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ORIGINAL PAPER

Assessment of late-term progression of cardiac allograft vasculopathy in patients with orthotopic heart transplantation using quantitative cardiac ^{82}Rb PET

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Abstract

The risk stratification and long-term survival of patients with orthotopic heart transplantation (OHT) is impacted by the complication of cardiac allograft vasculopathy (CAV). This study evaluates changes in myocardial blood flow (MBF) and myocardial coronary flow reserve (CFR) in a group of long-term OHT patients using quantitative cardiac ^{82}Rb-positron emission tomography (PET). Twenty patients (7 females and 13 males, mean age = 72.7 ± 12.2 years with CAV and 62.9 ± 7.2 years without CAV and post-OHT mean time = 13.9 years), were evaluated retrospectively using dynamic cardiac ^{82}Rb-PET at rest and regadenoson-induced stress. The patients also underwent selective coronary angiography (SCA) for diagnosis and risk stratification. CAV was diagnosed based on SCA findings and maximal intimal thickness greater than 0.5 mm, as defined by International Society of Heart and Lung Transplantation (ISHLT). Global and regional MBFs were estimated in three vascular territories using the standard 1-tissue compartment model for dynamic ^{82}Rb-PET. The myocardial CFR was also calculated as the ratio of peak stress MBF to rest MBF. Among twenty patients, seven had CAV in, at least, one major coronary artery (ISHLT CAV grade 1 or higher) while 13 patients did not have CAV (NonCAV). Mean rate-pressure products (RPP) at rest were significantly elevated in CAV patients compared to those without CAV ($P = 0.002$) but it was insignificant at stress (P = NS). There was no significant difference in the stress MBFs between CAV and NonCAV patients (P = NS). However, the difference in RPP-normalized stress MBFs was significant ($P = 0.045$), while RPP-normalized MBFs at rest was not significant (P = NS). Both CFR and RPP-normalized CFR were significantly lower in CAV compared to NonCAV patients ($P < 0.001$). There were significant correlations between MBFs and RPPs at rest for both CAV ($\rho = 0.764$, $P = 0.047$) and NonCAV patients ($\rho = 0.641$, $P = 0.017$), while there were no correlations at stress for CAV ($\rho = 0.232$, P = NS) and NonCAV patients ($\rho = 0.068$, P = NS). This study indicates that the resting MBF is higher in late-term post-OHT patients. The high resting MBF and reduced CFR suggest an unprecedented demand of blood flow and blunted response to stress due to impaired vasodilatory capacity that is exacerbated by the presence of CAV.

Keywords Dynamic PET · Regadenoson · Coronary flow reserve · Orthotopic heart transplant · Cardiac allograft vasculopathy · ^{82}Rb-PET

Abbreviations

CAD	Coronary artery disease
CAV	Cardiac allograft vasculopathy
CFR	Coronary flow reserve
IVUS	Intravascular ultrasonography
LAD	Left anterior descending artery
LCX	Left circumflex artery
MBF	Myocardial blood flow
OHT	Orthotopic heart transplantation
RCA	Right coronary artery
SCA	Selective coronary angiography

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Introduction

Cardiac allograft vasculopathy (CAV) is a major cause of long-term complications and mortality after successful orthotopic heart transplantation (OHT). According to the International Society for Heart and Lung Transplantation (ISHLT) on recent data from heart transplant recipients, there is about 25% chance of developing CAV after 5 years of transplantation [1, 2]. There is a higher risk of an angiographically evident coronary artery disease (CAD) including branch stenotic lesion during the late-stage of transplantation [3]. However, the progression of CAV is slower for patients who survive 10 years or more without occurrence of late antibody-mediated rejection [4]. A quantitative noninvasive imaging method such as dynamic cardiac PET has been utilized for the assessment of vasoreactivity on OHT, and is well suited to evaluate hemodynamically significant heart disease and long-term surveillance of vascular pathology in the allograft of OHT patients [5–8].

The late-stage evaluation of CAV in post-OHT patients should involve assessment of both epicardial lesion and microvascular dysfunction caused by functional vasoreactivity abnormalities. This underscores the importance of early noninvasive detection of microvascular dysfunction, which could trigger the development of CAV, with the estimation of absolute myocardial blood flow (MBF) and coronary flow reserve (CFR). Detection of CAV noninvasively has immense clinical significance as it would allow for changes in medical therapy and immunosuppressive drug administration, and possibly would help early intervention to slow the progression of CAV and eventually prevent CAV-related mortality. In a recent study by Fearon et al. [9] on a long-term survival of post-OHT patients, it was observed that the ACEI ramipril lead to significant improvement on microvascular function with beneficial changes in CFR but did not slow development of epicardial plaque volume during a period of 1 year.

