Journal of Cardiovascular Magnetic Resonance (2007) **9,** 701–707

ISSN: 1097-6647 print / 1532-429X online
DOI: 10.1080/10976640701198980

informa
healthcare

Magnetic Resonance Measurements of Coronary Flow Reserve in Heart Transplant Recipients: An Exploratory Study of the Relationship to Coronary Angiographic Findings

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INTRODUCTION

Coronary artery disease (CAD) is the major cause of long-term morbidity and graft loss in patients following cardiac transplantation (1, 2). These patients develop an accelerated form of coronary artery disease with a reported incidence of graft arteriopathy of 50% at 5 years (3), which may increase to as high as 90% beyond 5 years (4). Cardiac allograft vasculopathy (CAV) occurs in all vessels of the allograft including the coronary arterial system, coronary veins and the great vessels up to the suture line (1). Once patients have developed a single stenosis of greater than 70% confirmed by coronary angiography, the mortality rate may be as high as 70% at 1 year post diagnosis (5).

Conventional coronary angiography has been widely used to diagnose cardiac allograft vasculopathy CAV (6, 7). Due to the diffuse distribution of the disease, the presence or extent of disease in distal coronary vessels is difficult to detect using coronary angiography and therefore may underestimate the diagnosis of CAV (6, 8). Intracoronary ultrasound has proven to be more accurate at detecting CAV than conventional coronary angiography (9). Due to the invasiveness of coronary angiography and intracoronary ultrasound, other non-invasive techniques such as radionuclide thallium and sestamibi imaging have been studied. Unfortunately they have failed to provide the necessary sensitivity and specificity for CAV diagnosis (10–12).

Coronary flow reserve (CFR) provides a measurement of overall coronary flow (6) as it defines the ability of coronary blood flow to increase when metabolically required. Most of the published work on CFR has been performed using intravascular Doppler wire flow probes (13) or non-invasive positron emission tomography (PET). In the past several years, cardiovascular magnetic resonance (CMR) cine phase contrast (PC) velocity encoded sequences have been used to determine CFR (14–16). Van Rossum et al (14) compared CMR phase contrast measurements in the coronary sinus with results from a flow meter in phantoms and reported excellent correlation of the velocities ($r = 0.99$). CMR CFR determinations have been compared to the current gold standard, PET, by Koskenvuo et al (17) and Schwitter et al (18). Both groups determined that there were good correlations between the two techniques.

The purpose of the present study was to non-invasively assess the diagnostic utility of CFR, as determined by CMR, in predicting significant coronary artery stenoses in heart transplant recipients.

MATERIALS AND METHODS

Study population

Nineteen heart transplant recipients (mean 7.7 ± 3.9 years post transplant) were enrolled in the study. All but two of the patients were on cyclosporine (mean dose of 237 mg, range 125

Received 13 July 2006; accepted 22 December 2006.
Keywords: Cardiovascular Magnetic Resonance, Cardiac Transplantation, Coronary Flow Reserve, Cardiac Allograft Vasculopathy.
This study was supported in part by the Department of Medicine, London Health Sciences Centre and the Canadian Foundation for Innovation. We thank Tracey Pace and Carolyn Irving for administrative support and the MRI technologists (London Health Sciences Centre – University Campus) for assistance during the MRI procedure.
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to 300). The mean trough level was 125 ng/mL (range 59–191). The remaining two patients were on tacrolimus. There was no significant difference between any of the patients' ejection fractions, renal function or cholesterol levels. Two of the patients were diabetics. All patients had their CMR scan within 7.4 ± 3.8 weeks following their routine coronary angiogram. There was no evidence of rejection on any the most recent biopsies. Two of the patients did not complete their CMR study: one due to claustrophobia and the other due to chest congestion. Ten healthy volunteers were enrolled as control subjects. The ages of the control subjects (mean age 27 ± 2 years) were not specifically matched to the donors (31 ± 10 years at time of donation, 39 ± 10 at the time of the CMR), although the genders of the two groups were very similar (control 67% male, donors 65% male).

London Health Sciences Centre Institutional Ethics Committee approved the protocol in accordance with institutional guidelines, and informed consent was obtained from all subjects. All subjects were asked to refrain from caffeinated beverages for 24 hours and large meals for 6 hours preceding their CMR scan.

CMR imaging protocol

Imaging was performed on a 1.5T CV MRI scanner (General Electric, Milwaukee, Wisconsin, USA). Each subject was placed in the supine position and a four-element cardiac phased array coil was used to receive the MR signal. MR-compatible electrocardiographic monitoring leads were placed on the chest and were used to monitor the patient's heart rate and to trigger image acquisition.

