Prognostic Value of Rubidium-82 Positron Emission Tomography in Patients After Heart Transplant

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Background—Cardiac allograft vasculopathy is a key prognostic determinant after heart transplant. Detection and risk stratification of patients with cardiac allograft vasculopathy are problematic. Positron emission tomography using rubidium-82 allows quantification of absolute myocardial blood flow and may have utility for risk stratification in this population.

Methods and Results—Patients with a history of heart transplant undergoing dipyridamole rubidium-82 positron emission tomography were prospectively enrolled. Myocardial perfusion and left ventricular ejection fraction were recorded. Absolute flow quantification at rest and after dipyridamole stress as well as the ratio of mean global flow at stress and at rest, termed myocardial flow reserve, were calculated. Patients were followed for all-cause death, acute coronary syndrome, and heart failure hospitalization. A total of 140 patients (81% men; median age, 62 years; median follow-up, 18.2 months) were included. There were 14 events during follow-up (9 deaths, 1 acute coronary syndrome, and 4 heart failure admissions). In addition to baseline clinical variables (estimated glomerular filtration rate, previously documented cardiac allograft vasculopathy), relative perfusion defects, mean myocardial flow reserve, and mean stress myocardial blood flow were significant predictors of adverse outcome.

Conclusions—Abnormalities on rubidium-82 positron emission tomography were predictors of adverse events in heart transplant patients. Larger prospective studies are required to confirm these findings. **(*Circ Cardiovasc Imaging*. 2014;7:930-937.)**

Key Words: heart transplantation ■ positron emission tomography ■ prognosis

Heart transplantation (HT) has been performed with increasing success during the past 3 decades. Improvements in surgical techniques, postoperative care, and immune-suppressive regimens have diminished short-term mortality from acute rejection and infection.[1] However, there has been little impact on the incidence of long-term sequelae such as malignancy and chronic rejection because of cardiac allograft vasculopathy (CAV), which remain the most common causes of mortality after 12 months.[2]

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CAV results in diffuse concentric intimal thickening of the epicardial vessels affecting both the proximal and distal vessels as well as the microcirculation.[3] This progressive luminal narrowing and loss of vasodilatory capacity culminates in myocardial ischemia and contractile dysfunction. Immune-mediated injury plays a significant role in the development of epicardial vessel stenosis in addition to traditional risk factors.[4] Clinical symptoms such as angina are typically absent in cases of CAV because of allograft denervation, and therefore annual screening is used in most centers.

Recent guidelines recommend periodic invasive coronary angiography for at least the first 3 to 5 years after transplantation.[5] However, this is inconvenient and adds risk. Hence, many centers have elected to monitor patients with noninvasive testing, but this strategy may be suboptimal because of the lower sensitivity for the detection of early CAV.[6,7]

Rubidium-82 (Rb-82) positron emission tomography (PET) myocardial perfusion imaging is a noninvasive imaging modality that has the ability to quantify myocardial blood flow (MBF)[8] and has been shown to have prognostic value in patients being assessed for ischemia.[9–11] This technique may facilitate earlier detection of CAV and thus may have prognostic value in HT patients. The objective of this study was to evaluate the prognostic value of Rb-82 PET in patients with a history of HT.

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Methods

Between July 2009 and March 2013, consecutive HT patients were prospectively enrolled in either the cardiac PET or Rubidium-ARMI (Rubidium-82 Alternative Radiotracer for Myocardial Imaging) registries.[12] The study was approved by the institutional research ethics board and informed consent was obtained from all participating patients.

All HT patients completed a rest and stress Rb-82 PET scan ≥12 months after transplant. For patients who underwent >1 PET scan, only the results of the first scan were included for analysis.

PET Imaging Protocol

As previously described, patients refrained from the use of caffeine derivatives and antianginal medications before the imaging study.[12] Patients were positioned in a 3-dimensional (3D) PET system (Discovery 690 PET-VCT, GE Healthcare, Waukesha, WI), and a low-dose computed tomographic scan was acquired for attenuation correction. Then, 10 MBq/kg of Rb-82 was administered intravenously using a custom elution system, and an 8-minute Rb-82 PET scan was acquired with a parallel list-mode acquisition.

