Circulation: Heart Failure

EMERGING INVESTIGATORS

Reduced Myocardial Flow Reserve by Positron Emission Tomography Predicts Cardiovascular Events After Cardiac Transplantation

See Editorial by DePasquale

BACKGROUND: We evaluated the diagnostic and prognostic value of quantification of myocardial flow reserve (MFR) with positron emission tomography (PET) in orthotopic heart transplant patients.

METHODS AND RESULTS: We retrospectively identified orthotopic heart transplant patients who underwent rubidium-82 cardiac PET imaging. The primary outcome was the composite of cardiovascular death, acute coronary syndrome, coronary revascularization, and heart failure hospitalization. Cox regression was used to evaluate the association of MFR with the primary outcome. The relationship of MFR and cardiac allograft vasculopathy severity in patients with angiography within 1 year of PET imaging was assessed using Spearman rank correlation and logistic regression. A total of 117 patients (median age, 60 years; 71% men) were identified. Twenty-one of 62 patients (34%) who underwent angiography before PET had cardiac allograft vasculopathy. The median time from orthotopic heart transplant to PET imaging was 6.4 years (median global MFR, 2.31). After a median of 1.4 years, 22 patients (19%) experienced the primary outcome. On an unadjusted basis, global MFR (hazard ratio, 0.22 per unit increase; 95% confidence interval, 0.09–0.50; $P<0.001$) and stress myocardial blood flow (hazard ratio, 0.48 per unit increase; 95% confidence interval, 0.29–0.79; $P=0.004$) were associated with the primary outcome. Decreased MFR independently predicted the primary outcome after adjustment for other variables. In 42 patients who underwent angiography within 12 months of PET, MFR and stress myocardial blood flow were associated with moderate–severe cardiac allograft vasculopathy (International Society of Heart and Lung Transplantation grade 2–3).

CONCLUSIONS: MFR assessed by cardiac rubidium-82 PET imaging is a predictor of cardiovascular events after orthotopic heart transplant and is associated with cardiac allograft vasculopathy severity.

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WHAT IS NEW?

- In this retrospective study of heart transplant patients, noninvasive assessments of coronary flow and vasomotor function obtained with positron emission tomographic imaging were associated with the primary composite outcome of acute coronary syndrome, coronary revascularization, heart failure hospitalization, and cardiovascular death.
- These measures were also associated with the severity of cardiac allograft vasculopathy as assessed with coronary angiography.

WHAT ARE THE CLINICAL IMPLICATIONS?

- Coronary angiography is recommended for cardiac allograft vasculopathy screening because conventional stress imaging has decreased sensitivity, especially for earlier stages of allograft vasculopathy.
- Coronary angiography has limitations for the diagnosis of allograft vasculopathy and exposes patients to the risk of vascular complications and renal injury.
- Positron emission tomographic imaging may be able to identify early stages of allograft vasculopathy through its assessment of epicardial and microvascular blood flow and vasomotor function.
- Prospective studies should investigate whether positron emission tomographic imaging can serve as an adjunct to coronary angiography as a preferred method for cardiac allograft vasculopathy screening and treatment monitoring.

Cardiac allograft vasculopathy (CAV) is a leading cause of morbidity and mortality after cardiac transplantation.[1] CAV is a process of circumferential intimal thickening because of smooth muscle proliferation, inflammation, lipid deposition, and perivascular fibrosis. Unlike the focal lesions of coronary artery disease, it is a diffuse process affecting both the epicardial vessels and the microvasculature.[1,2] Both immune-mediated mechanisms and traditional cardiovascular risk factors have been implicated in the disease process.[1,2] Unfortunately, CAV is common after transplantation with registry data showing 30% of patients developing CAV within 5 years of transplantation.[3] Progressive CAV can lead to acute coronary syndrome, heart failure, arrhythmias, and sudden cardiac death.

Because of allograft denervation, CAV may remain asymptomatic until the onset of severe complications; therefore, routine surveillance is generally considered mandatory.[1] International Society of Heart and Lung Transplantation (ISHLT) guidelines currently recommend annual or biannual coronary angiography for at least the first several years after transplantation.[4] Unfortunately, even when angiography is performed regularly, it may not fully characterize CAV severity or the impact of CAV on allograft function. Because of the diffuse nature of intimal thickening, it can be missed on standard angiography, especially in the presence of vascular remodeling, which may counterbalance the impact of CAV on the epicardial coronary lumen.[1,2,5–9] The addition of intravascular ultrasound (IVUS) to coronary angiography has been shown to increase sensitivity for the detection of CAV.[9] However, both are invasive procedures that expose transplant patients to intravenous contrast and associated complications, including exacerbation of widely prevalent renal dysfunction.