Sagittal and long-axis fast cine images were acquired to act as localizing sequences. A fast cine gradient echo sequence was used to obtain a complete set of cine short axis slices of the left ventricle. The imaging parameters were as follows: repetition time (TR) of 8.0 ms, echo time (TE) of 4.5 ms, flip angle of 20°, receive bandwidth of ±31.2 kHz, views per segment of 8, 1 signal average (NEX), 256 × 128 matrix, field of view (FOV) of 40 × 30 cm and slice thickness of 10 mm. The short axis images were used for quantification of left ventricular mass. Double Inversion Recovery (DIR) images were then obtained in the axial plane to localize the coronary sinus. Measurements of flow through the coronary sinus were used to determine CFR, as it drains approximately 96% of venous blood flow from the left ventricle. Retrospective gating was used to acquire three, 5 mm thick oblique fast gradient echo cine phase contrast images, perpendicular to the flow in the coronary sinus (Fig. 1). The imaging parameters were as follows: TR 7.2–7.4 ms, TE 3.6–3.7 ms, flip angle of 20°, receive bandwidth of ±31.2 kHz, views per segment of 6, 1 NEX, 256 × 128 matrix and FOV of 36 × 27 cm were used for all fast cine PC images. The resulting in-plane resolution was 1.4 × 2.8 mm, and yielded an average of 20–60 pixels in the coronary sinus. Velocity encoding values of ±80 cm/s and ±140 cm/s were used for the baseline and hyperemic scans respectively. Velocity encoding was performed in the slice direction. View sharing allowed twenty phases to be acquired at each slice location within a 12–20 second breath-hold period and a temporal resolution of approximately 86 ms. Subjects were instructed to take a deep breath in and out, then to hold their breath with a shallow inspiration to avoid a Valsalva maneuver.

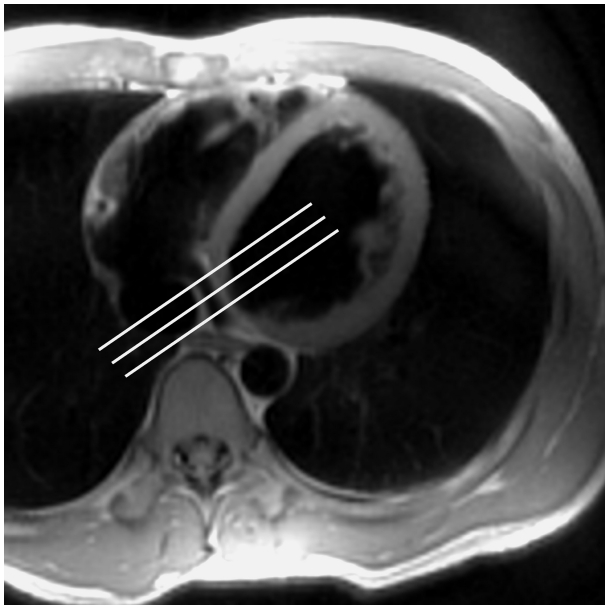

Figure 1. Axial double inversion recovery (DIR) image used for localizing the coronary sinus. Lines represent three 5 mm slice locations used for velocity encoded fast phase contrast (PC) images.

To induce reactive hyperemia, dipyridamole was infused at a rate of 0.14 mg/min for four minutes for a total dose of 0.56 mg/kg. At the time of peak effect (∼7–9 minutes following infusion, as suggested by the product monograph), repeat phase contrast imaging of the coronary sinus was performed as described above. Following the hyperemic phase contrast imaging, subjects were given a bolus of aminophylline (150 mg) to reverse the effects of the dipyridamole.

During the examination, each patient was monitored by pulse-oximeter and continuous ECG display. Blood pressure was also measured intermittently during the exam, and every two minutes during the dipyridamole infusion.

MR blood flow measurement

Flow measurements were performed on a Sun workstation using Medis FLOW software (Medis Medical Imaging Systems, Leiden, The Netherlands). The imaging slice closest to the right atrium, in which the coronary sinus was visible in all phases of the cardiac cycle, was used for analysis. Regions of interest (ROIs) were manually traced around the coronary sinus (CS) on the baseline and hyperemic phase contrast images (Fig. 2) by three observers blinded to the results of the coronary angiogram. Observer 3 performed all measurements twice with at least four weeks between repeat measurements. To compensate for background phase error, an additional ROI was placed on the myocardium. CS flow (mL/sec) was calculated by summing the flow of each phase of the cardiac cycle and multiplying

