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PET Assessment of Epicardial Intimal Disease and Microvascular Dysfunction in Cardiac Allograft Vasculopathy

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ABSTRACT

BACKGROUND Cardiac allograft vasculopathy (CAV) is a leading cause of graft failure and death after heart transplantation. Absolute myocardial blood flow (MBF) quantification using rubidium 82 (Rb-82) positron emission tomography (PET) could enable evaluation of diagnostically challenging diffuse epicardial and microvascular disease in CAV.

OBJECTIVES The authors aimed to evaluate Rb-82 PET detection of CAV.

METHODS Consecutive transplant recipients undergoing coronary angiography were prospectively evaluated with PET, multivessel intravascular ultrasound (IVUS), and intracoronary hemodynamics. CAV was defined as International Society of Heart and Lung Transplantation CAV_{1-3} on angiography and maximal intimal thickness ≥0.5 mm on IVUS.

RESULTS Forty patients (mean age 56 years, 4.8 years post-transplant) completed evaluation. CAV was detected in 32 patients (80%) by IVUS and 14 (35%) by angiography. PET correlated significantly with invasive coronary flow indices: r = 0.29, rate-pressure product-adjusted myocardial flow reserve (cMFR) versus coronary flow reserve; r = 0.28, relative flow reserve versus fractional flow reserve; and r = 0.37, coronary vascular resistance (CVR) versus index of microcirculatory resistance. Patients with CAV or microvascular dysfunction had reduced cMFR and stress MBF and increased CVR. Receiver operator characteristic curves demonstrated good accuracy of PET for CAV on IVUS (area under the curve 0.77 to 0.81) and optimal diagnostic cutoffs of cMFR <2.9, stress MBF <2.3, and CVR >55. Combined PET assessment for CAV yielded excellent >93% sensitivity (>65% specificity) for 1 abnormal parameter and >96% specificity (>55% sensitivity) for 2 abnormal parameters.

CONCLUSIONS Rb-82 PET flow quantification has high diagnostic accuracy for CAV, with potential for noninvasive evaluation after heart transplantation. (J Am Coll Cardiol 2018;71:1444–56) © 2018 by the American College of Cardiology Foundation.

Long-term graft survival after heart transplantation is limited by the development of cardiac allograft vasculopathy (CAV) in one-third of patients within 5 years of transplantation (1). Regular surveillance for CAV is critical to detect disease early and enable effective implementation of preventive and treatment interventions. Evaluation of CAV is problematic because of the diffuse nature of disease

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involving both the epicardial coronary arteries and microvasculature. Coronary angiography and intravascular ultrasound (IVUS) are recommended for CAV surveillance but are suboptimal for examining distal epicardial branch vessels and the microvasculature (2). Angiography is also limited by the capability to detect only obstructive, usually late epicardial disease. Noninvasive cardiac imaging techniques for CAV lack sensitivity and specificity, particularly to detect nonangiographic yet prognostically significant epicardial intimal and microvascular disease (3-5).

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Quantitative myocardial perfusion imaging could enable comprehensive assessment of CAV. Flow quantification is suited to evaluate CAV because it can determine global myocardial blood flow (MBF), which detects balanced or diffuse epicardial and microvascular coronary disease. Cardiac position emission tomography (PET) is the clinical gold standard for noninvasive quantification of MBF and myocardial flow reserve (MFR). The superior performance of PET, specifically for diffuse disease, has led to its increasing use for coronary artery disease diagnosis and risk stratification (6-10). We have also previously shown the prognostic value of reduced stress MBF and MFR on PET to predict adverse events after heart transplantation (11). However, the relationship of noninvasive PET flow to invasive flow has not been comprehensively characterized or evaluated prospectively in heart transplant patients. Additionally, the accuracy of PET flow measurements for defining CAV by angiography and IVUS has not been well studied. The purpose of this study was to assess rubidium 82 (Rb-82) PET as a diagnostic tool for CAV and to examine the correlation between PET-determined myocardial flow and comprehensive invasive coronary flow measures in heart transplant patients.

METHODS

Consecutive heart transplant patients at the University of Ottawa Heart Institute (Ottawa, Ontario, Canada) being considered for coronary angiography for CAV surveillance or other clinical indication were prospectively enrolled between May 2015 and February 2017. Major exclusion criteria included prior percutaneous coronary intervention, severe renal dysfunction (estimated glomerular filtration rate <30 ml/min/1.73 m^2), or contraindications to adenosine or dipyridamole. Cardiac PET was performed within 1 month of angiography. The study protocol was approved by the institutional research ethics committee, and informed consent was obtained from all participants.

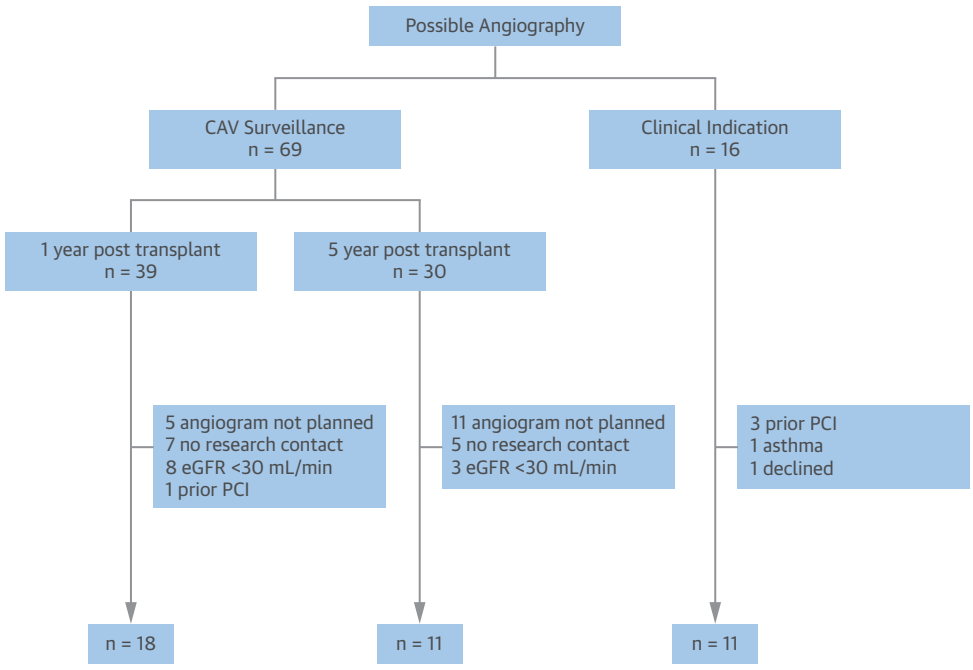
CORONARY ANGIOGRAM AND INTRAVASCULAR ULTRASOUND. Left-sided heart catheterization was performed in standard fashion. IVUS interrogation was performed by automated pullback (0.5 mm/s) through the target vessel over a ≥30-mm segment with a 45-MHz catheter (Revolution, Volcano, Rancho Cordova, California). Up to 3 vessels were examined based on angiographic results and vessel size. Angiogram and IVUS images were analyzed off-line by an independent core laboratory (Toronto General Hospital-University Health Network, Toronto, Ontario, Canada). Quantitative coronary angiographic software (QAngio XA, Medis Medical Image Systems Inc., Leiden, the Netherlands) was used to assess the maximum percentage diameter stenosis in each coronary segment. CAV severity was classified according to International Society for Heart and Lung Transplantation nomenclature (12): CAV_0 = not significant, CAV_1 = mild, CAV_2 = moderate, and CAV_3 = severe. IVUS images were analyzed with commercial software (Volcano s5 Intravascular Ultrasound Imaging System, Volcano). Maximal intimal thickness (MIT) was determined, and MIT ≥0.5 mm was used to define CAV. Volumetric analysis was performed by manual cross-sectional tracing of vessel, lumen, and intima contours at 1-mm axial intervals, multiplied by the analyzed axial length to determine respective volumes, and reported in cubic millimeters per millimeter (mm^3/mm) to adjust for variations in analyzed vessel segment lengths. Percentage intimal volume was calculated as the percentage of intimal to vessel volume.