For these reasons, noninvasive imaging that can reliably detect and quantify CAV, especially in its early stages, is needed. Although several noninvasive modalities have utility for identification of obstructive coronary disease, data are lacking to support their ability to detect early and nonobstructive CAV. Earlier CAV detection would allow for changes in medical therapy and immunosuppression that could possibly prevent progression of CAV, graft failure, and other cardiovascular outcomes.[2]

Myocardial perfusion imaging with rubidium-82 cardiac positron emission tomography (PET) has the ability to noninvasively assess both epicardial and microvascular coronary flow. Myocardial flow reserve (MFR)—the ratio of stress to rest myocardial blood flow (MBF)—is a well-validated evaluation of abnormal coronary vasodilatory capacity that is now routinely measured during PET imaging.[10] Among patients without orthotopic heart transplant (OHT), impaired MFR has been associated with cardiovascular outcomes, such as cardiac death, nonfatal myocardial infarction, revascularization, and heart failure hospitalization.[10] Although PET MFR has been shown to correlate with IVUS assessments of plaque burden,[11] only 1 study has evaluated the relationship between MFR assessed with PET imaging and cardiovascular outcomes among cardiac transplant patients.[5]

We sought to extend these findings to an independent population of heart transplant patients. We hypothesized that decreased MFR predicts cardiovascular events after heart transplantation. We also hypothesized that patients with CAV would have lower MFR values than those without CAV.

METHODS

Study Design and Patient Selection

The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure because of patient privacy regulations. We retrospectively identified patients with prior OHT who underwent rest/stress rubidium-82 cardiac PET imaging at any point after OHT. For patients who underwent multiple rest/stress rubidium-82 cardiac PET studies, the first scan was selected for analysis. For patients with serial scans, change in MFR between studies was recorded. Patient data, including demographics, comorbidities, medications, prior coronary angiography, and rejection history, were

gathered through chart review. The study was approved by the University of Michigan Institutional Review Board. Informed consent was not required from participants for this retrospective study.

PET Imaging Protocol

Patients were studied with a whole-body PET computed tomography scanner (Siemens mCT; Knoxville, TN) after an overnight fast. Patients refrained from caffeine- and methylxanthine-containing substances and drugs for 24 hours before their scans. MBF was measured during rest and peak stress with rubidium-82 as a perfusion tracer, as described previously.[12,13] Briefly, after transmission imaging and beginning with the intravenous bolus administration of rubidium-82, list mode images were acquired for 7 minutes. Then, a standard intravenous infusion of regadenoson was given. A second dose of rubidium-82 was injected 30 to 45 seconds after regadenoson administration, and images were recorded in the same manner. Heart rate, blood pressure, and 12-lead ECG were recorded at baseline and every minute during or after pharmacological stress.

Image Interpretation

Semiquantitative 17-segment visual interpretation of the gated myocardial perfusion images was performed by experienced observers using a standard 5-point scoring system.[14] Summed rest and stress scores were calculated as the sum of individual segmental scores on the respective images, and their difference was recorded as a summed difference score.

Absolute MBF (mL/g per min) was computed from the dynamic rest and stress imaging series with commercially available software (Corridor4DM; Ann Arbor, MI) and previously validated methods.[12,13,15] Factor analysis was used to generate blood pool (arterial input function) and tissue time–activity curves to a 2-compartment tracer kinetic model, as described previously.[15] Per-patient global MFR was calculated as the ratio of absolute MBF at stress over rest for the entire left ventricle. For survival analyses, an abnormal MFR was defined as a ratio <2.0 as this has been used to define coronary microvascular dysfunction in prior studies. Quantification of MBF was performed by 2 operators.

Primary Outcome Measure

The primary outcome was the composite of cardiovascular death, acute coronary syndrome, coronary revascularization, and heart failure hospitalization. The events were identified by reviewing each patient's electronic medical record. One patient in this study underwent retransplantation after PET imaging. Because this patient also experienced a heart failure hospitalization, we did not include retransplantation in the primary outcome.

Evaluation of MFR in Patients With CAV

For our comparison of MFR values in patients with and without CAV, we selected only patients who had undergone coronary angiography within 1 year of PET imaging. We excluded patients with intervening revascularization, myocardial infarction, or acute coronary syndrome between angiography and PET imaging. Catheterization and echocardiography reports were reviewed, and CAV presence and severity was characterized using ISHLT standardized nomenclature.[16] For the purpose of our analysis, ISHLT grade 2 to 3 was considered moderate–severe