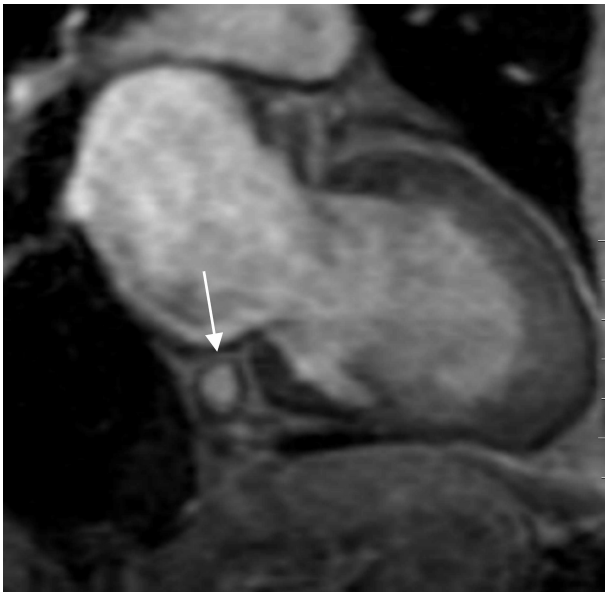

Figure 2. Representative baseline velocity encoded phase contrast image of the coronary sinus (arrow) used for flow calculations.

by the heart rate. CFR was calculated as the ratio of blood flow in the coronary sinus after dipyridamole infusion (hCSF) to the baseline blood flow (bCSF).

Left ventricular mass measurement

LV mass was determined by manually tracing epicardial and endocardial borders on the end diastolic image of each of the fast cine short axis series using Medis MASS software (Medis Medical Imaging Systems, Leiden, Netherlands) by a single observer (#3). LV mass was then normalized for body surface area. For calculation of myocardial perfusion per unit mass, the mean of the single observer's baseline and hyperemic flow measurements ($bCSF_{norm}$ and $hCSF_{norm}$) were divided by left ventricular (LV) mass.

Coronary angiography

Coronary angiography was performed using a Siemens biplane Hicor angiographic system (Erlangen, Germany) as part of standard heart transplant follow-up on all transplant recipients. The resulting images were analyzed by two experienced angiographers using the Stanford Scale for classification of coronary vascular disease in heart transplant recipients (19). Based on the coronary angiogram, the transplant patients were divided into three groups: normal (NTx), mild disease and severe disease. Patients with type A, B_1, B_2, and C lesions on the Stanford Scale were considered to have severe disease. Patients with isolated minor epicardial irregularities were considered to have mild disease.

Statistical analysis

Statistical analysis was performed using GraphPad Prism for Macintosh (GraphPad Software, San Diego California, USA). The means of the data determined by all of the investigators were used to calculate CFR. All values are expressed as mean ± standard error unless otherwise specified. Differences between groups were determined by a one-way analysis of variance with Newman-Keuls post test. Comparisons between baseline and hyperemic data were performed with paired Student's t tests. We considered $p < 0.05$ to be statistically significant. Reliability coefficients for inter-rater and intra-rater variability were calculated using SPSS for Windows V. 10.0 (SPSS Inc, Chicago, Illinois, USA).

RESULTS

CMR data from 26 of the 27 subjects (96%) were analyzed. The phase contrast images from one of the subjects in the control group could not be analyzed due to misalignment of the imaging plane. Heart rates increased in all of the subjects following dipyridamole infusion. There was no difference in heart rate between groups at either baseline or hyperemia.

Of the 17 heart transplant recipients, 7 were determined to have normal coronary angiogram results. Five had slight irregular epicardial abnormalities, and 5 had severe coronary disease (Table 1). Cyclosporine dosages and levels did not prove to be significantly different between transplant groups.

A representative flow curve of the baseline and hyperemic data are shown in Fig. 3. The results of the CMR flow measurements are given in Table 2. Hyperemic flow (mL/s) increased from baseline flow in all groups ($p < 0.001$). Figure 4 illustrates the significant difference between the CFR results of the control group (4.59 ± 0.58) and both groups of transplant recipients with some evidence of disease (mild 2.15 ± 0.44, severe 2.21 ± 0.59; $p < 0.05$). No significant difference was found between the control group and the normal transplant recipients (3.51 ± 0.56).

The mean left ventricular mass of the severe disease group (186 ± 53 g, mean ± SD) was significantly higher than the normal transplant and control group ($p < 0.05$) (Fig. 5). Normalizing for body surface area produced similar results. Coronary sinus flow normalized for mass (CSF_{norm}) revealed no significant difference between baseline groups. During hyperemia, a significant difference was seen between the control group (3.78 ± 0.40 mL/min/g) and the severe disease group (1.56 ± 0.40 mL/min/g; $p < 0.05$) (Fig. 6).