After rest PET, dipyridamole stress was performed (0.14 mg/kg per minute for 5 minutes).[12] Rb-82 was infused 3 minutes after vasodilator infusion and stress images were acquired.

Review of the PET-computed tomographic image alignment for attenuation correction was performed for each study manually using the vendor ACQC software. Dynamic (9×10 s, 3×30 s, 1×60 s, 2×120 s), static (2–8 minutes), and gated (1.5–8 minutes) images were reconstructed using the vendor ordered subset expectation maximization (OSEM) iterative reconstruction software (VuePoint HD) with 8, 12, and 16-mm Hann 3D postfiltering, respectively.

Image Interpretation

Expert readers performed semiquantitative perfusion analysis using a 17-segment (5 point) model and the summed stress score (SSS) and summed rest score (SRS) were calculated. Left ventricular ejection fraction at rest and peak stress was estimated from gated images using Corridor 4DM-PET software (INVIA, Ann Arbor, MI) and recorded for each patient.

For absolute quantification of MBF, automated software (FlowQuant, Ottawa, ON) was used to reorient images, extract mean myocardial and left ventricular (LV) cavity time–activity curves and to calculate absolute MBF at rest and peak stress.[8] Myocardial flow reserve (MFR) was then calculated as the ratio of the stress-to-rest MBF (Figure 1).[8]

Outcome Measures

The primary outcome was a composite of all-cause death, acute coronary syndrome, and hospitalization because of heart failure. Patient follow-up was obtained from transplant clinic records, hospital records, and the Ontario Trillium Gift of Life Database.

Patient Demographics

Patients' medical history (medications, comorbidities, baseline renal function, etc) was recorded at an outpatient clinic visit within 3 weeks of the PET scan. Renal function was determined based on estimated glomerular filtration rate (eGFR, mL/min per 1.73 m^2) and calculated based on the Modification of Diet in Renal Disease equation.[13]

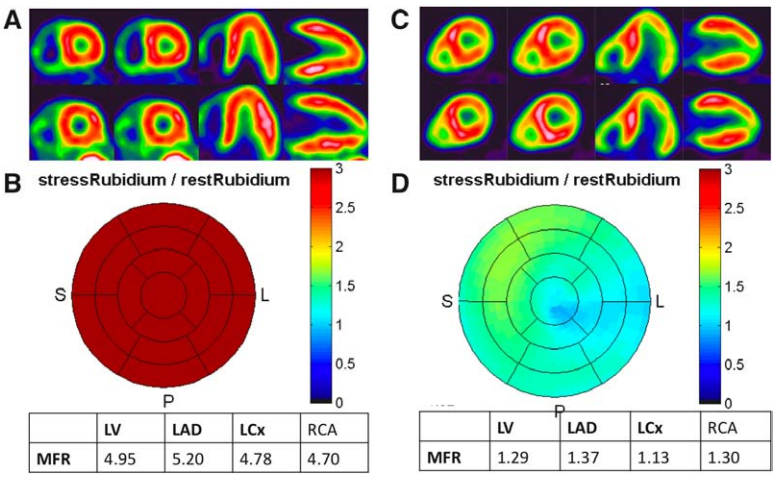
Statistical Analysis

Analysis was performed using SAS (version 9.3, SAS Institute Inc, Cary, NC), and statistical significance was defined as $P<0.05$. Medians with interquartile ranges were calculated for continuous variables, whereas categorical variables are expressed as frequencies with percentages. Continuous variables were compared using either a 2-tailed *t* test for normally distributed data or a Mann–Whitney test for non-normally distributed data. Categorical variables were compared using the χ^2 test.

Univariable analyses were performed to evaluate the prognostic value of PET variables to the adverse outcomes using the Cox proportional-hazards models. The validity of the proportional-hazards assumption was tested by adding a time-dependent interaction variable to the Cox proportional-hazards models for each of the predictors in the models, and the proportional-hazards assumption was met. To avoid overfitting the model, multivariable analysis was not performed because of a limited number of adverse outcomes. The discrimination ability of Cox proportional-hazards model to predict outcome was measured by the C-index of Harrell.[14] An unadjusted survival curve was generated using a dichotomized cutoff for MFR. Pearson correlation coefficient with 95% confidence interval (CI) was used to evaluate correlation among relevant variables.