Noninvasive imaging such as single-photon emission computed tomography (SPECT), positron emission computed tomography (PET), dobutamine stress echocardiography (DSE) and cardiac magnetic resonance (CMR) imaging are commonly utilized for detection of CAV along with invasive selective coronary angiography (SCA) and intravascular ultrasound (IVUS) [10]. Traditional noninvasive methods have shown limited sensitivity for detecting CAV [11]. Previous work has demonstrated that CFR can be measured in OHT patients using dynamic ^{82}Rb-PET that provides accurate estimation of MBF and CFR [12].

In this work, we assess the changes in MBF and CFR using dynamic ^{82}Rb-PET in late-term OHT patients who have developed documented CAV and compare them with a group of patients without CAV (NonCAV).

Methods

After the ethics approval by the Institutional Review Board (IRB) of the University of California, San Francisco (UCSF), twenty late-term post-OHT patients (7 females and 13 males, mean age = 72.7 ± 12.2 years (CAV) and 62.9 ± 7.2 years (NonCAV)), with mean post-OHT time of 13.9 ± 4.4 years, were evaluated for the presence and severity of myocardial lesions in this retrospective study. All twenty patients had dynamic cardiac ^{82}Rb-PET and selective coronary angiography (SCA) within 12 months of each other. There was no intervening revascularization between SCA and PET studies. Patient cohort characteristics and relevant clinical indicators such as blood pressure (BP), heart rate (HR), LVEF at rest and with stress, hyperlipidemia, and smoking habit as well as transplant rejection history and prior infection were recorded for each patient, and summarized in Table 1. The statistical significance of the difference in characteristics between CAV and NonCAV groups were also calculated in terms of *P* values.

PET imaging

PET imaging studies were performed on an ECAT EXACT HR + PET scanner (Siemens Healthcare). All patients fasted for at least 4 h and refrained from caffeine-containing beverages for 24 h before the scan.

Imaging protocol

The study protocol includes a rest scan with 1480 MBq (40 mCi) of ^{82}Rb IV bolus injection followed by a regadenoson (Lexiscan, Astellas Pharma)—induced stress scan with the injection of 1480 MBq (40 mCi) of ^{82}Rb.

After the intravenous administration of 1480 MBq (40 mCi) of ^{82}Rb at rest, dynamic myocardial PET images were acquired for 6 min in the supine position. After completion of the rest scan there was approximately 30 min break for the stress scan set up. Following the intravenous administration of 1480 MBq (40 mCi) of ^{82}Rb at peak pharmacologic stress, dynamic myocardial PET images were again acquired for another 6 min in the same fashion as rest scan. Rest and stress acquisitions were gated for calculation of left ventricular ejection fraction (LVEF). A transmission scan was performed for attenuation correction of the PET images.

A twelve-lead ECG, heart rate and blood pressure were monitored continuously and recorded at rest and after regadenoson administration. Peak stress heart rate was

Table 1 Patient characteristics

Characteristics	CAV (n = 7)	No CAV (n = 13)	*P* value
Gender	5 M, 2 F	9 M, 4 F	NS
Age (y)	73 ± 12	63 ± 7	0.047
HR Rest (bpm)	90 ± 7	75 ± 9	0.025
HR Stress (bpm)	104 ± 14	91 ± 8	0.003
Mean BP rest (mmHg)	108 ± 13	101 ± 16	NS
Mean BP stress (mmHg)	85 ± 15	88 ± 14	NS
Rate pressure product rest (mmHg.bpm)	10,195 ± 1442	8246 ± 1025	0.002
Rate pressure product stress (mmHg.bpm)	8989 ± 1348	8011 ± 1256	0.11
Ejection fraction (%)	54 ± 11	61 ± 7	NS
Total cholesterol (mg/dL)	163 ± 27	150 ± 12	NS
HDL (mg/dL)	57 ± 33	50 ± 12	NS
LDL (mg/dL)	77 ± 18	72 ± 17	NS
Weight (lb)	171 ± 41	176 ± 33	NS
Beta blockers	0	1	NS
Smoking	2	3	NS
Cardiomyopathy	0	4	NS
Immunosuppressive (Cyclosporine)	3	4	NS
Diabetes mellitus	0	2	NS
Prior heart transplant	0	2	NS
Prior antibody-mediated rejection (AMR)	2	3	NS
Sirolimus/everolimus	2	4	NS
Tacrolimus	1	4	NS
Prior cell-mediated rejection (CMR)	0	0	NS
Prior infection/viral disease	3	7	NS

defined as the highest heart rate at any time after regadenoson administration.