Table 1. Coronary angiogram results determined using Stanford Scale for heart transplant recipients. Individual patients may have had one or more lesion types

Classification	Lesion Type	No. of Patients
Normal		7
Mild Disease	Minor Epicardial Irregularity	5
Severe Disease	A	2
	B_1	1
	B_2	4
	C	3
	100% Occlusion	3

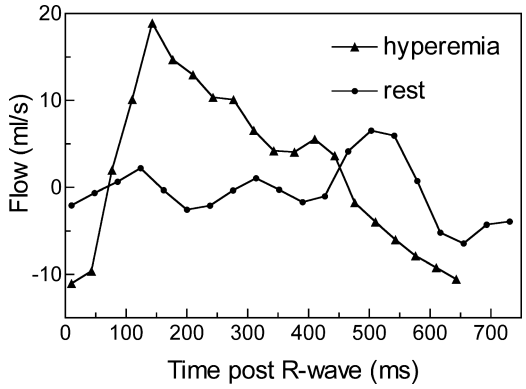

Figure 3. Plot of volumetric blood flow in the coronary sinus measured with velocity encoded CMR phase contrast. Reverse flow at the end of diastole into the coronary sinus in this subject was caused by the contraction of the right atrium.

For the CFR results, the inter-rater reliability expressed as a mean reliability coefficient for three observers was 0.739 and the intra-rater reliability was 0.741. For the hyperemic flow results, the mean inter-rater reliability coefficient was 0.928, and the intra-rater reliability was 0.941.

DISCUSSION

The current study results suggest that heart transplant recipients with severe allograft vasculopathy have decreased hyperemic flow per gram of myocardial mass in comparison to a control group and that they have increased LV mass in comparison to a control group and transplant patients without evidence of coronary disease. Most importantly, the study suggests that non-invasive estimates of CFR by CMR may be able to predict significant coronary artery disease in heart recipient patients.

Table 2. Myocardial blood flow at baseline and during dipyridamole-induced hyperemia as determined by CMR phase contrast imaging

	Controls	Normal	Mild Disease	Severe Disease
HR, bpm				
Baseline	72 ± 9	84 ± 12	80 ± 9	87 ± 15
Hyperemia	100 ± 12	95 ± 16	86 ± 12	94 ± 16
BP				
Baseline	125 ± 15	151 ± 14	151 ± 28	148 ± 26
	72 ± 7	90 ± 5	80 ± 29	91 ± 12
Hyperemia	128 ± 9	149 ± 4	143 ± 32	151 ± 14
	70 ± 4	89 ± 7	86 ± 26	88 ± 7
Post Transplant (yrs)	n/a	7.0 ± 3.6	5.3 ± 2.7	11.2 ± 3.0
CSF, mL/min				
Baseline	103 ± 24	107 ± 42	161 ± 72	147 ± 43
Hyperemia	431 ± 150	365 ± 220	311 ± 113	297 ± 103

All data expressed as mean ± standard deviation.HR = heart rate, CSF = coronary sinus flow.

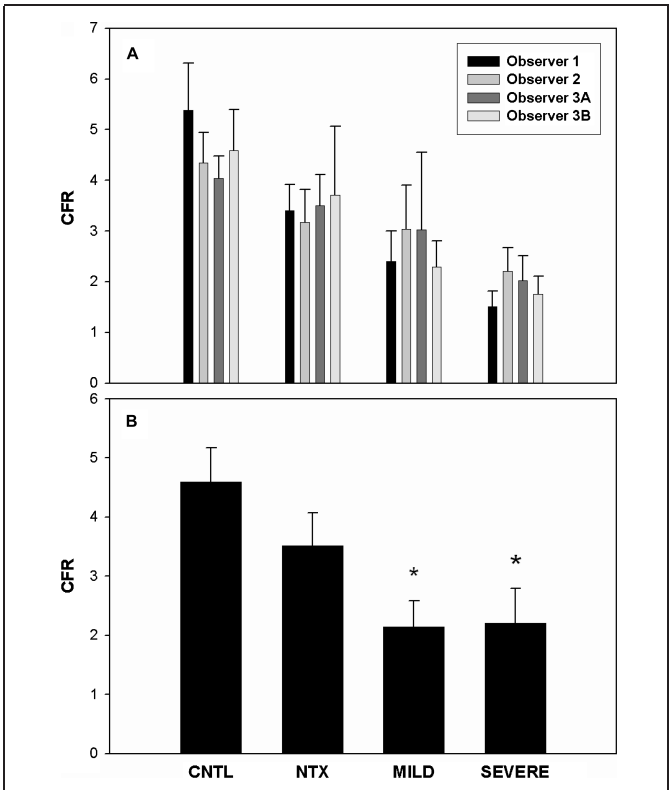

Figure 4. Comparison of coronary flow reserve (CFR) results obtained in heart transplant recipients and control group (CNTL). Transplant recipients categorized by coronary angiography as normal (NTX), MILD disease and SEVERE disease. Individual CFR measurements determined by three observers. Observer 3 performed the analysis twice (A). Means of the measurements by all investigators (B). Asterisk (*) indicates $p < 0.01$ compared to CNTL and NTX.