Results

A total of 143 patients underwent rest–stress Rb-82 PET between July 2009 and March 2013. However, there were 3 patients who did not complete the stress portion of the test and therefore they were excluded. The baseline characteristics of the remaining 140 patients (mean age, 58±14 years; 81% men) are outlined in Table 1.



	LV	LAD	LCx	RCA
MFR	4.95	5.20	4.78	4.70

	LV	LAD	LCx	RCA
MFR	1.29	1.37	1.13	1.30

Figure 1. Case examples from 2 heart transplantation patients. **A**, Relative perfusion images from a 17-year-old man who was 3 years after HT for congenital heart disease and who remained well during follow-up of 12 months. Both stress (**top**) and rest (**bottom**) images demonstrate normal relative perfusion. **B**, A polar map of myocardial flow reserve (MFR) in the left ventricle (LV) that is homogenously normal with a mean MFR of 4.95. **C**, Relative perfusion images from a 30-year-old man, 12 years after HT for congenital heart disease. Again both stress and rest relative perfusion images are shown with only a mild reduction in tracer uptake in the lateral wall after stress (yellow area) that partially improves at rest. This is indicative of mild ischemia in the left circumflex territory. **D**, Polar map of MFR from the same patient shows a severe reduction throughout the LV with a mean value of 1.27 indicative of global vasculopathy. During the next 12 months this patient had 2 hospitalizations with heart failure with evidence of cardiac allograft vasculopathy on angiography without focal obstruction. L indicates lateral; LAD, left anterior descending artery; LCx, left circumflex artery; P, posterior; RCA, right coronary artery; and S, septum.

The median time from transplantation to PET scanning was 8.2 years (interquartile range, 3.3–14.5 years). The interval between transplantation and PET scanning was <5 years in 45 patients (32%), between 5 and 10 years in 36 patients (26%), and >10 years in 59 patients (42%). The median follow-up after PET was 18.2 months (interquartile range, 12–26 months).

Nine patients (6%) had a diagnosis of CAV at baseline (before PET) based on invasive angiography performed for clinical reasons.

Table 1. Baseline Characteristics of Heart Transplant Patients

Baseline Characteristics	Total (n=140), n (%)
Age, y	62 (52–69)
Men	113 (81%)
Time since transplant, y	8.2 (3.3–14.5)
<5	45 (32%)
5–10	36 (26%)
>10	59 (42%)
Follow-up, mo	18.2 (12.1–26)
Transplant indication	
Ischemic heart disease, %	63 (45%)
Dilated cardiomyopathy, %	49 (35%)
Other, %	28 (20%)
Immune-suppressant medications	
Cyclosporine, %	83 (59%)
Tacrolimus, %	56 (40%)
Mycophenolate mofetil	98 (70%)
Azathioprine, %	13 (9%)
Sirolimus, %	1 (0.7%)
Statins, %	129 (92%)
Diabetes mellitus, %	41 (29%)
Hypertension, %	80 (57%)
Estimated GFR (mL/min per 1.73 m^2)	59 (42–78.5)
Previously documented CAV, n	9 (6%)
Previous revascularization	5 (3.5%)
History of rejection>ISHLT grade 1R (n)	16 (11%)
ISHLT grade 2, n	7 (5%)
ISHLT grade 3, n	4 (3%)
Antibody mediated rejection, n	5 (4%)
SSS=0 (%)	112 (80%)
SSS for patients>0	3 (2–5)
SRS=0 (%)	126 (90%)
SRS for patients>0	2 (1–2.5)
TID	3 (2%)
Rest flow, mL/g per minute	0.89 (0.61–1.0)
Stress flow, mL/g per minute	1.99 (1.49–2.36)
MFR	2.25 (1.8–2.89)
MFR≤1.75	33 (24%)

Continuous variables are reported as medians with 25% and 75% percentiles. CAV indicates cardiac allograft vasculopathy; GFR, glomerular filtration rate; ISHLT, International Society of Heart and Lung Transplantation; MFR, myocardial flow reserve; SRS, summed rest score; SSS, summed stress score; and TID, transient ischemic dilation.

