important factor affecting the survival after transplantation (1,2); Tx-CHD is often asymptomatic. Frequent assessment of the coronary circulation has been instituted to prevent severe cardiac events in transplant (Tx) patients. Evaluation of the coronary arteries solely by angiography is an insensitive method in the detection of mild-to-moderate coronary occlusive disease in Tx patients (3,4). Coronary flow reserve (CFR) and intracoronary ultrasound have been used to detect and assess the progression of Tx-CHD. However, these techniques are invasive and require arterial access with immobilization and a prolonged hospital stay with all the increased risks and costs. Magnetic resonance perfusion imaging (MRPI) using gadolinium-based contrast agents has recently been validated as a versatile noninvasive clinical tool to quantify myocardial perfusion (5). Using MRPI, it is possible to quantify myocardial perfusion reserve (MPR) (6). Myocardial perfusion reserve is a parameter that mirrors CFR as a measure of the hemodynamic significance of epicardial lesions in the respective perfusion territories.

In the present study we tested the hypothesis that Tx-CHD characterized by a decreased CFR can be noninvasively detected with MRPI in a heterogeneous group of Tx patients. Due to its spatial resolution and good image quality, MRPI allows not only determination of transmural perfusion reserve but also allows selective assessment of endomyocardial and epimyocardial perfusion (7,8). Because there is evidence that the resting endomyocardial/epimyocardial perfusion ratio (Endo/Epi ratio) decreases (9) with impaired coronary circulation, we computed the Endo/Epi ratio at rest to determine if a simple measurement of myocardial perfusion at rest would be sufficient to detect Tx-CHD.

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Abbreviations and Acronyms

AUC	= area under the curve
CFR	= coronary flow reserve (invasive)
CI	= confidence interval
Endo/Epi ratio	= resting endomyocardial/epimyocardial perfusion ratio
ICUS	= intracoronary ultrasound
LV	= left ventricle/ventricular
MPR	= myocardial perfusion reserve (noninvasive)
MRPI	= magnetic resonance perfusion imaging
RPP	= rate-pressure product
SI	= signal intensity
Tx	= transplant
Tx-CHD	= transplant arteriopathy

METHODS

Fifteen healthy volunteers (mean age 34 ± 9 years; 10 men) were assessed with MRPI to determine normal myocardial perfusion. Afterwards, 27 heart Tx recipients (mean age 56 ± 9 years; 20 men) were prospectively enrolled to undergo MRPI after their annual invasive assessment. For all subjects, written informed consent was acquired in accordance with the requirements of the Institutional Review Board for Protection of Human Subjects at the University of Minnesota.

Patients underwent MRPI and a coronary angiogram, including the assessment of CFR and a right ventricular biopsy, all within 6 h. Patients and volunteers were asked to refrain from caffeine intake 12 h before testing. Patients discontinued beta-blockers 24 h and calcium-antagonists 12 h before testing. At the time of the study, all Tx recipients were in stable clinical condition without signs of heart failure (New York Heart Association class >II or ejection fraction <30%) or unstable angina. Acute or ongoing rejection (International Society for Heart Transplantation classification >Ia [10]) was excluded in all patients by histopathologic analysis of their myocardial biopsy at the time of the study. Subjects who had contraindications for magnetic resonance imaging, such as metal implants, were not enrolled.

Definition of groups. According to their post-Tx follow-up evaluation (echocardiography, biopsy, angiogram, and CFR), Tx recipients were separated into three groups.

Group A (n = 10) included Tx recipients with no signs of left ventricular (LV) hypertrophy on echocardiogram, no episode of Tx rejection in their prior history, a normal coronary angiogram (<50% lumen obstruction determined by quantitative coronary angiography), and a CFR of >2.5 determined by coronary Doppler flow measurement.