Cardiac transplant patients with severe epicardial stenosis have historically been eliminated for bypass surgery, and their only option was retransplantation (6). It was believed that by the time epicardial disease was evident, the distal vessels were

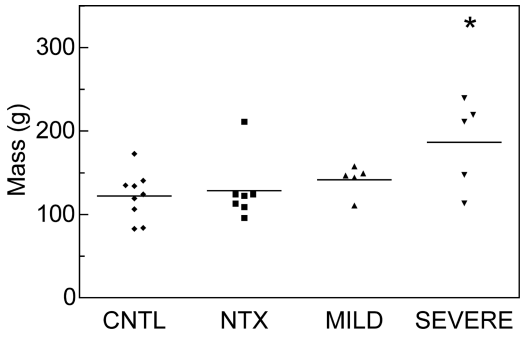

Figure 5. Scattergram comparison of left ventricular mass (g) results obtained in heart transplant recipients and control group. Transplant recipients categorized by coronary angiography as normal (NTX), MILD disease and SEVERE disease. Horizontal bars represent the means.

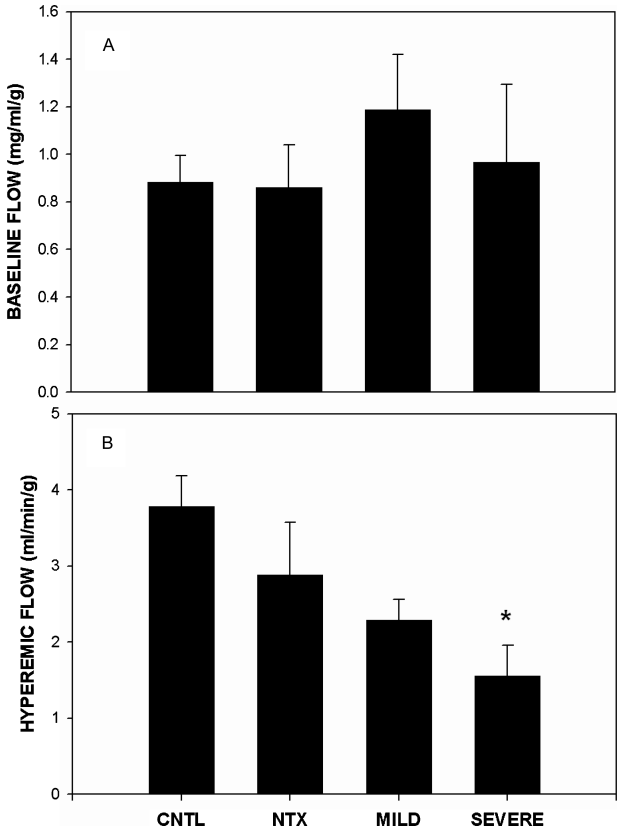

Figure 6. Comparison of volumetric flow normalized for left ventricular mass obtained in heart transplant recipients and control group (CNTL). Transplant recipients categorized by coronary angiography as normal (NTX), MILD disease and SEVERE disease. Asterisk (*) indicates $p < 0.01$ compared to all other groups. Bar graphs depict baseline normalized flow (A) and hyperemic normalized flow (B). Hyperemic normalized flow demonstrated significant difference between SEVERE and all other groups.

obliterated (20). Luyt et al (21) found that 50% of transplant patients with moderate stenosis (30 to 60% of vessel diameter) progressed to severe stenosis (>60% diameter) within one year. The assessment of the severity of stenoses is determined by either anatomic visualization by angiography or intravascular ultrasound or by determining the effect on blood flow and therefore its functional significance (22). In a study of non-transplant patients with coronary artery stenosis by Di Carli et al (23), a correlation was found between the degree of stenosis on angiography and CFR determined by PET ($r = 0.78$). CFR has been proposed as a more sensitive alternative to angiography to study new treatments that affect the onset or progression of CAV (24). Although PET CFR imaging is non-invasive, it is not widely available, and it uses ionizing radiation. To monitor these patients, a non-invasive technique such as CMR CFR would be beneficial. CMR can also provide additional information such as ejection fraction without additional imaging time.

Mazur et al (25) reported decreased CFR results using invasive Doppler flow wires in cardiac transplant recipients with severe disease as defined by angiography using the Stanford Scale. Using non-invasive CMR phase contrast imaging, we were able to achieve similar results. The study by Mazur et al did not categorize transplant recipients with minor epicardial irregularities. In comparison to a control group, we demonstrated a significantly reduced CFR in these patients who have minor irregularities on angiography. To our knowledge, this is one of the first CMR studies to report significant differences in CFR results in transplant recipients with evidence of coronary artery vasculopathy. Although significance was not achieved in our study between normal transplant recipients and patients with some evidence of disease, the mean value of the normal transplant group (3.5) is similar to the CFR reported in normal transplant recipients in a study by Caracciolo et al (26) (3.0).