Patient Outcomes

In total, 14 patients had the primary composite outcome of death (9 patients), ACS (1 patient), or heart failure admission (4 patients; 10% event rate). Of these patients, 1 occurred <5 years since undergoing transplantation, with 4 being between 5 and 10 years, and >10 years in 9 patients. On univariable analysis, time since transplantation (continuous variable) was not a significant predictor of adverse outcome (hazard ratio [HR], 1.05; 95% CI, 0.97–1.13; *P*=0.19) and neither was a time interval >10 years since transplantation (categorical variable; HR, 2.31; 95% CI, 0.77–6.87; *P*=0.13).

On univariable analysis, patients who experienced an adverse outcome had a significantly higher SSS and SRS and a lower global MFR and eGFR (Table 2). Patients with an adverse outcome also had a higher prevalence of CAV (documented on previous invasive angiography) than those who did not experience adverse outcome. At baseline, 11 patients had severe renal disease (defined as eGFR <30 mL/kg per minute), of whom 6 had end-stage renal disease requiring hemodialysis. There were 4 of the 11 patients with severe renal disease who had adverse events (3 deaths).

Rb-82 PET Results

The majority of patients (93%) had normal relative perfusion images (SSS <4). Patients with adverse events had a higher SSS and SRS on univariable analysis (Table 2). There was no significant difference in rest or poststress LV ejection fraction on ECG-gated PET images.

Incorporating only the results of relative perfusion and LV function, the event rate among patients with a normal PET scan, based on cutoffs used in multiple previous studies and in the ARMI registry (12; SSS <4 and rest LV ejection fraction >45%,) (n=131), was 8.7%, whereas the event rate for those with an abnormal scan (n=9) was 33% (*P*=0.066; Table 3).

Rb-82 PET Absolute Flow Quantification Results

The mean resting MBF was 0.87±0.28 mL/g per minute and peak stress MBF was 2.00±0.66 mL/g per minute with a mean MFR of 2.39±0.83. There was a weak inverse relationship between mean MFR and the time interval since transplantation (*r*=–0.18; 95% CI, –0.33 to –0.017; *P*=0.03) but no relationship between either resting or stress MBF and time since transplantation. Comparison of patients <2 years since transplant (n=45) and those between 2 and 5 years (n=37) and >5 years since transplant (n=58) showed no significant differences in MFR or MBF at rest or after stress.

On univariable Cox modeling, the PET parameters significantly associated with adverse outcomes were SSS (HR, 1.19; 95% CI, 1.07–1.23), SRS (HR, 1.3; 95% CI, 1.13–1.51), mean stress MBF (HR, 0.04; 95% CI, 0.16–0.98), and MFR (HR, 0.25; 95% CI, 0.1–0.65; Table 2). The Harrell c-statistic for the model with MFR was 0.66 (95% CI, 0.10–1.0).

When MFR was incorporated as part of the PET interpretation, there were a total of 107 patients with a normal PET scan (SSS <4, rest EF >45% and mean MFR >1.75). Among those with a normal PET, there were 5 adverse events (event rate, 4.6%) and of the remaining 33 abnormal PET, there were 9 adverse events (27%; *P*=0.0006; Table 3).