Patients in group B (n = 10) differed from group A by exhibiting myocardial hypertrophy (determined by an LV wall thickness of >12 mm in the septum and posterior wall on a standard short-axis echocardiogram) and/or a prior episode of rejection requiring medical therapy. Left ventricular hypertrophy was confirmed by measurement of LV mass by magnetic resonance cine imaging. Patients in group C (n = 7) had Tx-CHD; Tx-CHD was defined as diffuse concentric lumen narrowing (>50%) in all three main coronary arteries including the side branches, no eccentric stenosis, and a CFR <2.5.

Invasive procedure and determination of CFR. Right ventricular catheterization was performed via a femoral access, and a myocardial biopsy specimen was obtained. Thereafter, an arterial access was obtained, and sodium heparin intravenous was given to prolong activated clotting time to >300 s. After biplane selective coronary angiography, a Flowire (0.014-inch, Cardiometrics, California) was positioned via a 4F coronary catheter. The catheter position was adjusted to obtain an adequate signal of coronary blood flow velocity within the vessel. Mean arterial blood pressure and heart rate were continuously monitored during the procedure. Baseline measurement of coronary blood flow velocity was obtained. Increasing boluses (2, 4, 8, 12, and up to 16 μg intracoronary) of adenosine (Adenoscan, Fujisawa, Illinois) were administered through the coronary catheter into the coronary ostium to reach maximal level of vasodilation. Coronary flow reserve was determined by hyperemic/resting blood flow velocity as described previously (11).

Magnetic resonance image acquisition. The imaging protocol was identical for Tx recipients and volunteers. A 1.5-T magnetic resonance scanner (Siemens Vision, Erlangen, Germany) and a phase-array body coil were used for imaging. Scout images determined the short- and long-axis view of the heart. Perfusion imaging during rest and adenosine-induced hyperemia was then performed. Adenosine was titrated in three steps from 70 to 100 μg/kg/min to a maximum dose of 140 μg/kg/min. Each dose was administered approximately over 1 min. Image acquisition was started 1 min after the start of the of the maximal infusion rate. Total infusion time was approximately 3 min plus the time required for image acquisition under 140 μg/kg/min adenosine.

Perfusion was determined in three LV short-axis slices. The first slice was located close to the base of the heart just below the aortic outflow tract, the second in the middle of the LV, and the third close to the apex just below the base of the papillary muscles. A single shot gradient-echo sequence with saturation-recovery magnetization preparation for T1 weighting and linear k-spacing was used for imaging. The parameters were set to repetition time/echo time/flip angle of 2.4 ms/1.2 ms/18° and a slice thickness of 10 mm. Temporal resolution allowed acquisition of one image in each of the three selected slices within one heart beat up to a heart rate of 110 beats/min. Sixty images per slice location were acquired with a spatial resolution of 2 to 3 mm. Patients were asked to hold their breath at end expiration for the first 15 to 20 s of each perfusion scan such that the tracking of the first pass of the bolus at the three chosen slice locations was not affected by respiratory motion. Three heart beats after initiation of the sequence a compact bolus of 0.03 mmol/kg bodyweight gadolinium-DTPA (Magne-