Conflicting CFR results have been published on cardiac transplant recipients, especially those studied within the first 2 years following transplantation. To avoid possible implications from microvascular injury related to the transplant surgery, all patients in the current study were imaged a minimum of 2.5 years following transplantation.

We found a significant difference in LV mass in patients with severe coronary artery disease. The flow values normalized for mass during baseline and hyperemic flow reported in the present study are generally higher than those previously reported. In the study by Schwitter et al (18), they noted left ventricular hypertrophy in their normal transplant patients. As suggested by the results of previous studies, left ventricular hypertrophy is associated with an increased baseline flow and unchanged hyperemic flow (25). This may aid in explaining the difference with the results of the current study in which the control group and normal transplant patients had similar LV mass results. Kofoed et al (27) reported an increase in baseline flow in normal transplant patients using PET to determine flow in the coronary arteries. They suggested that an average higher heart rate in the patients was the reason for the difference. We found no significant difference in the baseline or hyperemic heart rates between any of the groups.

The baseline flow (mean $\pm$ sd) in control subjects in our study (103 ± 24 mL/min) are in line with CMR coronary sinus data previously published by van Rossum et al (14) (144 ± 62 mL/min) and Koskenvuo et al (17) (114 ± 17 mL/min). Although the mean bCSF and $bCSF_{norm}$ of the patient groups with some evidence of disease appear to be increased, statistical significance was not achieved between groups. Chan et al (28) reported similar baseline PET results between controls and normal transplant recipients. In the present study, the baseline flow rates of normal transplant patients (107 ± 42 mL/min) were very similar to the control group. Hyperemic CSF_{norm} demonstrated a significant difference between patients with severe disease and control subjects. These findings are similar to studies comparing flow in patients with varying degrees of stenosis (22, 29).

Very short scan times are critical when imaging with a pharmacological stress agent (16). Scan times of very short duration (10–30 seconds) are possible with breath holding as compared to respiratory compensated or gated techniques that typically take two to three minutes. Breath hold image acquisitions reduce

phase artifacts from respiratory motion; however, breath holding can change intrathoracic pressure and venous blood flow (18). We used shallow breath holds which have been suggested as having no significant effect on flow measurements (16) and we were able to acquire 20 phases in 12–20 seconds.

Various other CMR techniques have recently been studied in a search for non-invasive monitoring of transplant patients. Muehling et al (30) acquired resting and hyperemic CMR perfusion scans by imaging during a first pass of an injected gadolinium contrast agent. They determined the myocardial perfusion reserve (MPR) and the ratio of flow through the endocardium and epicardium (endo/epi ratio) in a group of normal volunteers and heart transplant recipients. They found a good correlation to the invasive CFR and determined that vasculopathy could be excluded using MPR. When LV hypertrophy and/or a history of rejection was excluded, they concluded that resting endo/epi ratios alone could be used to exclude vasculopathy. Schwitter et al (31) compared CMR perfusion to PET and coronary angiography in non-transplant patients. They concluded that they are able to identify patients with coronary artery disease, and their results were well correlated with PET measurements of the amount of compromised myocardium. CMR perfusion imaging, in comparison to our study, requires the use of an injected contrast material. Calculation of CFR is a more straightforward technique requiring no normalization of the data. A combination of CFR and perfusion data may provide high sensitivity and specificity using a single non-invasive modality.

Limitations

We performed the PC imaging in the coronary sinus as it represents near total flow from the myocardium. However, by imaging in the coronary sinus, regional distribution of each vessel cannot be distinguished. In a disease such as coronary artery vasculopathy in transplant patients, the disease process is diffuse and is not limited to individual vessels.

Although significance differences between group were detected with small numbers of subjects, larger numbers may have provided a greater degree of statistical power. In the current study, it is impossible to distinguish between the contribution of ventricular hypertrophy and arteriopathy as a cause for the decreased flow. Further research comparing non-transplant patients with ventricular hypertrophy would be beneficial.

Coronary angiography was used to divide the patients into groups. As stated previously, coronary angiography may underestimate the presence or extent of disease in distal coronary vessels due to the diffuse distribution of the disease. We used the Stanford Scale to classify the angiographic findings to limit errors; however, patients may have been categorized incorrectly. Intravascular ultrasound was not available during the cardiac angiograms to confirm the findings.