Table 2. Univariable Analysis Comparing Patients With or Without Adverse Events

Variables*	Outcome (n=14)	No Outcome (n=126)	Hazard Ratio (95% CI)	*P* Value
Age, y	66 (53–73)	61.5 (52–68)	1.01 (0.97–1.05)	0.53
Men	11 (78%)	101 (80%)	0.91 (0.25–3.26)	0.88
Time since transplant, y	11.7 (8.7–15.6)	7.6 (3.1–14.2)	1.05 (0.97–1.13)	0.18
>1 0 y since transplant	9 (64%)	49 (39%)	2.31 (0.77–6.87)	0.13
Hypertension	9 (64%)	69 (55%)	1.7 (0.53–5.4)	0.38
Diabetes mellitus	3 (21%)	38 (30%)	0.78 (0.19–2.46)	0.71
Estimated GFR, mL/min per 1.73 m^2	40.5 (15–60)	60.5 (44–80)	0.96 (0.94–0.99)	0.0062
Previously documented CAV	3 (21%)	6 (5%)	4.14 (1.15–14.8)	0.0296
Previous revascularization	1 (7%)	4 (3%)	2.3 (0.31–18.21)	0.71
SSS=0 (%)	10 (71%)	102 (81%)	1.19 (1.07–1.33)	0.0011
SSS for patients>0	9 (5.75–13)	2.5 (2–3.5)	...	...
SRS=0 (%)	12 (86%)	114 (90%)	1.3 (1.13–1.51)	0.0003
SRS for patients>0	6 (3.5–10)	1.5 (1–2)	...	...
Rest ejection fraction	58% (51–62)	60% (54–64)	0.98 (0.94–1.01)	0.29
Stress ejection fraction, %	60% (52–67)	65% (59–71)	0.96 (0.92–1.004)	0.08
TID present	1 (7%)	2 (1.5%)	3.2 (0.42–24.3)	0.29
Mean resting flow, mL/g per minute	0.82 (0.69–1.11)	0.81 (0.77–0.99)	2.3 (0.53–10.4)	0.26
Mean stress flow, mL/g per minute	1.5 (1.14–2.2)	2.0 (1.57–2.38)	0.4 (0.16–0.98)	0.04
Mean MFR (stress/rest flow)	1.6 (1.32–2.23)	2.32 (1.83–2.94).	0.25 (0.10–0.65)	0.0046
MFR≤1.75	7 (50%)	26 (20%)	4.41 (1.53–12.6)	0.006

*Continuous variables were reported as median (25% and 75% percentiles). Categorical variables were reported as n (%). CAV indicates cardiac allograft vasculopathy; CI, confidence interval; GFR; glomerular filtration rate; MFR, myocardial flow reserve; SRS, summed rest score; SSS, summed stress score; and TID, transient ischemic dilation >1.2.

Kaplan–Meier Analysis

An MFR threshold of 1.75 was selected for Kaplan–Meier analysis because previous studies have shown a good prognosis for patients with an MFR ≥2.0 and a poor prognosis for those with an MFR <1.5.[9,11] Furthermore, it is similar to the ischemic threshold as defined by models of flow.[15] On survival analysis patients with an MFR ≤1.75 had a HR of 4.41 (95%CI, 1.53–12.73; *P*=0.006) for adverse events. A Kaplan–Meier survival curve using an MFR cutoff of 1.75 is shown in Figure 2.

Subanalysis for All-Cause Death

There were a total of 9 deaths during follow-up because of heart failure (2), cardiovascular disease (2), complications from lung cancer and kidney disease (1), CMV viremia in a patient with heart failure (1), and unknown (3).

On univariable analysis mean MFR, SSS, SRS, and GFR were associated with death (Table 4). There were 3 patients with an MFR >1.75 who died during follow-up. Of these, the cause of death was not available in 2 patients, whereas the other died because of lung cancer and end-stage kidney disease.

Table 3. Event Rates According to Scan Results During Median Follow-Up of 18.2 Months

Scan Result	Normal Scan (Events/Patients), %	Abnormal Scan (Events/Patients), %	*P* Value
SSS <4+LVEF >45%	8.3% (11/131)	33% (3/9)	0.066
SSS <4+LVEF >45%+MFR >1.75	4.6% (5/107)	27% (9/33)	0.0006

MFR indicates myocardial flow reserve; and SSS, summed stress score.

Discussion

This prospective observational study of HT recipients suggests that Rb-82 PET has predictive value for adverse outcomes and overall mortality.

Beyond 1 year after HT, CAV is a principal cause of mortality and many mechanisms have been implicated in its pathogenesis.[2] Because of its diffuse nature and involvement of distal vessels and the microvasculature,[16] early detection with invasive angiography can be difficult. Similarly, changes in intimal thickness in epicardial arteries can be measured with intravascular ultrasound (IVUS) but assessment of distal vessels and the microvasculature is precluded by catheter size.

In addition to CAV, cellular and antibody-mediated rejection, cold ischemic injury pretransplantation, reperfusion injury, or infectious myocarditis can cause myocardial injury and microvascular dysfunction, but the effects of these factors cannot be assessed with invasive angiography.[4]

Furthermore, invasive angiography and IVUS are associated with significant health risks to the patient, because of both the procedure itself and the use of nephrotoxic contrast in this population where the incidence of renal dysfunction is high.