Table 1. Baseline Characteristics

Baseline Characteristics	Total (n=117), n (%)
Demographics	
Age, y	60 (52–66)
Men	83 (71%)
Time from transplant to PET imaging, y	6.4 (3.5–10.0)
Follow-up, y	1.4 (0.9–2.4)
Transplant indication	
Ischemic cardiomyopathy	77 (66%)
Nonischemic cardiomyopathy	40 (34%)
Immunosuppression	
Tacrolimus	102 (87%)
Sirolimus or everolimus	24 (21%)
Cyclosporine	12 (10%)
Mycophenolate mofetil	63 (54%)
Azathioprine	8 (7%)
Prednisone	77 (66%)
Other medications	
Aspirin	103 (88%)
Statin	102 (87%)
Vitamin C	88 (75%)
Vitamin E	82 (70%)
Comorbidities	
Diabetes mellitus	47 (40%)
Hypertension	101 (86%)
Chronic kidney disease (GFR <60 mL/min per 1.73 m^2)	75 (64%)
Body mass index, kg/m^2	30.0 (26.1–34.6)
Previously documented CAV, n	21 (18%)
Previous revascularization	4 (3%)
Prior ISHLT grade 2R or 3R cellular rejection or antibody-mediated rejection	42 (36%)
PET imaging data	
Summed stress score	1 (0–2)
Summed rest score	1 (0–2)
Summed difference score	0 (0–1)
Rest ejection fraction, %	61 (56–65)
LV volume ratio at stress/rest	1.02 (0.96–1.06)
Rest MBF, mL/g per min	1.59 (1.35–1.93)
Stress MBF, mL/g per min	3.60 (3.11–4.16)
MFR	2.31 (1.84–2.72)
MFR <2.0	33 (28%)

Continuous variables are reported as median (25% and 75% percentiles). CAV indicates cardiac allograft vasculopathy; GFR, glomerular filtration rate; LV, left ventricle; MBF, myocardial blood flow; MFR, myocardial flow reserve; and PET, positron emission tomography.

CAV because this represents the presence of at least 1 obstructive lesion in the proximal–mid segment of the left anterior descending, left circumflex, or right coronary arteries.

Statistical Analysis

Data were evaluated for normality and summarized with means and SDs or median and interquartile range (IQR), as appropriate. Kaplan–Meier analyses and unadjusted and adjusted Cox regression were used to evaluate the relationship between clinical variables and PET measurements with the primary outcome. Because of the small number of patients experiencing the primary outcome, adjusted analyses were limited to a single additional covariate per regression model. Spearman rank correlation, logistic regression, and receiver operating characteristic curves were used to assess the relationships between MFR, stress MBF, summed stress score (SSS), and angiographic CAV. The Kruskal–Wallis rank-sum test was used to compare differences in characteristics between patients with and without CAV. All statistical analyses were performed in R, version 3.4 (R Foundation for Statistical Computing).

RESULTS

A total of 117 patients (median age, 60 years; 71% men) underwent rest/stress rubidium-82 cardiac PET imaging between May 2011 and February 2016. Baseline characteristics are reported in Table 1. Comorbidities were common (40% diabetes mellitus, 86% hypertension, 64% chronic kidney disease [glomerular filtration rate < 60 mL/min per 1.73 m^2], median body mass index equal to 30.0 kg/m^2). Immunosuppression regimens varied but most commonly utilized tacrolimus. Twenty-one of 62 patients (34%) who received angiography before PET had CAV by ISHLT criteria. The median time from OHT to PET imaging was 6.4 years. The median global MFR was 2.31 (IQR, 1.84–2.72); 33 patients (28%) had an MFR <2.0. Forty-eight patients underwent repeat PET studies during the study period. The median change in MFR observed was as follows: 0.01 (IQR, –0.21 to 0.22) in 7 patients with a repeat study within 12 months, 0.10 (IQR, –0.12 to 0.36) in 25 patients with a repeat study 12 to 24 months later, and –0.10 (IQR, –0.28 to 0.02) in 16 patients with a repeat study >24 months later.

Primary Outcome Analyses

After a median of 1.4 years (IQR, 0.9–2.4 years), 22 patients experienced the primary outcome. There were