INVASIVE CORONARY PHYSIOLOGY. After administration of intravenous heparin (70 IU/kg) and intracoronary nitroglycerin (200 μg), a coronary pressure-tipped wire (PressureWire Certus Agile Tip, St. Jude Medical, Plymouth, Minnesota) was advanced into the distal target vessel. Intravenous adenosine (0.14 mg/kg/min for 2 min) was used to induce hyperemia. Fractional flow reserve (FFR) was calculated by dividing the mean distal coronary pressure by the mean proximal coronary pressure during hyperemia. A 3-ml bolus of room temperature saline was injected 3 times at hyperemia and at rest to determine mean transit time (RadiAnalyzer, St. Jude Medical) (13). The index of microcirculatory resistance (IMR) was calculated by multiplication of distal coronary pressure by hyperemic mean transit time (13,14). Coronary flow reserve (CFR) was calculated by mean rest transit time divided by mean hyperemic transit time (15,16).

ABBREVIATIONS AND ACRONYMS

CAV = cardiac allograft vasculopathy
CFR = coronary flow reserve
CI = confidence interval
cMFR = rate-pressure product-adjusted myocardial flow reserve
CVR = coronary vascular resistance
FFR = fractional flow reserve
IMR = index of microcirculatory resistance
IVUS = intravascular ultrasound
LAD = left anterior descending coronary artery
LCx = left circumflex coronary artery
MBF = myocardial blood flow
MFR = myocardial flow reserve
MIT = maximal intimal thickness
PET = positron emission tomography
RCA = right coronary artery
Rb = rubidium
RFR = relative flow reserve

FIGURE 1 Patient Screening and Enrollment



Numbers of patients screened, excluded, and recruited. CAV = cardiac allograft vasculopathy; eGFR = estimated glomerular filtration rate; PCI = percutaneous coronary intervention.

PET IMAGING. Myocardial perfusion imaging was performed on a 3-dimensional PET-VCT system (Discovery 690, GE Healthcare, Waukesha, Wisconsin). Low-dose (0.2 mSv) x-ray computed tomography images were acquired for attenuation correction. Rb-82 (10 MBq/kg at rest and stress; 1 mSv total) was administered intravenously using an automated elution system (RUBY-Fill, Jubilant DraxImage, Kirkland, Quebec, Canada). Dynamic imaging acquisition of Rb-82 kinetics was performed for 6 min, starting at the time of tracer injection, for quantification of MBF and MFR. Pharmacological stress was induced with intravenous dipyridamole 0.14 mg/kg/min for >5 min. To ensure maximal vasodilatory response to dipyridamole, all caffeinated beverages and antianginal medications were withheld for at least 24 h before imaging.

PET ANALYSIS. PET analysis was performed blinded to clinical data and invasive coronary studies. For qualitative myocardial perfusion analysis, images were reconstructed for review in short, vertical, and horizontal long-axis orientations. A 17-segment model of the left ventricle and 5-point scoring system was used for visual grading of tracer uptake in each segment to calculate summed stress score (SSS), summed rest score, and summed difference score (SSS - summed rest score). Absolute MBF quantification (ml/min/g) at rest and stress was determined by fitting a 1-tissue-compartment tracer-kinetic modeling to regional myocardial time radiotracer activity-versus-time curves using automated software (FlowQuant, Ottawa, Ontario, Canada) (17). MFR was calculated as the ratio of stress to rest MBF and rate-pressure product-adjusted MFR (cMFR) determined to account for high resting heart rates in transplant patients (10,18). For cMFR, rest MBF was corrected for rate-pressure product as follows: rest MBF multiplied by 8,500 divided by rate-pressure product (resting heart rate multiplied by resting systolic blood pressure). Additionally, coronary vascular resistance (CVR; stress systolic blood pressure divided by stress MBF) and relative flow reserve (RFR; minimum segment MFR divided by maximum segment MFR) were measured for separate evaluation of microvascular and epicardial disease burden, respectively (19).

STATISTICAL ANALYSIS. Categorical variables are expressed as count (percentage) and continuous variables as mean ± SD or median (interquartile range). Comparisons between groups of observations

TABLE 1 Baseline Patient Demographics (N = 40)

Male	31 (77)
Age, yrs	56.1 ± 14.3
Body mass index, kg/m^2	29.3 ± 4.9
Transplant indication	
Ischemic	14 (35)
Dilated cardiomyopathy	17 (43)
Other	9 (23)
Donor age, yrs	35.8 ± 13.8
Donor sex, male	29 (73)
Ischemic time, min	206 ± 68
Years post-transplant	4.8 ± 5.8
Diabetes mellitus	17 (43)
Smoking	1 (3)
Hyperlipidemia	17 (43)
Hypertension	15 (38)
Prior treated rejection	10 (25)
Prior left ventricular assist device	14 (35)
Lipids, mmol/l	
Total cholesterol	3.94 ± 1.10
Low-density lipoprotein cholesterol	1.80 ± 0.74
High-density lipoprotein cholesterol	1.22 ± 0.36
Triglyceride	1.96 ± 1.34
Creatinine, μmol/l	105 ± 21
Estimated glomerular filtration rate, ml/min/1.73 m^2	66 ± 20
Cyclosporine/Tacrolimus	40 (100)
Mycophenolic acid	39 (98)
Prednisone	35 (88)
Sirolimus	1 (3)
Aspirin	37 (93)
Statin	40 (100)
Beta blocker	12 (30)
Calcium-channel blocker	20 (50)
ACE inhibitor	14 (35)

Values are n (%) or mean ± SD.
ACE = angiotensin-converting enzyme.