Image reconstruction

The dynamic PET data for each patient were reconstructed using an iterative algorithm (ordered subsets expectation maximization algorithm with 8 subsets) provided by the scanner manufacturer (Siemens Healthcare). All transmission-based attenuation-corrected PET images were sampled at 20 × 6 s, 5 × 12 s, 2 × 30 s, and 2 × 60 s with a total of 29 dynamic frames for further kinetic analysis. The registration accuracy between the attenuation map derived from CT and reconstructed PET volume was verified for each study.

PET data analysis and estimation of MBF

Reconstructed dynamic images were processed using the PMOD Cardiac PET Modeling Tool (PCARDP) (PMOD Technologies, Zurich, Switzerland). The myocardium was oriented along the long-axis and short-axis, and subdivided into 17 segments from base through mid-cavity to apical regions following the segmentation scheme recommended by the American Heart Association (AHA). The time activity curves (TACs) for 17 myocardial regions as well as activity concentrations of left and right ventricular blood pools for each rest-stress pair were extracted. Regional and global rest and peak stress MBF were then calculated by fitting the ^{82}Rb time-activity curves to a 1-tissue compartment model. The flow-dependent extraction fraction correction for Rb was implemented as described by Lortie et al. [13]. The double spillover correction [14] for the activity in the myocardium from the left and right ventricle was also incorporated. The regional MBF (ml/min/g) at rest and during stress were estimated, and corresponding CFR were calculated as the ratio of peak stress MBF to rest MBF.

The segments related to the conventional regions supplied by the three major coronary arteries in the territory of the left anterior descending artery (LAD), the right coronary artery (RCA), the left circumflex artery (LCX), respectively were combined to calculate territorial MBF both at rest and stress. The MBFs were also adjusted with mean rate pressure product (RPP), defined as the product of heart rate and mean blood pressure, by the following formula: (MBF/RPP) * 10,000.

Coronary angiography

Selective coronary angiography (SCA) was performed using a 5 French guide catheter to engage the left main and right

coronary arteries. Right and left coronary arteriography was performed in multiple views by hand injections of iodixanol (Visipaque, GE Healthcare). Normal and abnormal vessels were classified based on the ISHLT recommended grading system for CAV (CAV0: not significant, CAV1: mild, CAV2: moderate, CAV3: severe) [15] to evaluate the extent and severity of CAV. Any patient with ISHLT grade 1 or higher was considered to be abnormal and designated in a group with CAV. Remaining patients were classified in the Non-CAV group.

Statistical analysis

All calculated values were expressed as mean ± SD. Median and quartile values were also calculated and expressed in box plot. *P* values were calculated for two-tailed *t*-test to draw statistical significance between two groups. Any *P* value less than 0.05 were considered statistically significant. The Pearson correlation coefficient (ρ) with 95% confidence interval (CI) was used to evaluate the correlation and the *P* value was calculated to see their significance by converting the ρ to a t-statistic with two-tailed analysis. The data distribution is presented in whiskers plots with the 25th to 75th percentiles while the midlines in the box represent the median values. All statistical analyses were performed using statistical software R (R Foundation for Statistical Computing, Vienna, Austria).

Results

Clinical characteristics

Clinical characteristics of the patients in both groups (CAV and NonCAV) are shown in Table 1. Based on clinical assessment, five patients had evidence of prior antibody-mediated rejection episode with two patients having had a second heart transplant. Two patients had also clinical SPECT MPI study in addition to dynamic ^{82}Rb-PET. There were three patients with a repeat dynamic ^{82}Rb-PET study within 12 months of SCA. For those patients with multiple ^{82}Rb-PET studies, only the data closest to the SCA were included in this study.

Of the twenty patients, eight had demonstrated evidence of ischemia, myocardial infarction or atherosclerosis of native coronary artery at the time of PET studies either in a clinical SPECT MPI or a dynamic ^{82}Rb-PET study evaluated cliniclally. Five patients had abnormal tracer distribution with defects of mild intensity while three with defects of severe intensity. Seven patients had angiographically significant CAV in at least one major coronary artery at the time of the PET study. One patient had ISHLT CAV grade 2 and the remaining patients with ISHLT CAV grade 1 disease. Three patients had cardiomyopathy, one with hypertrophic and two with ischemic. Two patients had documented evidence of viral disease after OHT while eight were treated for infection of some forms. The details are reported in Table 1.