Table 2. Unadjusted Predictors of Cardiovascular Events

Variables	Outcome (n=22)	No Outcome (n=95)	Hazard Ratio (95% CI)	χ^2	*P* Value
Age, y	57 (44–65)	61 (55–66)	0.98 (0.95–1.02)	0.69	0.405
Men	16 (73%)	68 (72%)	0.88 (0.34–2.25)	0.07	0.788
Time since OHT, y	9.9 (6.4–13.0)	6.0 (3.2–9.2)	1.08 (1.00–1.16)	4.16	0.041
Hypertension	19 (86%)	82 (86%)	0.86 (0.25–2.95)	0.06	0.814
Diabetes mellitus	8 (36%)	39 (41%)	0.91 (0.38–2.17)	0.05	0.825
GFR <60 mL/min per 1.73 m^2	17 (77%)	58 (61%)	1.90 (0.70–5.16)	1.59	0.207
BMI, kg/m^2	28 (27–36)	30 (26–34)	1.03 (0.95–1.10)	0.47	0.492
Previous revascularization	2 (9%)	2 (2%)	4.22 (0.97–18.32)	3.69	0.054
Previous CAV*	8 (8/14; 57%)	13 (13/48; 27%)	4.70 (0.61–36.08)	2.21	0.137
Prior ISHLT grade 2R or 3R cellular rejection or antibody-mediated rejection	10 (45%)	32 (34%)	1.60 (0.69–3.72)	1.20	0.272
SSS	3 (1–6)	0 (0–2)	1.23 (1.13–1.34)	22.6	<0.001
SRS	1.5 (0–5)	0 (0–2)	1.16 (1.06–1.27)	10.46	0.001
SDS	1 (0–2)	0 (0–0)	1.25 (1.09–1.43)	10.35	0.001
Rest EF, %	56 (42–62)	62 (58–66)	0.92 (0.88–0.96)	17.88	<0.001
EF reserve with stress, %	4 (1–8)	5 (2–8)	0.97 (0.88–1.07)	0.32	0.570
LV volume ratio (stress/rest)	1.04 (1.01–1.06)	1.02 (0.98–1.06)	9.62 (0.02–5856)	0.48	0.489
Rest MBF, mL/g per min	1.62 (1.46–1.94)	1.57 (1.32–1.93)	1.79 (0.68–4.68)	1.41	0.234
Stress MBF, mL/g per min	2.90 (2.34–4.03)	3.67 (3.22–4.24)	0.48 (0.29–0.79)	8.15	0.004
MFR	1.86 (1.38–2.37)	2.38 (2.05–2.79)	0.22 (0.09–0.50)	12.62	<0.001
MFR <2.0	12 (54%)	21 (22%)	0.21 (0.09–0.50)	12.59	<0.001

AMR indicates antibody-mediated rejection; BMI, body mass index; CAV, cardiac allograft vasculopathy; CI, confidence interval; EF, ejection fraction; GFR, glomerular filtration rate; LV, left ventricle; MBF, myocardial blood flow; MFR, myocardial flow reserve; OHT, orthotopic heart transplantation; PET, positron emission tomography; SDS, summed difference score; SRS, summed rest score; and SSS, summed stress score.

*Only 63 patients had angiography before PET imaging (14 patients experienced primary outcome). Continuous variables are reported as median (25% and 75% percentiles) unless otherwise stated. Categorical variables are reported as n (%).

Table 3. Adjusted Analyses for Positron Emission Tomographic Measures of Myocardial Flow and the Primary Outcome

Covariates	Hazard Ratio (95% CI)	χ^2	*P* Value
MFR			
MFR+rest EF	0.31 (0.13–0.76)	23.58	0.010
MFR+SSS	0.36 (0.15–0.86)	27.35	0.021
MFR+SDS	0.27 (0.11–0.64)	18.51	0.003
MFR+SRS	0.26 (0.11–0.60)	20.75	0.002
MFR+time since OHT	0.23 (0.10–0.53)	16.76	<0.001
MFR+prior diagnosis of CAV*	0.20 (0.07–0.58)	9.97	0.003
Stress MBF			
Stress MBF+rest EF	0.67 (0.38–1.18)	19.59	0.165
Stress MBF+SSS	0.68 (0.40–1.16)	24.37	0.155
Stress MBF+SDS	0.54 (0.32–0.92)	14.55	0.023
Stress MBF+SRS	0.56 (0.34–0.91)	16.77	0.020
Stress MBF+time since OHT	0.52 (0.30–0.88)	9.50	0.015
Stress MBF+prior diagnosis of CAV*	0.51 (0.27–0.96)	5.84	0.037

CAV indicates cardiac allograft vasculopathy; CI, confidence interval; EF, ejection fraction; MBF, myocardial blood flow; MFR, myocardial flow reserve; OHT, orthotopic heart transplantation; SDS, summed difference score; SRS, summed rest score; and SSS, summed stress score.

*Analyses included 62 patients because 55 patients did not have angiography available. Of the 62 patients, 21 patients had a prior diagnosis of CAV. The primary outcome was observed in 17 of 62 patients.

2 cardiovascular deaths. Five patients experienced an acute coronary syndrome, 8 patients underwent revascularization, and 15 patients were hospitalized for heart failure.

In unadjusted analyses, when evaluated as continuous variables, MFR (hazard ratio, 0.22 per unit increase in MFR; 95% confidence interval [CI], 0.09–0.50; *P*<0.001) and stress MBF (hazard ratio, 0.48 per unit increase in stress MBF; 95% CI, 0.29–0.79; *P*=0.004) were associated with the primary outcome. Other PET measures, including SSS, summed rest score, summed difference score, and rest ejection fraction, were also significantly associated with the primary outcome (Table 2). Time since OHT was significantly associated with the primary outcome; however, no other clinical variables, including patient comorbidities and history of rejection, predicted the primary outcome.

On several adjusted analyses, each with the addition of a single covariate, MFR remained a significant predictor of the primary outcome (Table 3). In contrast, stress MBF remained a significant predictor of the primary outcome on some but not all of the adjusted analyses (Table 3).