TABLE 2 Intravascular Ultrasound (n = 23)*

	LAD	LCx	RCA	p Value†
Maximal intimal thickness, mm	0.50 (0.40-0.80)	0.30 (0.20-0.40)	0.40 (0.30-0.50)	<0.001
Intimal volume, mm^3/mm‡	1.66 (0.81-2.13)	0.90 (0.54-1.80)	0.87 (0.56-1.87)	0.023
Percent intimal volume	10.46 (7.93-17.80)	7.12 (5.37-12.59)	6.02 (3.80-10.39)	<0.001
Lumen volume, mm^3/mm‡	10.35 (7.91-14.63)	10.30 (7.98-14.95)	12.67 (10.64-15.44)	0.065
Vessel volume, mm^3/mm‡	12.36 (9.60, -15.63)	11.44 (8.76-16.51)	13.48 (11.50-16.92)	0.568

Values are median (interquartile range). *23 of 40 patients had all 3 vessels examined. †Friedman test. ‡Intimal, lumen, and vessel volumes standardized for analyzed vessel segment length.
LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; RCA = right coronary artery.

were performed using Student's *t*-test, Mann-Whitney *U* test, and Friedman test depending on the number of paired/unpaired groups of observations and parametric/nonparametric distribution of results. Comparisons between vessels were restricted to those patients in whom all 3 vessels were able to be examined. The relationship between PET flow parameters (cMFR, stress MBF, CVR, and RFR) and invasive coronary references (CFR, IMR, FFR, and intimal volume) were evaluated by correlation analysis and Bland-Altman plots. Data were analyzed on a per-patient and per-coronary vessel basis. Per-coronary vessel correlation analyses were evaluated with the clustering of vessels within the patient taken into account, and the 95% confidence intervals (CIs) incorporated the variance inflation factor caused by the clustering (20). Receiver operating characteristic curve analysis was used to assess the diagnostic performance of PET flow parameters (cMFR, stress MBF, and CVR), in conjunction with Youden's index to determine optimal cutpoints for detecting CAV by angiography (CAV_{1-3}) and IVUS (MIT ≥0.5 mm). Statistical analyses were performed with GraphPad Prism 7 (GraphPad Software, La Jolla, California) and SAS version 9.4 software (SAS Institute Inc., Cary, North Carolina).

RESULTS

STUDY POPULATION. Of 85 consecutive patients identified for possible coronary angiography, 47 underwent angiography, and 40 patients were enrolled in the study (Figure 1). Invasive coronary studies and PET were performed at a mean interval of 17.2 ± 13.8 days apart. Patient demographics are shown in Table 1. The median time post-transplantation was 3.2 years (interquartile range: 1.0 to 5.2 years). All patients were receiving treatment with aspirin, and most were taking a statin and maintenance triple immunotherapy that included a calcineurin inhibitor, mycophenolic acid, and steroid. Only 1 patient was taking sirolimus.

CAV ON CORONARY ANGIOGRAM AND IVUS. Angiographic CAV was evident in 14 patients (35%): 9 (23%) with CAV_1, 2 (5%) with CAV_2, and 3 (8%) with CAV_3. Average maximum vessel stenosis was 23 ± 23%. Examination with IVUS was performed for 101 vessels, and identified a higher proportion of patients (80% [n = 32]) with CAV. Epicardial intimal disease measured by MIT, intimal volume, and percentage intimal volume were significantly greater in the left anterior descending coronary artery (LAD) than in the left circumflex (LCx) and right coronary artery (RCA) (Table 2).

VASODILATOR STRESS. Table 3 shows the hemodynamic response to vasodilatory stress for adenosine during invasive coronary studies and dipyridamole

TABLE 3 Vasodilator Stress

	Rest	Stress	p Value
Adenosine: invasive coronary studies			
Heart rate, beats/min	83 ± 13	87 ± 14	0.102
Systolic blood pressure, mm Hg	126 ± 19	110 ± 12	<0.001
Rate-pressure product	10,432 ± 2,203	8,866 ± 3,162	0.005
Dipyridamole: PET			
Heart rate, beats/min	83 ± 13	88 ± 17	0.011
Systolic blood pressure, mm Hg	123 ± 15	129 ± 19	0.029
Rate-pressure product	10,109 ± 1,778	11,262 ± 1,931*	<0.001

Values are mean ± SD. Rate-pressure product was calculated by multiplying heart rate by blood pressure. *p < 0.001 vs. adenosine stress rate-pressure product.
PET = positron emission tomography.

during PET studies. Mean total adenosine dose per patient was 89.0 ± 34.4 mg, without significant differences in dose administered between coronary arteries: 34.0 ± 10.3 mg for LAD, 34.4 ± 11.1 mg for LCx, and 35.1 ± 10.9 mg for RCA. Adenosine resulted in a significant reduction in blood pressure, whereas heart rate and blood pressure increased after dipyridamole. Mean rate-pressure product at peak stress was significantly higher post dipyridamole (11,262 ± 1,931) than after adenosine (8,866 ± 3,162).

INVASIVE CORONARY PHYSIOLOGY. Invasive coronary physiology was assessed in 100 vessels. Corresponding to greater epicardial intimal disease on IVUS, both CFR and FFR were lower in the LAD than in the LCx and RCA (Table 4). Abnormal FFR ≤0.80, CFR <2.0, and IMR ≥20 were present in 6 (15%), 17 (57%), and 21 (53%) patients, respectively. Mean FFR per vessel was normal, and FFR correlated with intimal volume on IVUS (r = −0.33; 95% CI: −0.51 to −0.12). Mean IMR was increased in all coronary vessels and correlated with CFR (r = −0.36; 95% CI: −0.53 to −0.17) but not FFR (r = −0.06; 95% CI: −0.28 to 0.16). There was no correlation between IMR (r = −0.03; 95% CI: −0.24 to 0.17) or CFR (r = −0.10; 95% CI: −0.30 to 0.12) and intimal volume on IVUS.