As the coronary sinus moves with contraction of the heart, there is translational movement of the sinus as noted by Van Rossum et al (14) that can lead to misalignment of the flow and overestimation of the ROI. This movement may have introduced an error during the analysis. To reduce blurring of the vessel contour and subsequent overestimation of the vessel size, high temporal and spatial resolution must be used (16). To ensure the breath hold acquisitions were less than 20 seconds in the current study, a spatial resolution of 1.4×2.8 mm. was required. Kawada et al (32) performed CMR breath hold imaging in the coronary sinus using similar spatial resolution (approx. 1×2 mm); however, in the study by Schwitter et al (18), they performed non-breath hold imaging and were able to acquire images with 0.8×0.8 mm in plane resolution. A reduction in spatial resolution may cause intravoxel averaging of flowing blood and the vessel edge, which can lead to an overestimation of the flow volume (15). The coronary sinus measures approximately 80 mm^2, and our ROI's included 20 to 60 pixels, which provides adequate spatial resolution (33, 34).

Although our analysis program has an automated contour function, we found that it was unable to produce reliable contours on the coronary sinus, and all contours had to be traced manually. This was relatively time consuming and took approximately 10 to 15 minutes per subject. Advancements in automated contours that eliminate intraobserver variability and reduce analysis time will make CMR PC a more attractive tool.

CONCLUSIONS

In conclusion, CMR CFR determinations in the coronary sinus may be a useful tool in evaluating coronary allograft vasculopathy in heart transplant recipients. In patients with severe disease, increased LV mass and decreased hyperemic flow normalized for mass were demonstrated. Non-invasive CMR CFR measurements may be a method of monitoring heart transplant recipients without the use of ionizing radiation. Further investigations will help to more accurately identify those individuals at greatest risk, and a combination of CMR CFR and perfusion imaging may aid in the diagnoses of these patients.

REFERENCES

1. Arkonac B, Hosenpud JD. Pathogenesis of cardiac allograft vasculopathy (chronic rejection). In: Cooper DKC, Miller LW, Patterson GA, eds. The transplantation and replacement of thoracic organs. Hingham MA: Kluwer Academic, 1996: 321–331.
2. Miller LW. Transplant coronary artery disease: Editorial. J Heart Lung Transplant 1992;11:S1–4.
3. Billingham ME. Cardiac transplant atherosclerosis. Transplant Proc 1987;19:19.
4. Young JB. Cardiac allograft arteriopathy: an ischemic burden of a different sort. Am J Cardiol 1992;70:9F.
5. Keogh AM, Valantine HA, Hunt SA, Schroeder JS, McIntosh N, Oyer PE, et al. Impact of proximal or midvessel discrete coronary artery stenosis on survival after heart transplantation. J Heart Lung Transplant 1992;11:892–901.
6. Miller LW, Donahue T, Wolford T, Drury J. Diagnosis and management of cardiac allograft vasculopathy (chronic rejection). In: Cooper DKC, Miller LW, Patterson GA, eds. The transplantation and replacement of thoracic organs. Hingham MA: Kluwer Academic, 1996:333–345.
7. Weis M, Von Scheidt W. Cardiac allograft vasculopathy. A review. Circulation 1997;96:2069–2077.
8. Dressler FA, Miller LW. Necropsy versus angiography: how accurate is angiography? J Heart Lung Transplant 1992;11:S56.