Kaplan–Meier analysis demonstrated that patients with an MFR <2.0 were at increased risk for experiencing the primary outcome (cox proportional hazard ratio, 0.21; 95% CI, 0.09–0.50; *P*<0.0001; Figure 1). In contrast, a stress MBF below the mean for this sample (<3.7 mL/g per min) was not significantly associated with the primary outcome (cox proportional hazard ratio, 0.55; 95% CI, 0.22–1.34; *P*=0.18; Figure 1).

MFR, Stress MBF, and Cardiac Allograft Vasculopathy

A total of 42 patients (median age, 59 years; IQR, 55–65 years; 64% men; Table 4) underwent cardiac

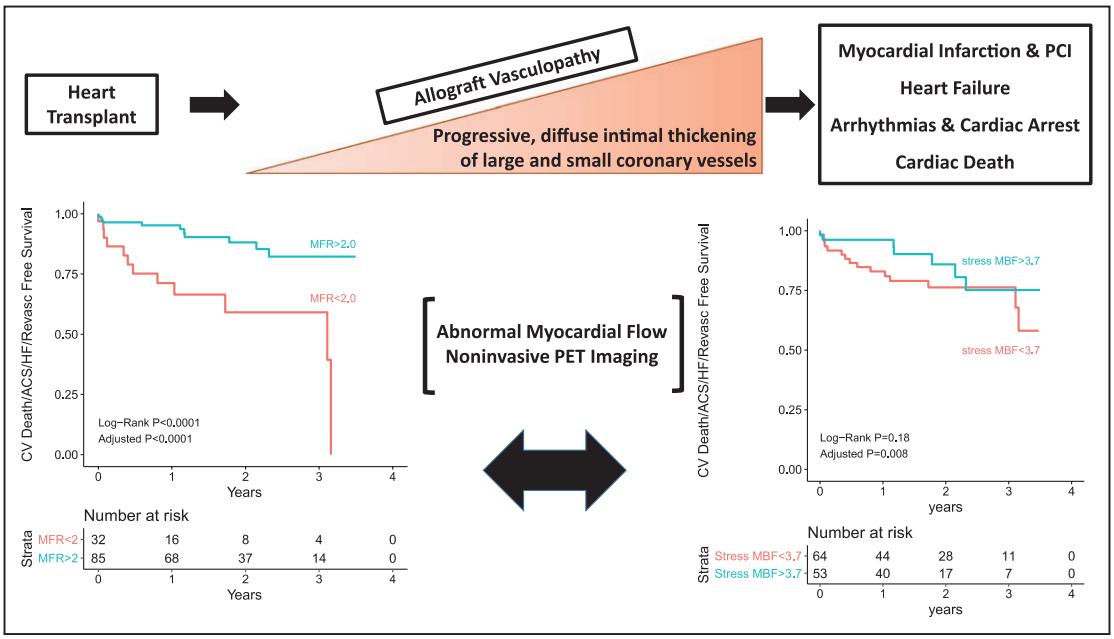

Figure 1. Kaplan–Meier analysis for the primary outcome using myocardial flow reserve (MFR) and stress myocardial blood flow (MBF) as dichotomous variables.

ACS indicates acute coronary syndrome; CV, cardiovascular; PET, positron emission tomography; and PCI, percutaneous coronary intervention.

Table 4. Baseline Characteristics for Patients With and Without CAV by ISHLT Criteria

Variables	CAV (n=22)	No CAV (n=20)	*P* Value
Age, y	58.5 (53.5–64.5)	61.0 (56.0–66.3)	0.503
Men	12 (54%)	15 (75%)	0.289
Time from OHT to PET, y	8.69 (4.34–14.4)	3.84 (2.22–5.44)	0.001
Immunosuppression			
Tacrolimus	17 (77%)	20 (100%)	0.073
Sirolimus or everolimus	11 (50%)	2 (10%)	0.014
Cyclosporine	3 (14%)	0	0.265
Mycophenolate mofetil	8 (36%)	12 (60%)	0.222
Azathioprine	2 (9%)	0	0.512
Prednisone	14 (64%)	12 (60%)	0.999
Comorbidities			
Diabetes mellitus	9 (41%)	11 (55%)	0.546
Hypertension	18 (82%)	16 (80%)	0.999
CKD (GFR <60 mL/min)	18 (82%)	10 (50%)	0.512
Body mass index, kg/m^2	31.2 (26.5–35.4)	28.1 (24.5–32.0)	0.064
Hx prior ISHLT grade 2R or 3R cellular rejection or antibody-mediated rejection	8 (36%)	7 (35%)	0.999
PET imaging data			
SSS	4.5 (2.0–7.5)	1.0 (0–3.25)	0.220
Summed rest score	2.0 (1.0–3.0)	1.0 (0–2.0)	0.272
Summed difference score	1.5 (0–4.8)	0 (0–0.2)	0.034
Rest ejection fraction, %	58 (55–64)	63 (59–68)	0.398
Rest MBF, mL/g per min	1.55 (1.37–1.93)	1.66 (1.31–2.08)	0.537
Stress MBF, mL/g per min	2.96 (2.42–3.48)	3.90 (3.31–4.90)	<0.001
MFR	1.75 (1.46–2.52)	2.46 (2.14–2.84)	0.017
MFR <2.0	12 (54%)	3 (15%)	0.019