RB-82 PET. Few patients had abnormal qualitative myocardial perfusion (Table 5): 5 (13%) had SSS >3 and 8 (20%) had a summed difference score >0. Mean quantitative myocardial flow parameters measured on PET were within normal clinical range (MFR >2, stress MBF >1.7). Scatter and Bland-Altman plots showed significant moderate correlation and good agreement between PET cMFR and invasive CFR (Figure 2). Greater differences in cMFR and CFR were observed at high flow reserves (Figures 2C and 2D). Correlation was similar between minimum segment cMFR and CFR: r = 0.33, p = 0.040 for per-patient analysis and r = 0.35 (95% CI: 0.15 to 0.52) for per-vessel analysis. Significant moderate correlation was also demonstrated between other PET myocardial flow and invasive coronary hemodynamic parameters (Table 6).

PET cMFR and stress MBF were reduced and CVR was increased in patients with epicardial CAV or microvascular dysfunction (Figure 3). In general, there was weak correlation between IVUS intimal volume and PET flow measures, including cMFR (r = −0.08; 95% CI: −0.28 to 0.12), stress MBF (r = −0.26; 95% CI: −0.44 to −0.06), RFR (r = −0.16; 95% CI: −0.35 to 0.04), and CVR (r = 0.30; 95% CI: 0.11 to 0.47). PET flow correlated with IMR: r = −0.31 (95% CI: −0.47 to −0.12) for cMFR, and r = 0.37 (95% CI: 0.19 to 0.53) for CVR.

CAV DIAGNOSIS BY RB-82 PET. On receiver operating characteristic curve analysis, PET cMFR, stress MBF, and CVR demonstrated poor diagnostic performance for detecting angiographic CAV_{1-3} (Figure 4A). The diagnostic accuracy of PET for moderate or severe angiographic CAV_{2-3} was improved and was highest for stress MBF: area under the curve (AUC) 0.83, p = 0.017 (Figure 4B). In contrast, PET cMFR, stress MBF, and CVR displayed high diagnostic performance for detecting CAV on IVUS, with AUC of 0.77 to 0.81 (Figure 4C). The same PET parameters had reduced ability to predict microvascular dysfunction, defined as IMR ≥20: AUC 0.62 to 0.68 (Figure 4D). The optimal diagnostic PET cutoff values for CAV were cMFR <2.9, mean stress flow <2.3, and CVR >55. On the basis of these thresholds, PET showed moderate to high (69% to 84%) sensitivity and specificity (75% to 88%) for CAV on IVUS but high (71% to 100%) sensitivity and low (42% to 54%) specificity for angiographic CAV (Table 7). The use of prognostically important abnormal cutoffs of <2.0 for cMFR and <1.7 for stress MBF yielded lower accuracy for detecting CAV on IVUS: 29% sensitivity and 62% specificity for cMFR, and 57% sensitivity and 58% specificity for stress MBF. The single best PET diagnostic parameter was CVR for both angiographic-determined (AUC: 0.67) and IVUS-determined (AUC: 0.81) CAV. Combined assessment of any 2 PET parameters

TABLE 4 Invasive Coronary Physiology (n = 23)*

	LAD	LCx	RCA	p Value†
Fractional flow reserve	0.91 (0.88–0.93)	0.98 (0.96–1.00)	0.98 (0.94–1.00)	<0.001
Coronary flow reserve	2.4 (1.6–3.2)	3.3 (2.4–4.4)	3.7 (2.1–4.9)	0.035
Index of microcirculatory resistance	25 (17–34)	20 (13–24)	24 (12–35)	0.438

Values are median (interquartile range). *23 of 40 patients had all 3 vessels examined. †Friedman test.
Abbreviations as in Table 2.

TABLE 5 Positron Emission Tomography (n = 40)

Left ventricular ejection fraction at rest, %	57 ± 7
Left ventricular ejection fraction during stress, %	62 ± 10
Transient ischemic dilation ratio	0.9 ± 0.1
Summed stress score	
0	24 (60)
1-3	11 (28)
≥4	5 (13)
Summed rest score	
0	26 (65)
1-3	10 (25)
≥4	4 (10)
Summed difference score	
0	32 (80)
1-3	6 (15)
≥4	2 (5)
Myocardial flow reserve	2.38 ± 0.82
Myocardial flow reserve, RPP adjusted*	2.87 ± 1.18
Minimum segment myocardial flow reserve	1.99 ± 0.71
Minimum segment myocardial flow reserve, RPP adjusted*	2.40 ± 1.03
Mean stress myocardial blood flow	1.95 ± 0.75
Minimum segment stress myocardial blood flow	1.45 ± 0.64
Coronary vascular resistance	76.19 ± 30.37
Minimum vessel relative flow reserve	0.578 ± 0.116

Values are mean ± SD or n (%). *Flow reserve rest myocardial blood flow calculated as: (rest myocardial blood flow × 8,500) / (resting heart rate × resting systolic blood pressure).

RPP = rate-pressure product.

(cMFR <2.9, stress MBF <2.3, or CVR >55) improved diagnostic accuracy (Table 8). The combination of stress MBF and CVR yielded the highest sensitivity and specificity for CAV: 97% sensitivity for stress MBF or CVR, and 97% specificity for stress MBF and CVR.