Rate-pressure product (RPP)

In Fig. 1 we show a comparison of RPP at rest and stress for CAV and NonCAV patients. The resting mean RPP were 10,195 ± 1442 and 8246 ± 1025 while the stress mean RPP were 8989 ± 1348 and 8011 ± 1256 for CAV and NonCAV patients, respectively. The RPP at rest were significantly higher for patients with CAV than without CAV ($P = 0.002$) while this difference is insignificant for stress ($P = 0.11$). In both cases, the mean blood pressures were not statistically different in stress and rest (P = NS).

Estimation of MBF and CFR

In Fig. 2 we show the comparison between rest and stress MBFs (top row) and RPP-normalized MBFs (bottom row) for CAV and NonCAV patients along with their corresponding CFRs.

The mean territorial MBFs at rest and stress in Non-CAV patients were 1.17 ± 0.54 and 2.86 ± 1.17 ml/g/

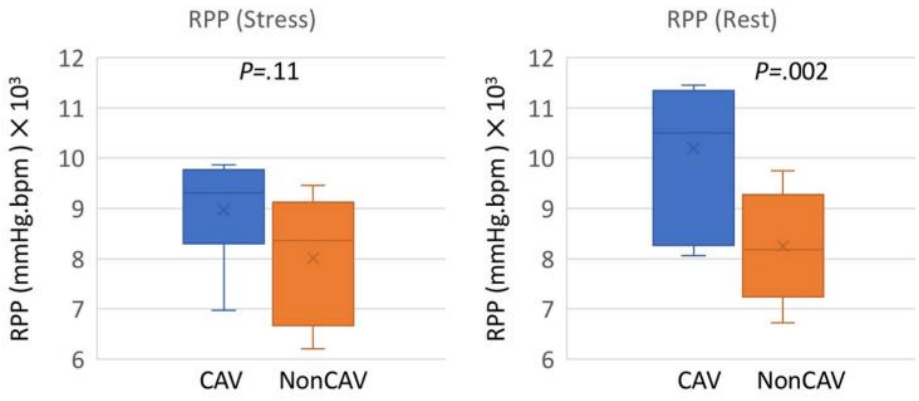

Fig. 1 Comparison of rate-pressure product (RPP) between patients with documented CAV and those without CAV (NonCAV) at rest and stress. The mean RPP was significantly higher for patients with CAV than without CAV for rest ($P = 0.002$) while the difference is not significant for stress ($P = 0.11$)