Continuous variables are reported as median (25% and 75% percentiles). AMR indicates antibody-mediated rejection; CAV, cardiac allograft vasculopathy; CKD, chronic kidney disease; GFR, glomerular filtration rate; ISHLT, International Society of Heart and Lung Transplantation; MBF, myocardial blood flow; MFR, myocardial flow reserve; OHT, orthotopic heart transplantation; PET, positron emission tomography; and SSS, summed stress score.

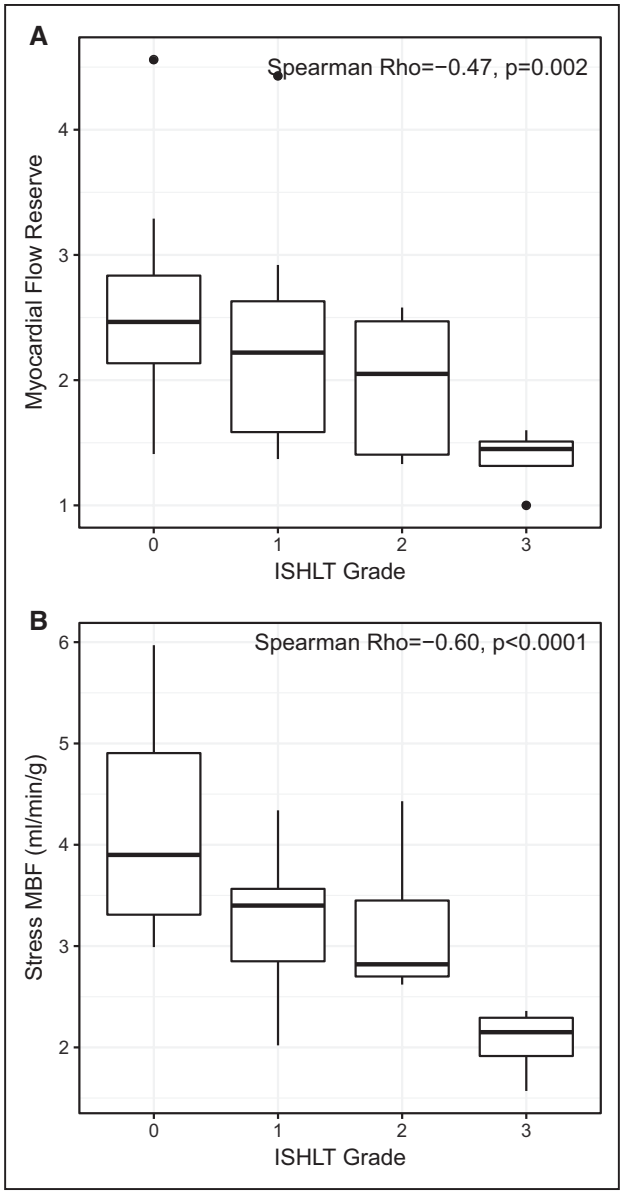

Figure 2. Correlations between (A) myocardial flow reserve and (B) stress myocardial blood flow (MBF) with severity of cardiac allograft vasculopathy.

rubidium-82 PET imaging within 12 months of coronary angiography (median, 110 days between PET and angiogram; IQR, 26–270 days). The median time from OHT to first PET imaging was 5.6 years (IQR, 3.0–9.7 years). Comorbidities were common (48% diabetes mellitus, 81% hypertension, 67% chronic kidney disease [glomerular filtration rate, <60 mL/min], and 50% obesity). The median global MFR was 2.18 (IQR, 1.62–2.60). Twenty-two patients (52%) had CAV by ISHLT criteria with 11 patients having moderate–severe CAV (ISHLT grade 2–3).

MFR was significantly correlated with ISHLT CAV grade (Spearman ρ, −0.47; *P*=0.002; Figure 2A). MFR was associated with the presence of moderate–severe CAV on unadjusted analysis (odds ratio, 0.15 per unit increase in MFR; 95% CI, 0.03–0.58; *P*=0.01; Table 5) and when adjusted for SSS (odds ratio, 0.19 per unit increase in MFR; 95% CI, 0.03–0.80; *P*=0.04; Table 5). Stress MBF was also significantly correlated with ISHLT CAV grade (Spearman ρ, −0.60; *P*<0.0001; Figure 2B). Stress MBF was associated with the presence of moderate–severe CAV on unadjusted analysis (odds ratio, 0.21 per unit increase in stress MBF; 95% CI, 0.05–0.58; *P*=0.009; Table 5) and when adjusted for SSS (odds ratio, 0.24 per unit increase in stress MBF; 95% CI, 0.06–0.70; *P*=0.03; Table 5). We did not identify a statistically significant association between SSS (*P*=0.07; Table 5), summed rest score, left ventricular ejection fraction or rest MBF, and moderate–severe CAV.