Because Rb-82 PET estimates the absolute myocardial blood flow throughout the arterial vascular bed, it has the potential ability to detect changes in both epicardial and microcirculatory systems. Several observational studies, using

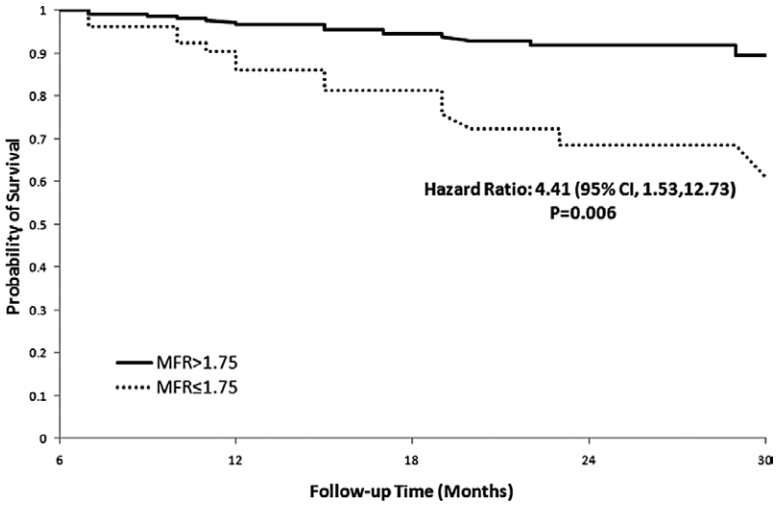


Figure 2. Kaplan–Meier survival curves for event-free survival according to abnormal myocardial flow reserve (MFR) <1.8 corrected for summed rest score. CI indicates confidence interval.

PET for HT patients, have focused on changes in absolute MBF and MFR as markers of incipient CAV.

Wu et al[17] performed both IVUS and PET using N-13-ammonia on 27 patients with angiographically normal coronary arteries and normal LV function. They found an inverse relationship between MFR and plaque volume as measured on IVUS. Allen-Auerbach et al[18] studied 19 HT patients who underwent both IVUS and N-13-ammonia PET at baseline and follow-up IVUS at 15 months. They found that abnormalities in vasodilatory capacity, reflected by MFR, were associated with subsequent changes found on follow-up IVUS. Another study correlated abnormal resting MBF and MFR in HT patients with acute rejection that subsequently improved after treatment.[19]

However, none of the aforementioned studies evaluated clinical outcomes. Our study is the largest to evaluate the use of PET imaging in HT patients and to our knowledge is the first to correlate PET findings with HT patient outcomes.

Other noninvasive imaging modalities have been used to screen for CAV. Dobutamine ECHO has variable sensitivity and specificity for detection of angiographically visible CAV, but a normal dobutamine stress echocardiography has a low rate of subsequent adverse events (1.3%).[20] This finding is comparable with that in our study, where the rate of adverse events was 4.6% (annualized rate 3% per year) after a normal PET scan with an MFR >1.75.

Single photon emission computed tomography imaging has been used in many centers and the presence of relative perfusion defects has been shown to have prognostic value for prediction of adverse events and mortality.[21–24] However, flow quantification with single photon emission computed tomography is not available in clinical practice. PET can estimate MFR and therefore may identify patients at an earlier stage of disease; however, this hypothesis requires further study. Furthermore, because the radiation dose from Rb-82 PET (<2 mSv per patient) is lower than single photon emission computed tomography (10–20 mSv per patient), it could be a preferred modality, especially in a population that requires repeated follow-up testing.[25]

Late gadolinium enhancement on cardiac MRI was evaluated in 39 HT patients and correlated with lower EF and a higher incidence of adverse events.[26] In a recent article, Miller et al[27] performed absolute flow quantification using cardiac MRI in 4 HT patients and correlated MFR with invasive measures of CAV using fractional flow reserve and IVUS.[27] They found that MFR was predictive of the presence of CAV affecting both the epicardial vessels and the microvasculature and was superior to standard angiography alone. However, flow quantification with MRI remains investigational and requires the use of gadolinium, which is problematic in HT patients because of the high prevalence of renal dysfunction in this population. Head-to-head studies are needed to identify the most clinically useful test for risk-stratifying HT patients.