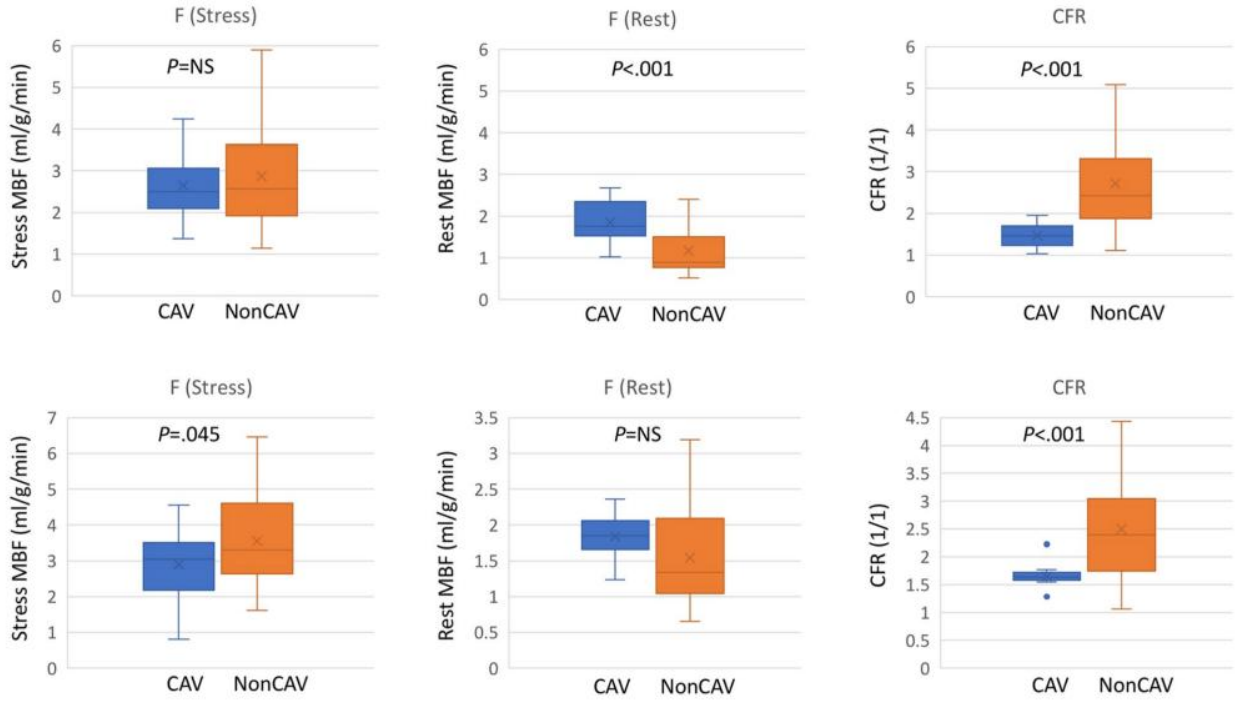

Fig. 2 (Top) stress MBF, rest MBF and CFR values for OHT patients with documented CAV (n = 7) and without CAV (n = 13) over three vascular territories (LAD, RCA, and LCx). CAV was classified based on the findings of SCA. There were significant differences in resting MBFs ($P < 0.001$) and CFRs ($P < 0.001$) between CAV and NonCAV patients while the difference was insignificant for stress MBFs ($P =$ NS). (Bottom) RPP-normalized stress MBFs, rest MBFs and calculated CFRs. There were significant differences in RPP-normalized stress MBFs ($P = 0.045$) and CFRs ($P < 0.001$) between CAV and NonCAV patients. However, RPP-normalized rest MBFs were not statistically different ($P =$ NS)

min averaged over three main coronary arteries (LAD, RCA, LCx), respectively. The corresponding CFR was 2.70 ± 1.18. Similarly, for patients with angiographically significant CAV, the mean territorial MBFs at rest and stress were 1.84 ± 0.57 and 2.64 ± 0.75 ml/g/min, and corresponding CFR was 1.46 ± 0.78. There were significant differences in resting MBFs ($P < 0.001$) and CFRs ($P < 0.001$) between CAV and NonCAV patients. However, mean stress MBFs were not statistically different ($P =$ NS).

The mean RPP-normalized MBFs at rest and stress in NonCAV patients were 1.53 ± 0.62 and 3.55 ± 1.31 ml/g/min, respectively while the mean RPP-normalized CFR was 2.49 ± 0.88. Similarly, for patients with CAV, the mean RPP-normalized MBFs at rest and stress were 1.84 ± 0.32 and 2.89 ± 0.94 ml/g/min, respectively, and the corresponding CFR was 1.64 ± 0.22. There were significant differences in RPP-normalized MBFs at stress ($P = 0.045$) between CAV and NonCAV patients while no statistically significant difference was observed at rest MBFs ($P =$ NS). Similarly, RPP-normalized CFRs were significantly lower in CAV compared to NonCAV patients ($P < 0.001$).

Correlation between MBF and RPP

In Fig. 3 we have plotted the estimated global MBF as a function of RPP for CAV (n = 7) and NonCAV (n = 13) patients. The rest MBFs were linearly correlated with the RPP for both CAV and NonCAV patient groups with the correlation coefficients ($\rho = 0.764$, $P = 0.047$) for CAV and ($\rho = 0.641$, $P = 0.017$) for NonCAV. There were no statistically significant correlations at stress both for CAV ($\rho = 0.232$, $P =$ NS) and NonCAV ($\rho = 0.068$, $P =$ NS) patient groups (Table 2).

Case example 1 (NonCAV)

In Fig. 4 we show an example myocardial perfusion image of a patient with no documented evidence of CAV (NonCAV) to add the potential diagnostic value of the quantitative measurement of MBF and CFR in heart transplant patient. The patient was 45 years old man with congenital dextrocardia and pulmonic stenosis, and ascending aortic aneurysm whose course was complicated by transplant rejection.