DISCUSSION

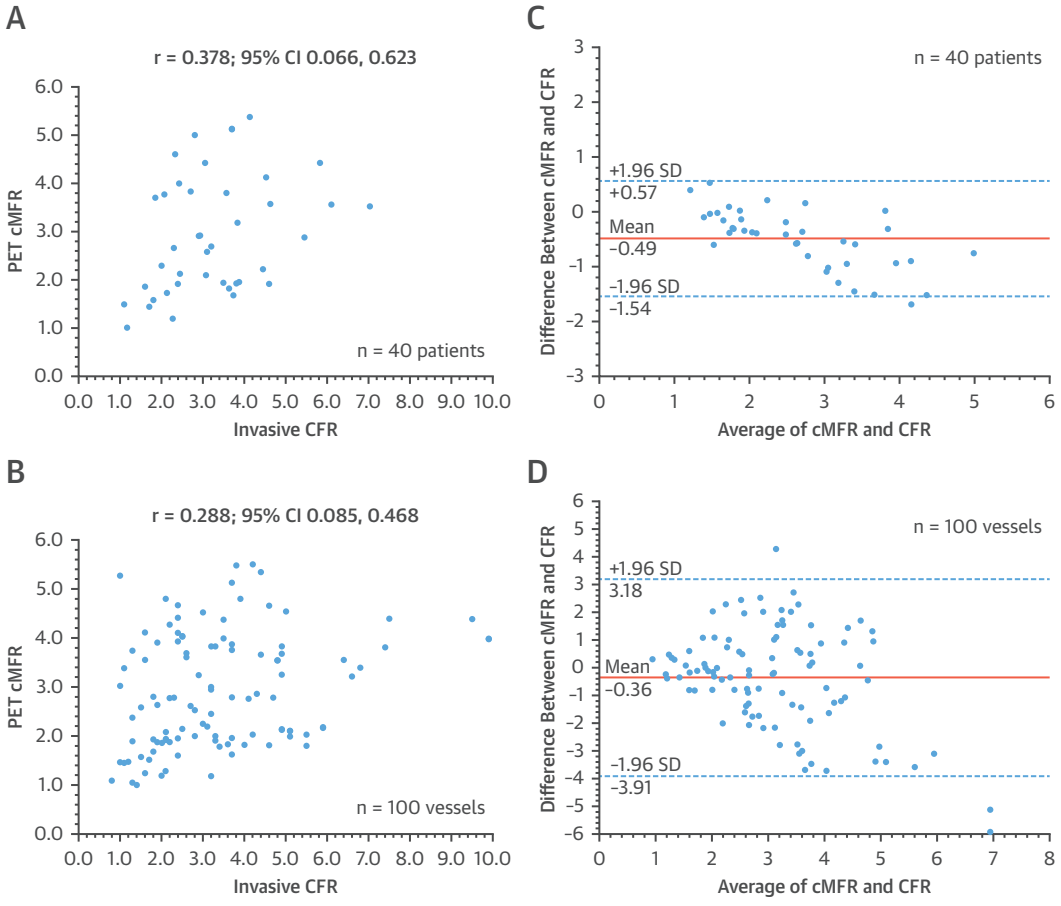
This study is the first to investigate Rb-82 PET myocardial flow quantification for CAV in heart transplant patients alongside comprehensive invasive evaluation of coronary artery anatomy and physiology with multivessel IVUS, FFR, CFR, and IMR. We demonstrate several important findings: 1) a correlation between noninvasive PET myocardial flow and invasive coronary flow measures in heart transplant patients; 2) high diagnostic performance of PET for detecting epicardial intimal disease in CAV; 3) optimal PET diagnostic cutoffs for CAV of cMFR <2.9, stress MBF <2.3, and CVR >55; and 4) high sensitivity for IVUS-determined CAV of combined PET assessment for any 1 abnormal PET cMFR, stress MBF, or CVR parameter, as well as high specificity for any 2 abnormal parameters. These results support a highly promising role for Rb-82 PET in noninvasive assessment of CAV.

EPICARDIAL AND MICROVASCULAR DISEASE IN CAV. We evaluated PET against angiographic and IVUS reference standards for CAV. Coronary angiography is widely available and commonly used in clinical practice as a gross screening tool for CAV, and angiographic disease bears prognostic significance (21,22). Consequently, the International Society for Heart and Lung Transplantation has recommended an angiography-based grading system (CAV_{0-3}) to evaluate CAV (12). However, recognizing the low sensitivity of angiography, we also defined CAV according to epicardial intimal disease on IVUS. In the absence of universally accepted definitions for CAV severity on IVUS, we selected an MIT ≥0.5 mm cutoff based on the well-established prognostic importance of this cutpoint (4,23-25). Importantly, both angiography and IVUS clinical gold standards focus on epicardial CAV. There is no universally accepted method for identifying microvascular disease after heart transplantation. We used functional assessment of the microvasculature by thermodilution-derived IMR. Unlike CFR, which evaluates the entire coronary circulation, IMR is specific for the microcirculation. Because IMR is measured at maximal hyperemia, it is independent of resting hemodynamic conditions such as blood pressure, heart rate, and cardiac contractility (14).

As expected, CAV was detected in a higher proportion of patients on IVUS (80%) than with angiography (35%). Most patients with angiographic-evident CAV had only mild disease: 9 of 14 patients (64%) with angiographic CAV had mild CAV_1, and the mean maximum vessel stenosis was 23 ± 23%. Microvascular dysfunction as measured by increased IMR ≥20 was present in 21 patients (53%). Post-transplantation microvascular disease has been reported to occur independent of epicardial disease (26,27). In keeping with this, we found no correlation between IMR and intimal volume on IVUS or FFR. Furthermore, microvascular dysfunction was present in 4 of 8 patients (50%) without epicardial CAV (MIT <0.5 mm), whereas 15 of 19 patients (79%) without microvascular dysfunction had epicardial CAV (MIT ≥0.5 mm). Similarly, both epicardial CAV and microvascular dysfunction were present in only 17 of 36 patients with any disease.

Microvascular dysfunction is associated with the development of coronary intimal thickening, angiographic CAV, ischemic events, and cardiac death

FIGURE 2 PET cMFR and Invasive CFR



(A, B) Moderate correlation and **(C, D)** good agreement between positron emission tomography (PET) rate-pressure product-adjusted myocardial flow reserve (cMFR) and invasive coronary flow reserve (CFR) by per-patient and per-vessel analysis.

(28-31). Yang et al. (5) reported lower event-free survival in patients with increased IMR ≥20 at 1-year post-transplantation than in patients with decreased or unchanged IMR (36% vs. 66%, p = 0.03). These data highlight the importance of coronary microvasculature assessment. In our study, microvascular dysfunction on PET was assessed by CVR, stress MBF, and cMFR. CVR distinguishes abnormal microvascular from epicardial physiology. We demonstrated increased CVR in patients with microvascular dysfunction, as well as a significant modest correlation of CVR with IMR (r = 0.37; 95% CI: 0.19 to 0.53). There was a weaker correlation between cMFR, which estimates absolute MBF throughout the entire coronary vascular bed, and IMR (r = −0.31; 95% CI: −0.47 to −0.12).

TABLE 6 Correlation Between PET and Invasive Coronary Hemodynamics*

PET Parameter	Invasive Parameter	r	95% CI
cMFR	CFR	0.29	0.08–0.47
Minimum segment cMFR	CFR	0.35	0.15–0.52
RFR	FFR	0.28	0.07–0.46
CVR	IMR	0.37	0.19–0.53

*n = 100 vessels.

CI = confidence interval; CFR = coronary flow reserve; cMFR = rate-pressure product-adjusted myocardial flow reserve; CVR = coronary vascular resistance; FFR = fractional flow reserve; IMR = index of microcirculatory resistance; RFR = relative flow reserve; other abbreviations as in Table 3.