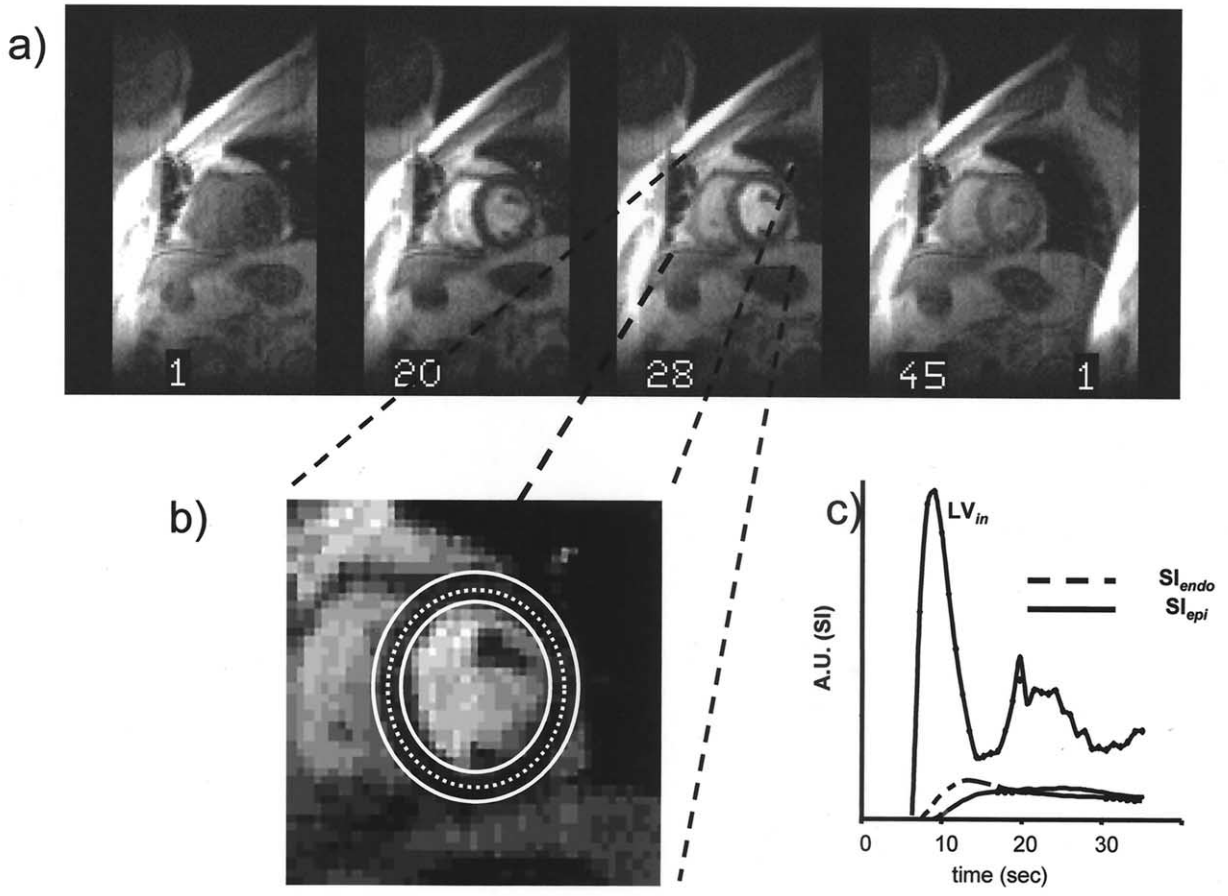

Figure 1. Perfusion analysis. **(a)** Four (of 50) images per slice showing the first pass of the contrast through the heart (**picture 1** = baseline image; **picture 2** = contrast in the right ventricle; **picture 3** = contrast in the left ventricle; **picture 4** = contrast in the myocardium). **(b)** Manual endomyocardial and epimyocardial contour delineation, an automated algorithm matches the contours to the remaining images of the slice. **(c)** Signal intensity (SI) curves of the contrast media through the left ventricle (LV_{in}), the endomyocardium (endo) and epimyocardium (epi). Model-constrained deconvolution was used to calculate the maximum amplitude of the impulse response function from the SI curves (12).

vist, Berlex, New Jersey) was injected over an antecubital vein at a rate of 7 ml/s using a power injector (MedRad, Pennsylvania). Heart rate, peripheral blood pressure, and O_2 saturation were continuously monitored during the magnetic resonance procedure. For best reproducibility we transferred the geometric slice parameters (x-, y-, z-axis) of the resting study to the hyperemic study using "copy slice parameters" from the scanner menu. The rate-pressure product (RPP) was calculated for rest and hyperemia at the maximum rate of adenosine infusion.