Although retransplantation remains the only definitive treatment option for patients with advanced CAV, earlier detection of CAV may facilitate the initiation of medical therapy such as mammalian target of rapamycin inhibitors, which have been shown to reduce intimal thickness on IVUS when initiated in the earlier stages of CAV.[28–30] Therefore, a noninvasive means of early diagnosis of incipient CAV is highly desirable. Although the results of this study are preliminary in nature, they demonstrate a potential role for PET with absolute flow quantification as a marker of CAV, with prediction of subsequent adverse outcome and detection of more diffuse CAV involving both the epicardial vessels and the microvasculature at an earlier stage compared with other noninvasive imaging modalities.

At our center, we currently perform Rb-82 PET in all HT patients as part of regular screening for CAV. Those patients with relative perfusion defects or those with significantly decreased MFR are referred for invasive angiography to assess for obstructive epicardial vessel disease, with percutaneous coronary intervention performed where it is deemed appropriate. Those with a decreased MFR and no lesions amenable to percutaneous coronary intervention are considered for intensification of their risk factor management and potentially an alteration in their immunosuppressive medications.

There was a significant association between abnormal renal function and adverse outcomes. Abnormal renal function both before and after transplantation is well recognized as a marker of increased mortality risk.[31] The prevalence of severe renal dysfunction (eGFR <30 mL/kg per minute) in this cohort was 7.8% (11 patients), which is similar to that observed in other studies.[32] In this study, we observed a significant correlation

Table 4. Univariable Analysis Comparing Patients With and Without All-Cause Mortality

Variables*	Death (n=9)	No Death (n=131)	Hazard Ratio (95% CI)	*P* Value
Age, y	73 (61–75)	61 (52–68)	1.06 (0.99–1.13)	0.75
Men	7 (78%)	105 (80%)	0.91 (0.19–4.42)	0.91
Time since transplant, y	12 (9.7–14.2)	7.8 (3.3–14.6)	1.04 (0.94–1.14)	0.39
>10 y since transplant	6 (66%)	52 (40%)	2.55 (0.64–10.1)	0.18
Hypertension	6 (66%)	74 (56%)	1.41 (0.35–5.65)	0.62
Diabetes mellitus	3 (33%)	38 (29%)	1.24 (0.31–4.9)	0.75
Estimated GFR, mL/min per 1.73 m^2	37 (7–50)	61 (44–80)	0.95 (0.92–0.98)	0.0028
Previously documented CAV	1 (11%)	8 (6%)	1.99 (0.25–15.9)	0.51
Previous revascularization	0	5 (4%)	0	0.96
SSS=0 (%)	6 (66%)	106 (81%)	1.23 (1.09–1.39)	0.0006
SSS for patients>0	11 (6.5–15)	3 (2–4)	...	...
SRS=0 (%)	7 (77%)	118 (90%)	1.33 (1.11–1.58)	0.0016
SRS for patients>0	7.5 (4.25–10.75)	2 (1–2.5)	...	...
Rest ejection fraction	60% (53–63)	59% (54–64)	0.96 (0.90–1.03)	0.36
Stress ejection fraction, %	62% (55–67)	64% (59–71)	0.96 (0.91–1.01)	0.19
TID present, n	1 (11%)	2 (1.5%)	3.2 (0.42–24.6)	0.26
Mean resting flow, mL/g per minute	0.9 (0.72–1.1)	0.81 (0.7–1.0)	3.82 (0.79–18.4)	0.09
Mean stress flow, mL/g per minute	1.48 (1.2–2.3)	1.99 (1.54–2.4)	0.36 (0.12–1.1)	0.07
Mean MFR (stress/rest flow)	1.4 (1.3–1.8)	2.31 (1.83–2.9)	0.14 (0.03–0.57)	0.006
MFR≤1.75	6 (66%)	27 (21%)	6.43 (1.62–25.7)	0.008

*Continuous variables were reported as median (25% and 75% percentiles). Categorical variables were reported as n (%).CAV indicates cardiac allograft vasculopathy; CI, confidence interval; GFR, glomerular filtration rate; MFR, myocardial flow reserve; SRS, summed rest score; SSS, summed stress score; and TID, transient ischemic dilation.

between eGFR and mean MFR (r=0.41; 95% CI, 0.27–0.54; P<0.0001). This may have been expected because abnormal renal function is associated with microvascular dysfunction as well as premature coronary artery disease.