9. Pflugfelder PW, Boughner DR, Rudas L, Kostuk WJ. Enhanced detection of cardiac allograft arterial disease with Intracoronary ultrasonographic imaging. Am Heart J 1993;125:1583–1591.
10. Rodney R, Johnson L. Myocardial perfusion scintigraphy to assess heart transplant vasculopathy. *J Heart Lung Transplant*. 1992;11:S74–78.
11. Rodney R, Johnson L, Blood D, Barr ML. Myocardial perfusion scintigraphy in heart transplant recipients with and without allograft atherosclerosis: a comparison of thallium-201 and technetium 99 m sestamibi. J Heart Lung Transplant 1994;13:1039–1044.
12. Jackson PA, Akosah KO, Kirchberg DJ, Mohanty PK, Minisi AJ. Relationship between dobutamine-induced regional wall motion abnormalities and coronary flow reserve in heart transplant patients without angiographic coronary artery disease. J Heart Lung Transplant 2002;21:1080–1089.
13. Pinto FJ, St. Goar FG, Fischell TA, Stadius ML, Valantine HA, Alderman EL, et al. Nitroglycerin-induced coronary vasodilation in cardiac transplant recipients: evaluation with in vivo intracoronary ultrasound. *Circulation* 1992;85:69.
14. Van Rossum AC, Visser FC, Hofman MBM, Galjee MA, Westerhof N, Valk J. Global left ventricular perfusion: noninvasive measurement with cine MR imaging and phase velocity mapping of coronary venous outflow. Radiology 1992;182:685–691.
15. Sakuma H, Kawada N, Takeda K, Higgins CB. MR measurement of coronary blood flow. J Mag Res Imag 1999;10:728–733.
16. Davis CP, Liu P, Hauser M, Gohde SC, von Schulthess GK, Debatin JF. Coronary flow and coronary flow reserve measurements in humans with breath-hold magnetic resonance phase contrast velocity mapping. Magn Reson Med 1997;37:537–544.
17. Koskenvuo JW, Sakuma H, Niemi P, Toikka JO, Knuuti J, Laine H, et al. Global myocardial blood flow and global flow reserve measurements by MRI and PET are comparable. J Magn Reson Imaging 2001;13:361–366.
18. Schwitter J, DeMarco T, Kneifel S, von Schulthess GK, Ciopor Jorg M, Arheden H, et al. Magnetic Resonance-based assessment of global coronary flow and flow reserve and its relation to left ventricular functional parameters: A comparison with positron emission tomography. *Circulation* 2000;101:2696–2702.
19. Gao S, Alderman EL, Schroeder JS, Silverman JF, Hunt SA. Accelerated coronary vascular disease in heart transplant patient: Coronary arteriographic findings. J Am Coll Cardiol 1988;12:334–40.
20. Roberts M, Parameshwar J, Wallwork J, Large S, Schofield P. Coronary revascularization after cardiac transplantation. J Heart Lung Transplant 1994;13:S48.
21. Luyt CE, Drobinski G, Dorent R, Ghossoub JJ, Collet JP, Choussat R, et al. Prognosis of moderate coronary artery lesions in heart tranplant patients. J Heart Lung Transplant 2003;22:130–136.
22. Bache RJ. Vasodilator reserve: A functional assessment of coronary health. Circulation 1998;98:1257–1260.
23. Di Carli M, Czernin J, Hoh CK, Gerbaudo VH, Brunken RC, Huang SC, et al. Relation among stenosis severity, myocardial blood flow, and flow reserve in patients with coronary artery disease. Circulation 1995;91:1944–51.
24. Parameshwar, J. Coronary flow reserve in cardiac allograft vasculopathy. Transplanatation 1999;68:1435–1436.
25. Mazur W, Bitar JN, Young JB, Arif Khalil A, Vardan S, Cocanougher Short B, et al. Progressive deterioration of coronary flow reserve after heart transplantation. Am Heart J 1998;136:504–509.
26. Caracciolo EA, Wolford TL, Underwood RD, Donohue TJ, Bach RG, Miller LW, et al. Influence of intimal thickening on coronary blood flow responses in orthotopic heart transplant recipients: A combined intravascular Doppler and ultrasound study. Circulation 1995;92:182–190.
27. Kofoed KF, Czernin J, Johnson J, Kobashigawa J, Phelps ME, Laks H, et al. Effects of cardiac allograft vasculopathy on myocardial blood flow, vasodilatory capacity, and coronary vasomotion. Circulation 1997;95:600–606.
28. Chan SY, Kobashigawa J, Stevenson LW, Brownfield E, Brunken RC, Schelbert HR. Myocardial blood flow at rest and during pharmacological vasodilation in cardiac transplants during and after successful treatment of rejection. Circulation 1994;90:204–212.
29. Uren NG, Melin JA, De Bruyne B, Wijns W, Baudhuin T, Camici PG. Relation between myocardial blood flow and the severity of coronary-artery stenosis. N Engl J Med 1994;330:1782–1788.
30. Muehling OM, Wilke NM, Panse P, Jerosch Herold M, Wilson BV, Wilson RF, et al. Reduced myocardial perfusion reserve and transmural perfusion gradient in heart transplant arteriopathy assessed by Magnetic Resonance Imaging. J Am Coll Cardiol 2003;42:104–60.
31. Schwitter J, Nanz D, Kneifel S, Bertschinger K, Buchi M, Knusel PR, et al. Assessment of myocardial perfusion in coronary artery disease by Magnetic Resonance: A comparison with positron emission tomography and coronary angiography. Circulation 2001;103:223–35.
32. Kawada N, Sakuma H, Yamakado T, Takeda K, Isaka N, Nakano T, et al. Hypertrophic cardiomyopathy: MR measurement of coronary blood flow and vasodilator flow reserve in patients and healthy subjects. Radiology 1999;211:129–135.
33. Tang C, Blatter DD, Parker DL. Accuracy of phase-contrast flow measurements in the presence of partial-volume effects. J Magn Reson Imaging 1993;3:377–85.
34. Hoogeveen RM, Bakker CJ, Viergever MA. MR phase-contrast flow measurement with limited spatial resolution in small vessels: value of model-based image analysis. Magn Reson Med 1999;41:520–8.