Both MFR (area under the curve [AUC], 0.76; *P*=0.36 versus SSS; Figure 3A) and stress MBF (AUC,

Table 5. Logistic Regression of Positron Emission Tomographic Variables and ISHLT Grade 2 to 3 Cardiac Allograft Vasculopathy (n=11)

	Odds Ratio (95% CI)	*P* Value
SSS		
Unadjusted	1.18 (0.99–1.44)	0.070
MFR		
Unadjusted	0.15 (0.03–0.58)	0.010
Adjusted for SSS	0.19 (0.03–0.80)	0.040
Stress MBF		
Unadjusted	0.21 (0.05–0.58)	0.009
Adjusted for SSS	0.24 (0.06–0.70)	0.030

CI indicates confidence interval; ISHLT, International Society of Heart and Lung Transplantation; MBF, myocardial blood flow; MFR, myocardial flow reserve; and SSS, summed stress score.

0.79; *P*=0.22 versus SSS; Figure 3B) had nonsignificantly higher AUC values for ISHLT moderate–severe CAV than SSS (AUC, 0.66). The addition of MFR to SSS (AUC, 0.76; *P*=0.30 versus SSS; Figure 3A) and stress MBF to SSS (AUC, 0.80; *P*=0.15 versus SSS; Figure 3B) showed nonsignificantly higher AUC values for ISHLT moderate–severe CAV.

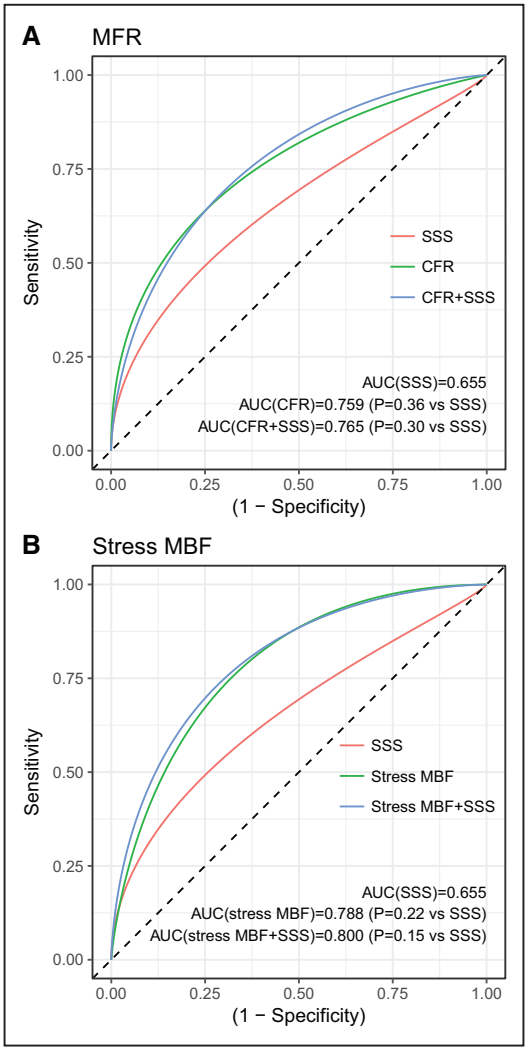

Figure 3. Receiver operator curves for (A) myocardial flow reserve (MFR) and (B) stress myocardial blood flow (MBF) for the diagnosis of cardiac allograft vasculopathy.
SSS indicates summed stress score.

DISCUSSION

In this study of cardiac transplant patients, decreased global MFR was the most significant predictor of the composite primary outcome of cardiovascular death, acute coronary syndrome, coronary revascularization, and heart failure hospitalization. In addition, MFR and stress MBF were both associated with the severity of CAV. These findings demonstrate the added value of quantitative measures of MBF and vasomotor function provided by PET imaging.