For cine magnetic resonance imaging, an electrocardiogram-gated, nonbreathold, segmented sequence was used with TR/TE/flip angle 33 ms/6 ms/25°. Spatial resolution of the cine sequence was 2×1.4 mm^2 with a slice thickness and increment of 10 mm. The temporal resolution was 30 to 50 ms, with 14 to 16 cardiac phases/plane. The whole LV was imaged from base to apex.

Magnetic resonance image analysis. Image analysis was performed blinded to the patient's name, clinical status, and results from the invasive measurements. Perfusion studies were analyzed (ARGUS Software, Siemens, Iselin, New Jersey) by manually applying endo- and epimyocardial contours to the image with the brightest contrast enhancement in the LV. An automated algorithm matched the contours to the remaining images of the slice. Endomyocardial and epimyocardial perfusion in the resting state were assessed separately by applying the endomyocardial or epimyocardial border and a midventricular line ("centerline") (Fig. 1). Spatially averaged signal intensity (SI) values were used to plot SI curves over time of the whole myocardial circumference and for a region of interest in the center of the LV blood pool (input function). Model-constrained deconvolution was used to calculate the maximum amplitude of the impulse response function from the SI curves (12) using the input function measured in the LV center. Based on the central volume theorem, the maximum amplitude of the impulse response function measured in the LV center can be interpreted as a measure of flow (13). Myocardial perfusion reserve was calculated as the ratio of the maximum amplitude of the impulse response function for hyperemia and rest. This approach has been validated in an animal model using radiolabeld microspheres (14). Myocardial perfusion reserve and the CFR were normalized for the RPP by the factor: mean group/individual RPP (15).

Table 1. Demographic Data and Hemodynamic Data During the MR Study

	Volunteers	Group A	Group B	Group C
Age (yrs)	34 ± 9	57 ± 13*	56 ± 6*	56 ± 3*
Male gender (%)	73	80	60	85
Years after Tx	—	9 ± 3	6 ± 4	10 ± 4
Tx organ age (yrs)	—	35 ± 8	34 ± 11	42 ± 11
Cold ischemia time (min)	—	148 ± 44	168 ± 42	169 ± 5
Ejection fraction (%)	65 ± 3	59 ± 4*	56 ± 5*	51 ± 11*
LV mass/BSA (g/m^2)	91 ± 8	94 ± 11	118 ± 9‡	97 ± 10
Heart rate (min^{-1})				
Rest	67 ± 10	85 ± 12*	87 ± 5*	94 ± 13*
Hyperemia	91 ± 18†	85 ± 12	87 ± 3	88 ± 5
Mean blood pressure (mm Hg)				
Rest	95 ± 8	98 ± 10	102 ± 9	94 ± 11
Hyperemia	92 ± 11	87 ± 12	92 ± 6	91 ± 12
RPP (mm Hg/min)				
Rest	6.3 ± 1.0	8.4 ± 1.5*	9.0 ± 0.7*	9.0 ± 1.6*
Hyperemia	8.5 ± 2.5†	7.3 ± 1.6	8.3 ± 0.5	7.5 ± 0.7

*$p < 0.001$ vs. volunteers; †$p < 0.01$ vs. rest; ‡$p < 0.01$ vs. volunteers, A and C.
LV mass/BSA = left ventricular mass normalized to the body surface area; MR = magnetic resonance; RPP = rate-pressure product; Tx = transplant.

For cine analysis (MASS software, Leiden, the Netherlands [16]), determination of ejection fraction (%) and LV myocardial mass, myocardial borders of the LV were defined in each end-diastolic and end-systolic frame in contiguous slices to create a three-dimensional set of data. Left ventricular mass was normalized to the body surface area.