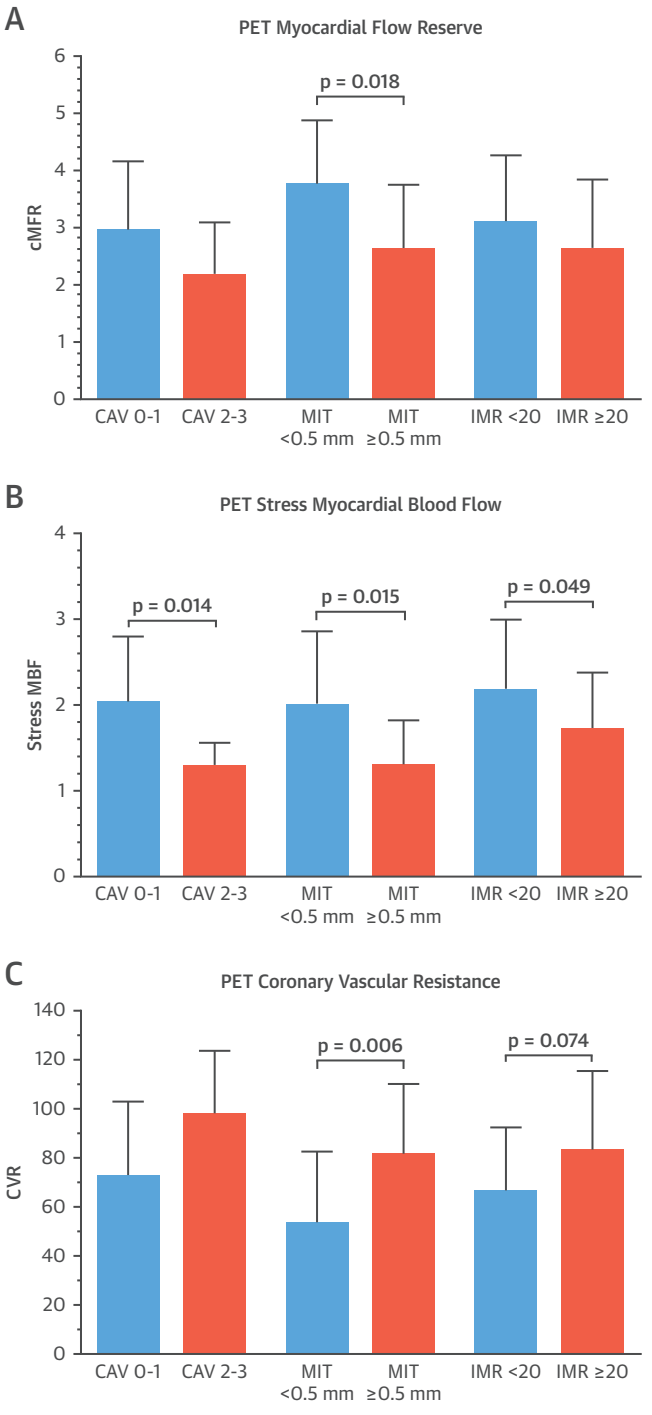
PET MBF AND INVASIVE CORONARY FLOW. The results of this study validate the use of PET myocardial flow quantification as a surrogate measure of invasive coronary flow in heart transplant patients. We demonstrated consistent significant modest

correlations of PET cMFR (r = 0.29), RFR (r = 0.28), and CVR (r = 0.37) with invasive CFR, FFR, and IMR, respectively. Less than perfect correlation between noninvasive and invasive flow measures relate in part to blood flow for the whole myocardium being measured by PET, whereas blood flow is measured regionally for individual coronary vessels on invasive studies. Variable hemodynamic response to vasodilatory stress can also account for differences in stress flow. This was evidenced by a significant reduction in average systolic blood pressure after adenosine during invasive coronary studies, which suggests greater hyperemic potency (resulting in higher stress flow: increased CFR and FFR and reduced IMR) compared with dipyridamole during PET imaging (which resulted in lower stress flow: reduced cMFR and RFR and increased CVR). Relevant to the potential clinical utility of PET, there was particularly good agreement between PET cMFR and invasive CFR at abnormal low flow reserves.

CORRELATION BETWEEN ABNORMAL CORONARY ANATOMY AND PHYSIOLOGY. Two small single-center studies of PET using N-13 ammonia in heart transplant patients demonstrated reduced stress MBF and MFR post-transplantation and moderate correlation of stress MBF (r = −0.46 to −0.49) and MFR (−0.40 to −0.61) with IVUS-assessed epicardial CAV (32,33). In another small study of 19 heart transplant patients, baseline PET MFR at 18 ± 6 months after transplantation was associated with morphological indices of epicardial artery disease progression on IVUS 15 ± 5 months later (34). In contrast, we observed weak agreement between IVUS intimal volume and PET myocardial flow measures, including stress MBF (r = −0.26; 95% CI: −0.44 to −0.06) and RFR (r = −0.16; 95% CI: −0.35 to 0.04). We also observed no correlation of CFR (and IMR) with IVUS findings on invasive studies. Similarly, other investigators have previously reported poor correlation of Doppler-derived CFR with intimal disease on IVUS and similar CFR in patients with minimal angiographic compared with no angiographic disease (35-39). These conflicting data reflect the complex interplay between coronary physiology and anatomy, as well as epicardial and microvascular physiology in heart transplant patients.