Limitations

Albeit the largest study of its kind, this was a single-center study of 140 patients with a limited number of adverse outcomes, and therefore larger prognostic studies are still needed.

Standard of care, at our center, is to perform annual noninvasive testing with referral for invasive angiography being reserved for symptomatic patients or those with significant abnormalities on noninvasive testing. Patients undergo annual imaging for a minimum of 5 years after HT. Beyond 5 years, the frequency of screening is extended to every 2 years at the discretion of the treating physician. Because invasive angiography is not routinely performed we could not correlate our results with those from invasive studies. The authors acknowledge that practice differs at different institutions; however, our approach has yielded similar outcomes to other international centers.[33]

IVUS was not routinely performed and therefore we could not correlate PET measures with the extent of epicardial CAV. However, MFR is a measure of flow in both the epicardial vessels and the microcirculation. Conversely, IVUS cannot be used to assess the microcirculation and therefore direct correlations between IVUS findings and MFR may not be reflective of true CAV burden.

PET imaging was not performed within the 12 months of HT, therefore we were unable to evaluate alterations in MBF that may occur in the early post-HT period, particularly in response to episodes of acute rejection, which are less likely to occur >24 months after HT.

There was wide variation among our patients in the time between transplantation and PET scanning with the majority of patients undergoing PET scanning >5 years after transplant, but this was explained by the recent change in practice from the routine use of single photon emission computed tomography to PET. We did not observe any differences in stress or rest MBF, or in global MFR between patients who were <5 years, those who were 5 to 10 years, or those who were >10 years after HT.

The number of adverse events was relatively low and therefore a multivariable analysis could not be performed and so the predictive value of individual PET parameters could not be evaluated. Furthermore, the cause of death was not available for 3 patients, 2 of whom who had normal PET scans with an MFR >1.75. We speculate that the cause of death in these patients was noncardiac, but this cannot be confirmed.

Access to PET facilities may be a potential barrier to more widespread adoption of this technology in this specific population. However, transplant centers are highly specialized and therefore more likely to have access to PET. In addition, the incremental prognostic information from MFR, in addition to its lower radiation dose and faster imaging times, means that PET may become the preferred choice for noninvasive imaging in this patient population.

Conclusions

In heart transplant patients, Rb-82 PET including absolute flow quantification seems to have prognostic value. Larger

studies with longer follow-up are needed to confirm, but these findings suggest that PET may be a suitable modality for noninvasive assessment in HT patients.

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CLINICAL PERSPECTIVE

Cardiac allograft vasculopathy is a condition that limits long-term survival in heart transplant recipients and annual screening is performed in most centers. Currently, there is heterogeneity among transplant centers in how to screen for cardiac allograft vasculopathy with many performing routine invasive coronary angiography, which incurs not unsubstantial risk. Rubidium-82 positron emission tomography perfusion imaging had been shown to be an accurate modality for diagnosis and prognostication in patients with known or suspected coronary artery disease and allows estimation of myocardial blood flow in absolute terms. However, the prognostic value of rubidium-82 positron emission tomography in heart transplant patients has not been evaluated previously. We studied 140 heart transplant patients who underwent rubidium-82 positron emission tomography at our center and followed up them for a median of 18 months. Overall, there were 14 patients who experienced an adverse outcome. We found that abnormalities on relative imaging (summed stress score and summed rest score), as well as mean left ventricular stress myocardial blood flow and myocardial flow reserve (ratio of stress over rest myocardial blood flow), were predictive of an adverse outcome in these patients in addition to clinical variables. Our results suggest that rubidium-82 positron emission tomography, and in particular absolute flow quantification, has prognostic value in heart transplant patients although larger studies with longer follow-up are required to confirm these findings.

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