Statistics. Data were analyzed using SPSS (Release 10, SPSS Inc., Chicago, Illinois). Analysis of variance was used to test levels of significance. If significance was indicated by analysis of variance, a Bonferonni correction was used as a post-hoc test for multiple comparisons. Threshold values for MPR and Endo/Epi ratios for the detection of Tx-CHD in the Tx population were determined by receiver operating characteristics and the area under the curve (AUC). All data are mean ± standard deviation. A value of $p < 0.05$ was considered significant.

RESULTS

Magnetic resonance image acquisition was successfully performed in all volunteers and Tx recipients. All subjects tolerated the procedure and contrast injection well. During adenosine infusion some Tx recipients experienced shortness of breath (n = 4), chest discomfort (n = 4), or the urge to breath deeply (n = 2).

Demographic and hemodynamic data. The data are displayed in the Table 1. Volunteers were younger than Tx recipients, but the age of the hearts were not different. No significant difference was seen in age, ejection fraction, cold ischemia time, or years after transplantation between the three groups of Tx patients.

The resting heart rate in volunteers was significantly lower compared with any of the Tx group. Therefore, the RPPs in all Tx groups were significantly higher at rest compared with volunteers. Heart rate increased during adenosine infusion in volunteers but not in Tx patients. Therefore, the RPP increased in volunteers during adenosine infusion but not in Tx recipients. The ejection fraction was significantly higher in volunteers than in any of the Tx groups. Left ventricular mass in group B was significantly higher compared with the other Tx groups or volunteers.

CFR, MPR, and Endo/Epi ratio. Coronary flow reserve for group A, B, and C were 4.0 ± 0.7, 3.2 ± 0.7, and 1.9 ± 0.9, with $p < 0.01$ for B versus A and C and $p < 0.0001$ for C versus A and B. Data for MPR and Endo/Epi ratios are shown in Figures 2 and 3. Coronary flow reserve correlated significantly with MPR for group A ($r = 0.82$, $r < 0.01$, $y = 0.97x - 0.30$), B ($r = 0.77$, $p < 0.01$, $y = 0.74x + 0.49$), and C ($r = 0.73$, $p < 0.01$, $y = 0.84x + 0.05$) and with Endo/Epi ratios for group A ($r = 0.74$, $p < 0.01$, $y = 0.23x + 0.68$), B ($r = 0.72$, $p < 0.01$, $y = 0.13x + 1.04$), and C ($r < 0.70$, $p < 0.01$, $y = 0.34x + 0.48$) (Figs. 4A and 4B).

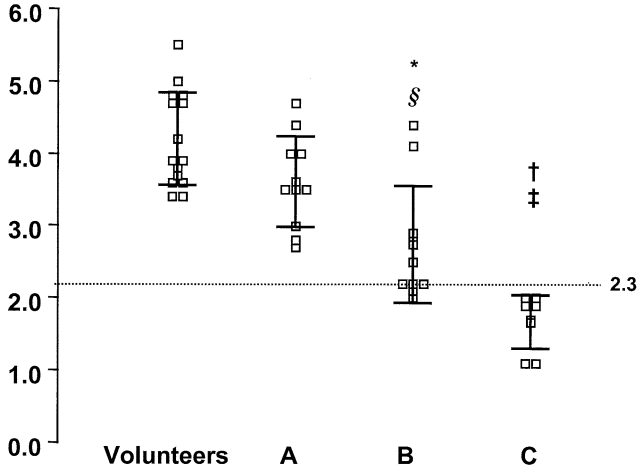

Figure 2. Myocardial perfusion reserve in volunteers group A, B, and C of the transplant recipients. *$p < 0.0001$ versus volunteers; †$p < 0.0001$ versus volunteers and A; ‡$p < 0.01$ versus B; §$p < 0.03$ between A and B.