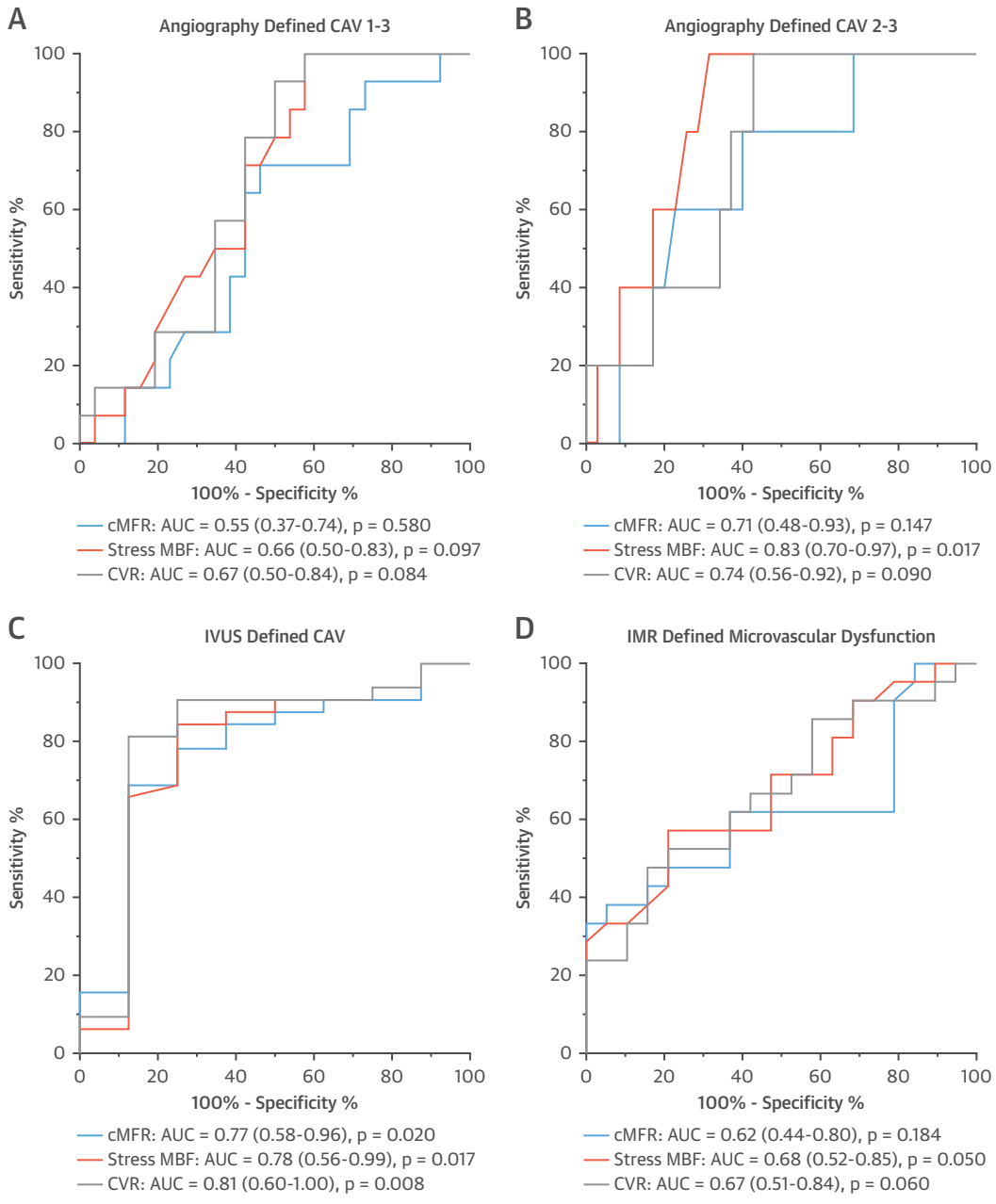
RB-82 PET DIAGNOSTIC ACCURACY AND THRESHOLDS FOR CAV. We demonstrate high diagnostic performance of PET for detecting epicardial intimal disease in CAV, with an AUC of 0.77 for cMFR, 0.78 for stress MBF, and 0.81 for CVR. In contrast, the same PET parameters detected angiographic disease poorly (AUC: 0.55 to 0.67) and moderate or severe

FIGURE 3 PET cMFR, Stress MBF, and CVR in Epicardial CAV and Microvascular Dysfunction



(A) Reduced PET cMFR and **(B)** stress myocardial blood flow (MBF) and **(C)** increased coronary vascular resistance (CVR) in patients with epicardial CAV on angiography (CAV_{2-3}) and intravascular ultrasound (maximal intimal thickness [MIT] ≥0.5 mm) and patients with microvascular dysfunction (index of microcirculatory resistance [IMR] ≥20). Abbreviations as in Figures 1 and 2.

FIGURE 4 PET Receiver Operating Characteristics Curves for CAV



Poor diagnostic performance of PET cMFR, stress MBF, and CVR for detecting **(A)** any angiographic CAV (CAV_{1-3}) and improved accuracy for **(B)** moderate or severe angiographic CAV_{2-3}. **(C)** High diagnostic performance of PET for detecting CAV on IVUS (maximal intimal thickness ≥0.5 mm), and **(D)** moderate diagnostic accuracy for microvascular dysfunction (IMR ≥20). AUC = area under the curve; IVUS = intravascular ultrasound; other abbreviations as in Figures 1 to 3.

angiographic CAV_{2-3} with improved accuracy (AUC: 0.71 to 0.83). Given the low sensitivity of angiography compared with IVUS for detecting early epicardial artery disease, these results reflect superiority in diagnostic performance of PET over invasive angiography for CAV.

Abnormal thresholds for MBF and MFR on PET have not been established in the heart transplant

TABLE 7 Diagnostic Accuracy of PET for CAV

	Sensitivity (%)	Specificity (%)
Intravascular ultrasound MIT ≥0.5 mm		
cMFR 2.9*	69	88
Minimum segment cMFR <2.3*	66	88
Stress MBF <2.3	84	75
Minimum segment stress MBF <1.6	78	88
CVR >55	81	88
Angiography CAV_{1-3}		
cMFR <2.9*	71	54
Minimum segment cMFR <2.9	86	42
Stress MBF <2.3	100	42
Minimum segment stress MBF <1.7	100	46
CVR >55	93	50

*Estimated uncorrected MFR <2.4 and minimum segment MFR <1.9.

CAV = cardiac allograft vasculopathy; MBF = myocardial blood flow; MIT = maximal intimal thickness; other abbreviations as in Tables 3 and 6.

population. Post-transplantation alterations in MBF have been reported, particularly in the early post-operative period, influenced by factors such as ischemia-reperfusion injury, rejection, infection, and immunosuppression (5,40–42). Resting MBF in transplant patients is increased, related in part to an increased resting heart rate from vagal denervation (32–34). In this study, we determined MFR corrected for resting rate-pressure product (cMFR), adjusting for otherwise reduced MFR. Of note, the young average donor age in our patient population (35.8 ± 13.8 years) could have contributed to a higher cMFR (2.87 ± 1.18) and stress MBF (1.95 ± 0.75) compared with older, nontransplant patient cohorts with a mean age >60 years, in whom prognostic MFR cutpoints <2.0 have been reported (9,10,18).

We determined ideal diagnostic cutoffs for CAV of PET cMFR <2.9, stress MBF <2.3, and CVR >55. Combined assessment of PET cMFR, stress MBF, or CVR parameters, with the presence of 1 parameter considered as criteria for IVUS-determined CAV, achieved >93% sensitivity (with >65% specificity), whereas the use of the presence of 2 abnormal parameters as criteria for diagnosis achieved >96% specificity (with >55% sensitivity). High sensitivity for angiographic CAV plus high specificity for IVUS-determined CAV suggests the potential of PET to facilitate earlier detection of epicardial intimal disease, as well as the opportunity for treatment to delay disease progression. In clinically practical terms, high MBF (stress MBF or cMFR) or low coronary resistance (CVR) measured on PET indicates CAV is unlikely, whereas reduced myocardial flow and increased coronary resistance indicates a high likelihood of CAV. Our results support a diagnostic algorithm for CAV that combines PET cMFR, stress MBF, and CVR parameters to guide invasive testing with coronary angiography and IVUS (Central Illustration).