Stress echocardiography and other forms of perfusion imaging rely on heterogeneity in perfusion or contractility to identify disease.[2] These changes occur with obstructive epicardial disease, which would be a late manifestation of CAV. This results in these modalities having a decreased sensitivity for identifying CAV, particularly in its earliest stages. This may explain why ejection fraction reserve—a measurement used to assess for CAV risk on stress echocardiography—was not a significant predictor of the primary outcome in this study. The limitations of stress echocardiography and other forms of perfusion imaging explain why guidelines continue to recommend angiography as the preferred assessment for CAV.[4] Unfortunately, angiography is an invasive procedure, which exposes patients to risk of vascular complications and worsening renal function. Standard angiography can also miss a diagnosis of CAV because the diffuse nature of intimal thickening and vascular remodeling may lead to no appreciable disease on longitudinal assessment of the epicardial coronary lumen.[1,2,5–9] As a result, IVUS is frequently added, with additional limitations and risk. Most notably, although IVUS provides excellent assessment of the coronary arterial wall structure, vasomotor function and the coronary microvasculature cannot be evaluated. Importantly, multiple coronary arteries must be imaged to maximize the sensitivity of IVUS for CAV, further increasing the risk of complications.[17]

Rather than relying solely on an anatomic characterization of CAV, MFR provides an integrated assessment of both macrovascular and microvascular function. Factors other than luminal narrowing, such as inflammation from rejection, infection, or other risk factors, can contribute to impaired vasomotor function and decreased MFR.[18] Abnormal coronary vasodilation, assessed by Doppler echocardiography MFR, has been associated with increased prevalence of CAV, reduced left ventricle longitudinal myocardial deformation, and decreased exercise capacity after cardiac transplantation.[19] Similarly,

angiographic markers of endothelial dysfunction precede the development of CAV and other cardiovascular events in cardiac transplant patients.[20–22] These data argue that CAV is more than simply a disease of luminal narrowing; it has effects on coronary vasomotor function that may signify CAV progression and impact allograft function.

Global MFR, as assessed with PET imaging, has the potential to detect homogenous reductions in blood flow seen in CAV—a diffuse process affecting both the epicardial coronary vessels and the microvasculature. MFR, as assessed with cardiac magnetic resonance imaging, has been shown to have a high sensitivity for CAV and reliably exclude severe CAV at a value >2.3.[23,24] Similar to cardiac magnetic resonance measurements of MFR, PET MFR may be superior to other forms of stress imaging by identifying earlier stages of CAV. Indeed, in studies of patients within the first few years of transplantation, MFR by ^{13}N-ammonia PET imaging has been found to correlate with plaque volume index and maximal intimal thickness as assessed by IVUS.[11,25] In another study of 19 patients 18±6 months after transplantation, MFR by ^{13}N-ammonia PET imaging was associated with IVUS measurements of total vessel area and lumen diameter.[26] Similar to IVUS measurements of CAV,[27–31] MFR assessed with PET previously has been shown to predict adverse outcomes after cardiac transplantation.[5]

The assessment of MFR by PET imaging has clinical implications for the diagnosis and management of CAV. Future studies should continue to evaluate the relationship between abnormal PET MFR and the characterization of CAV by coronary angiography. In patients with contraindications to or a preference to avoid coronary angiography at regular intervals, measurement of MFR may serve as a screening tool to determine which patients should proceed with coronary angiography. Through its assessment of blood flow and vasomotor function of the entire coronary arterial bed, MFR has the potential to identify CAV in its early stages, even before it can be detected by angiography or IVUS. Treatment of CAV appears to be more effective when initiated early in its course[32–35]; this suggests that earlier detection by PET imaging could impact cardiovascular outcomes although this requires further study.[21] The mammalian target of rapamycin inhibitors sirolimus and everolimus have been shown to reduce CAV incidence and progression,[36–41] as well as improve coronary artery function.[42] However, the adverse effects associated with these agents lead many providers to avoid routine use of these therapies in the absence of CAV. More data are needed to determine whether PET imaging could identify patients who would benefit from an earlier transition to an mammalian target of rapamycin inhibitor and whether serial imaging could also noninvasively monitor treatment response and disease progression.

There are several limitations to this study. First, although one of the largest studies of PET imaging in cardiac transplant patients, this was a single-center study with a limited number of adverse outcomes. Our findings do support those from a previous study that demonstrated prognostic value of PET imaging after cardiac transplantation.[5] In addition, specialists at our center vary in their preferred means for CAV screening. Patients varied in regard to the timing and number of PET studies and coronary angiograms performed. Most patients underwent PET imaging several years after transplant, limiting our evaluation of imaging early after transplant when CAV presumably is less severe. Thus, recommendations on the appropriate clinical use of PET imaging cannot be made based on these data alone. For example, because of selection bias, we cannot conclude that abnormal MFR predicts the presence of CAV. Future prospective studies are needed to determine whether protocols utilizing PET imaging could replace routine coronary angiography or have implications for the therapy of CAV. Last, PET imaging may not be widely available although it is the authors' impression that most transplant centers have access to this technology.

CONCLUSIONS

MFR noninvasively assessed by cardiac rubidium-82 PET imaging is a powerful predictor of cardiovascular events after OHT. We also observed that MFR and stress MBF are decreased in patients with CAV. Prospective studies are needed to determine whether PET imaging can serve as an adjunct to coronary angiography as a preferred method for CAV screening and treatment monitoring.

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Heart Failure

Reduced Myocardial Flow Reserve by Positron Emission Tomography Predicts Cardiovascular Events After Cardiac Transplantation

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