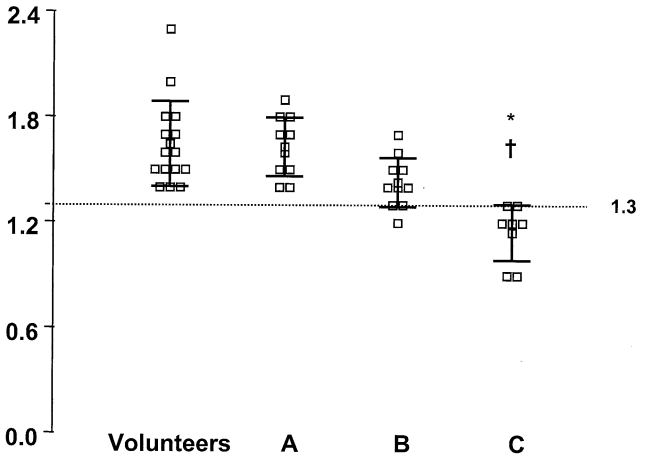

Figure 3. Endomyocardial/epimyocardial perfusion ratio in volunteers group A, B, and C of the transplant recipients. *$p < 0.0001$ versus volunteers and A; †$p < 0.04$ versus B.

Using ROC analysis a cutoff value of MPR >2.3 for the exclusion of Tx-CHD was determined with a sensitivity and specificity of 100% and 85%. The positive predictive value was only 63%, but the negative predictive value was 100% (confidence interval [CI] 0.77 to 0.99; AUC 0.94). For the Endo/Epi ratio, a cutoff value of >1.3 for the exclusion of Tx-CHD was calculated by ROC analysis with only fair sensitivity and specificity of 80% and 70% (positive and negative predictive value: 40% and 93%; CI 0.58 to 0.93; AUC 0.79). However, after exclusion of LV hypertrophy and/or prior rejection, sensitivity and specificity rose to 100% and 80% using a cutoff value of >1.3 for the exclusion of Tx-CHD (positive and negative predictive value: 78% and 100%; CI 0.76 to 0.98; AUC 0.97).

DISCUSSION

There are three important findings in our study:

1) Patients with Tx-CHD showed a reduced MPR and resting Endo/Epi ratio; MPR of >2.3 excluded Tx-CHD (negative predictive value 100%). Using only the resting Endo/Epi ratio, we were able to exclude Tx-CHD (negative predictive value 100%) when LV hypertrophy and/or prior rejection was excluded.
2) A significant correlation between invasive measurement of CFR and the noninvasive evaluation of resting Endo/Epi ratio using MRPI was shown, along with the known significant correlation between CFR and MPR (5).
3) Myocardial perfusion reserve and Endo/Epi ratios are normal in heart Tx recipients without myocardial hypertrophy, prior or acute rejection, or Tx-CHD. Transplant recipients with a history of rejection or LV hypertrophy even in the absence of clinical symptoms showed significant decrease in vasodialator reserve. These results are consistent with the findings of McGinn et al. (17), who showed normal coronary reserve in Tx recipients in the absence of allograft rejection (18) and LV hypertrophy. Coronary vasodialator reserve was diminished when LV hypertrophy or rejection was present.