TABLE 8 Diagnostic Accuracy of Combined PET Assessment for CAV*

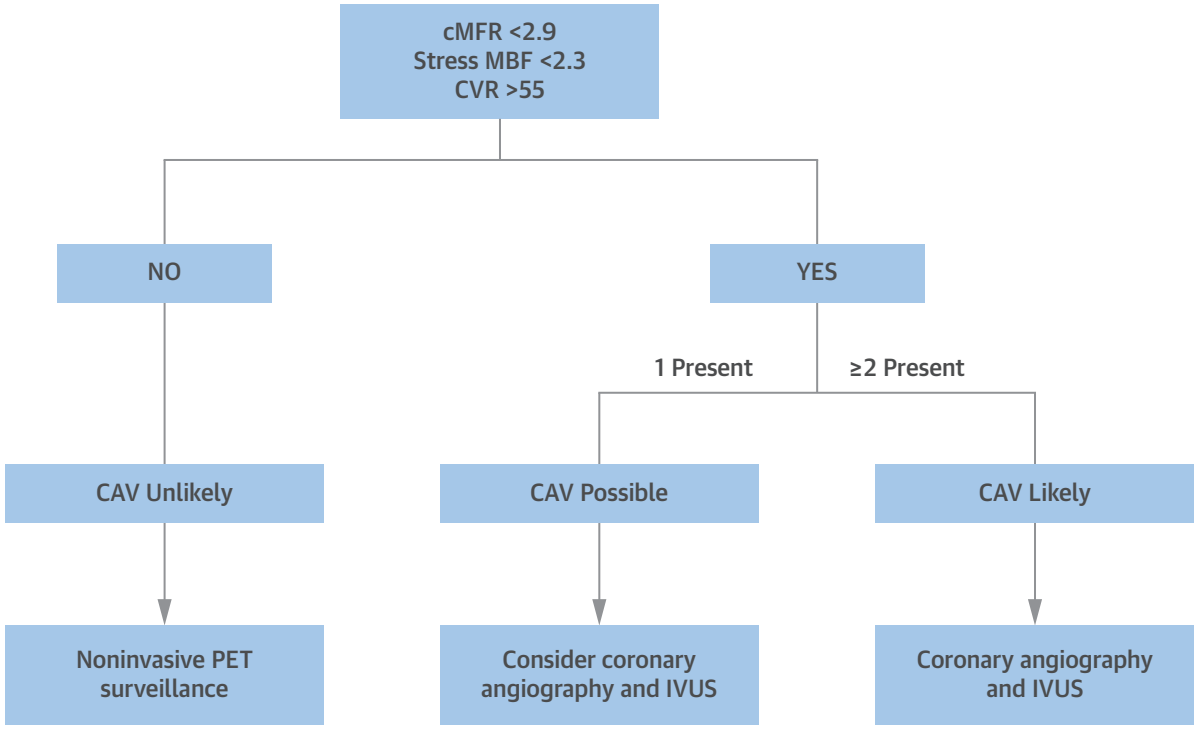
	Sensitivity (%)	Specificity (%)
cMFR <2.9 and stress MBF <2.3	58	97
cMFR <2.9 or stress MBF <2.3	95	66
cMFR <2.9 and CVR >55	56	99
cMFR <2.9 or CVR >55	94	77
Stress MBF <2.3 and CVR >55	68	97
Stress MBF <2.3 or CVR >55	97	66

*Intravascular ultrasound maximal intimal thickness ≥0.5 mm.

Abbreviations as in Tables 3, 6, and 7.

STUDY LIMITATIONS. Our study was limited by small patient numbers; however, the performance of multivessel coronary assessment provided complete data for 100 vessels. Hence, this is the largest study of PET, IVUS, and invasive coronary hemodynamics in heart transplant patients. Because this was a cross-sectional study, we are unable to differentiate between donor-transmitted and de novo CAV. Importantly, although it is widely accepted that an increase in MIT ≥0.5 mm within the first year of transplantation on serial IVUS studies defines early CAV, cross-sectional studies have also shown adverse clinical outcomes in transplant patients with abnormal intimal thickening defined variably as an MIT 0.3 mm or >0.5 mm (4,23,24). This provides justification for the use of MIT ≥0.5 mm as an endpoint defining CAV in our study. The median time post-transplantation for our cohort was 3.2 years. It is unclear whether PET would also be able to detect milder degrees of epicardial or microvascular disease in early CAV. Relevant considerations specific to PET imaging include radiation exposure, costs, and accessibility. PET imaging is achieved with a lower 1- to 3-mSv radiation dose, which is 3- and 5-fold less than invasive angiography (7 mSv) and standard technetium-99m-based single-photon emission computed tomography myocardial perfusion imaging (6 to 10 mSv), respectively (43,44). Importantly, Rb-82 has a short 75-s half-life, which enables rapid sequential rest-stress testing that improves laboratory efficiency, patient throughput, and costs. Access to PET has increased, and PET is currently available in most North American and European heart transplant

CENTRAL ILLUSTRATION **Rb-82 PET Diagnostic Algorithm**



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Combined positron emission tomography (PET) assessment for cardiac allograft vasculopathy (CAV) using abnormal rate-pressure product-adjusted myocardial flow reserve (cMFR) <2.9, stress myocardial blood flow (MBF) <2.3, and coronary vascular resistance (CVR) >55 to guide invasive coronary angiography and intravascular ultrasound (IVUS) testing.

centers. Recent data also indicate the reproducibility of quantitative PET flow measurements across different sites (45). Furthermore, clinical application has also been aided by greater availability of Rb-82, which does not require an onsite cyclotron.

CONCLUSIONS

Rb-82 PET flow quantification measuring cMFR, stress MBF, and CVR has high diagnostic accuracy for CAV and promising potential for noninvasive evaluation after heart transplantation. Larger multicenter studies are warranted to confirm our findings and to validate our defined optimal diagnostic PET cutoffs for CAV.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: CAV is characterized by diffuse epicardial and microvascular coronary disease that can be detected and measured at a relatively early stage by Rb-82 PET.

TRANSLATIONAL OUTLOOK: Further studies are needed to validate the thresholds for myocardial blood flow and coronary vascular resistance measured by PET that are diagnostic of CAV and determine how these can be used to select patients for invasive coronary evaluation.

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KEY WORDS **cardiac allograft vasculopathy, flow quantification, flow reserve, heart transplantation, intravascular ultrasound, positron emission tomography**