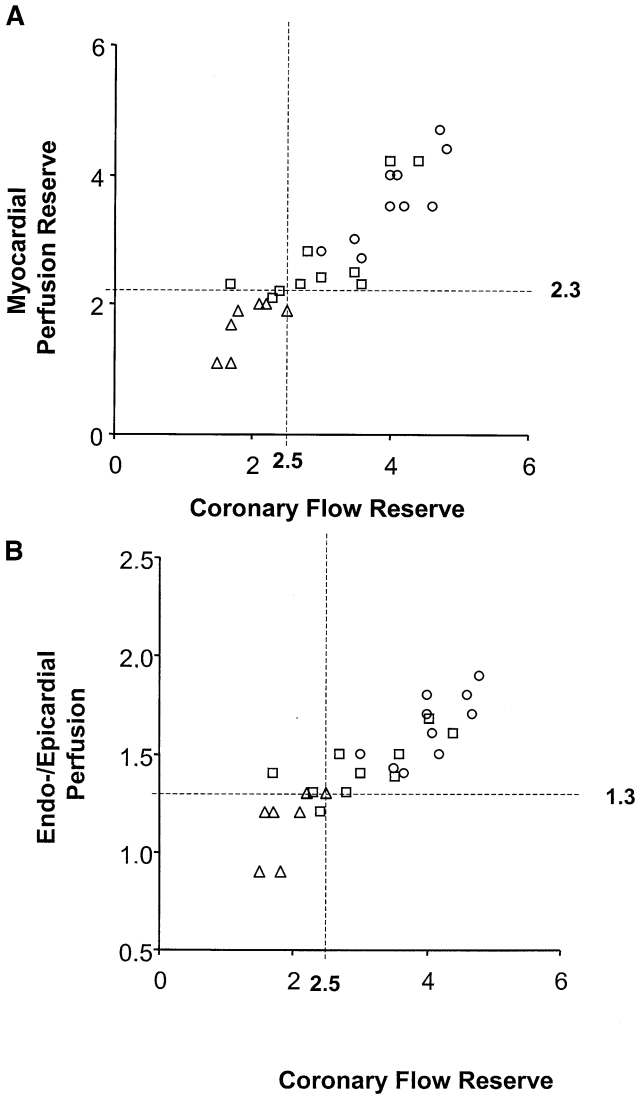

Figure 4. Linear correlation of **(A)** coronary flow reserve (CFR) and myocardial perfusion reserve (MPR) and **(B)** endomyocardial/epimyocardial perfusion ratios (Endo/Epi ratios) and CFR in transplant patients. Values in the right lower quadrant represent false positive for transplant arteriopathy (Tx-CHD) as determined by the MPR **(A)** or Endo/Epi ratios **(B)**; values in the left upper quadrant represents false-negative for Tx-CHD as determined by the MPR **(A)** or Endo/Epi ratio **(B).** Cutoff values **(dotted lines)** for MPR **(A)** and Endo/Epi **(B)** ratios as determined by receiver operating characteristic analysis (see text for details). **Circles** = group A; **squares** = group B; **triangles** = group C of the transplant patients.

Using the Endo/Epi ratio and a cutoff value of >1.3, healthy Tx recipients without LV hypertrophy or prior rejection would not require further invasive or hyperemic testing to exclude Tx-CHD. Hyperemic testing must be considered in patients with LV hypertrophy or prior episodes of rejection for a more secure diagnosis of Tx-CHD. Adding the information provided by hyperemic testing,

patients with an MPR of >2.3 could have been excluded from further invasive testing.

Performing only a resting study would result in several advantages. Besides the reduction in scan time, costs and risks due to pharmacologic stress testing, hyperemic data add a higher scatter to the values of quantitative perfusion analysis (19). Despite a good sensitivity of hyperemic testing for the detection of significant coronary artery disease, hyperemic data results in a higher standard deviation (compare standard deviation in Figs. 2 and 3) and might explain the low positive predictive value of the MPR in this study (63%).

Endo/Epi ratio. Healthy Tx recipients and volunteers have the same level of Endo/Epi ratios, while patients with Tx-CHD show a significant reduction in their Endo/Epi ratios. A reduction in Endo/Epi ratio is likely to be related to the reduced CFR, as seen in patients with Tx-CHD. Two factors may explain the relationship between endomyocardial/epimyocardial perfusion and vasodilatory capacity.

First, due to the closer proximity of the endomyocardial layer to the LV cavity, there is a greater intramural pressure in the endomyocardium compared with the epimyocardium. This hampers the perfusion in the endomyocardium as compared with the epimyocardium, and a reduction of perfusion would be expected. However, an active reduction in the coronary vascular tone in the endomyocardial layer has been shown to result in a higher endomyocardial versus epimyocardial perfusion. Subsequently, the Endo/Epi ratio is >1 under resting conditions (20) as confirmed by our data. Therefore, the endomyocardial layer will be more sensitive to a compromised vasodilatory capacity because part of the vasodilatory capacity has already been used.

Second, an increase in heart rate causes a decrease in the Endo/Epi ratio (21,22). After cardiac Tx, resting heart rate is increased. However, the Endo/Epi ratios in the healthy Tx recipients (group A) of our groups were not different from that in volunteers. Thus, Endo/Epi ratio in group A most likely is sustained by partially recruiting the vasodilatory capacity in the endomyocardium.

Coronary reserve is compromised, and heart rate is elevated in the group of patients with Tx-CHD. Consequently, the Endo/Epi ratio decreases because endomyocardial perfusion highly depends on an intact vasodilatory capacity.

Study limitations. The small sample size is a limitation of our study. However, even with the small samples, our results were significant emphasizing the advantage of quantitative magnetic resonance imaging.

All patients in group C were in an advanced stage of Tx-CHD and had major abnormalities in their coronary angiogram. Whether patients with mild disease would have been clearly distinguished from healthy Tx recipients by MR perfusion imaging cannot be determined. Studies using intracoronary ultrasound (ICUS) are needed to test the sensitivity of MRPI for detection of early stages of Tx-CHD. A close relationship of the degree of intimal thickening assessed by ICUS with abnormalities in coronary function in Tx patients has already been demonstrated (23).

Although there is evidence for regional and segmental heterogeneity in the endothelial response (24), MPR and Endo/Epi ratios were not assessed regionally but over the whole myocardial circumference. This might also explain the good, but not perfect, correlation between MR perfusion parameters and invasive CFR, which was only assessed in the left anterior descending coronary artery. Assessing regional differences is crucial in patients with coronary artery disease. A segmentation of the myocardial circumference in a different region is possible and has been performed (6). In addition, we were only able to assess myocardial perfusion in three slices. This was related to the high heart rate in the Tx population. Using a higher temporal resolution would allow covering of more than three slices, but would cause a loss in spatial resolution. Therefore, the analysis of a transmural perfusion gradient would have been cumbersome. Because Tx-CHD is a diffuse disease of the LV myocardium, sensitivity to detect the disease was still good using a three-slice coverage. In patients where perfusion is regionally impaired, that is, in patients with coronary artery disease, coverage of the whole LV myocardium would be of great advantage. Good sensitivities and specificities for the detection of coronary artery disease have been demonstrated with magnetic resonance first pass imaging using a four-slice approach (8).

Determination of endo- or epimyocardial perfusion in patients with a thin LV wall, that is, after transmural myocardial infarction or dilative cardiomyopathy, might be cumbersome with the image resolution currently available. However, the available resolution assesses a transmural gradient of myocardial perfusion in subjects with normal or increased LV wall thickness. In our subjects LV wall thickness was ≥7 mm, and resolution was ~2 mm in-plane. Therefore, we did not face problems with transmural image resolution.

Conclusions and clinical implications. Evaluation of myocardial perfusion with MRPI was tested to detect patients with Tx-CHD. Noninvasive determination of myocardial perfusion reserve with magnetic resonance imaging allows exclusion of Tx-CHD and closely correlates with the invasive data on coronary flow reserve. Furthermore, we were able to identify patients with Tx-CHD using only the Endo/Epi ratio when LV hypertrophy and/or prior rejection were excluded. In combination with the clinical evaluation, MRPI might be an effective screening tool for Tx-CHD. Using noninvasive MRPI for the annual follow-up of Tx recipients might reduce the number of patients needing invasive testing. In addition, in combination with magnetic resonance cine imaging for cardiac function, MRPI might be a good method for routine surveillance of patients after cardiac transplantation. The present study demonstrates that perfusion can be reliably

assessed by MRPI not only in patients with coronary artery disease (6) or syndrome X (7) but also in heart Tx patients.

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