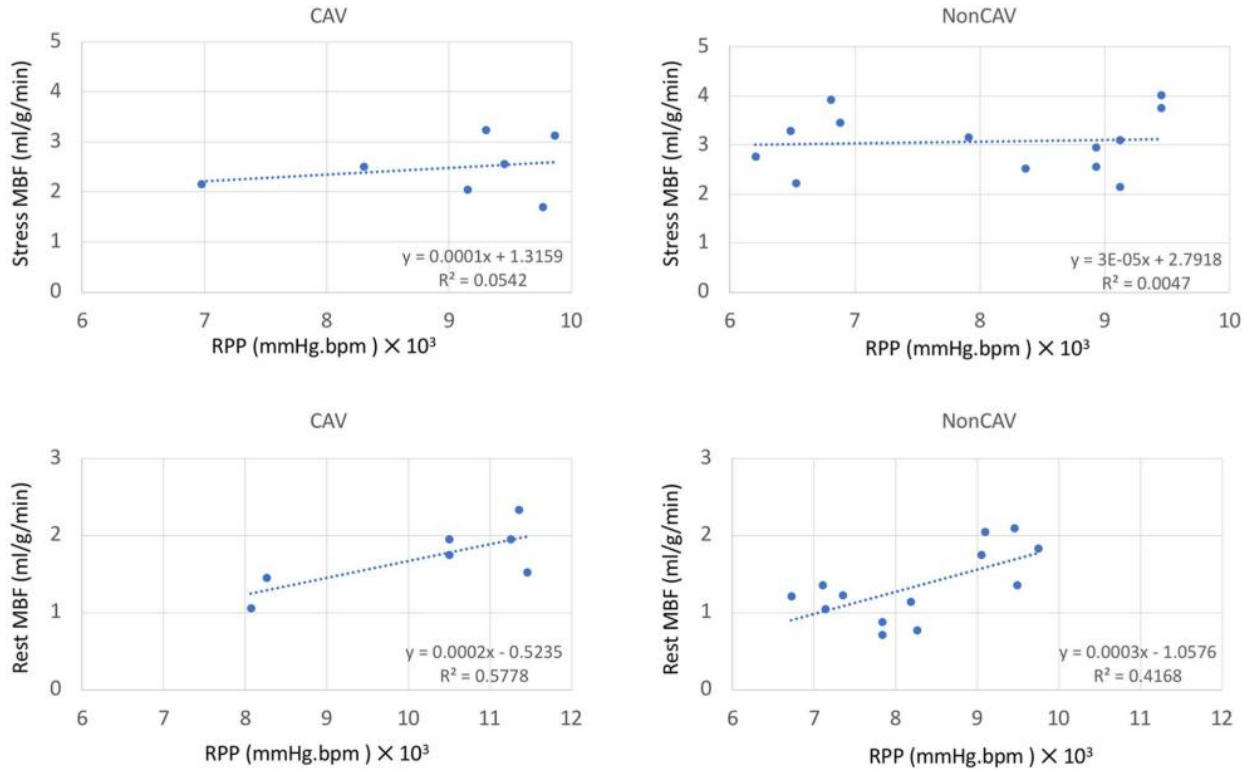

Fig. 3 Correlation between RPPs and global MBFs at rest and stress for CAV (n = 7) and NonCAV (n = 13) patients. There were significant correlations for both CAV (ρ = 0.764, $P = 0.047$) and NonCAV (ρ = 0.641, $P = 0.017$) patients groups at rest while there were no statistically significant correlations for CAV (ρ = 0.232, P = NS) and NonCAV (ρ = 0.068, P = NS) at stress

Table 2 Correlations between RPP and MBF

	Rest		Stress	
	CAV	NonCAV	CAV	NonCAV
ρ	0.764	0.641	0.232	0.068
ρ2	0.573	0.412	0.054	0.004
t-statistic	2.612	2.850	0.535	0.221
P value	0.047	0.017	0.613	0.823

The patient was evaluated in a clinical imaging study and underwent left and right heart catheterization for further diagnosis. The ^{82}Rb-PET clinical image analysis showed a small, subtle perfusion abnormality within the apex. However, the coronary angiogram showed no angiographically significant coronary artery disease in all vascular territories. The quantification of MBF and CFR was also performed on the data acquired dynamically. Both MBF and CFR were found to be within the normal range except there was a mild reduction in the stress MBF in the LAD region (Table 3), consistent with the finding of the clinical image analysis and SCA.

Case example 2 (CAV)

In Fig. 5 we show another case example of a patient with earlier diagnosis of CAV. An 81 years old man with a history of hypertension and on chronic immunosuppression underwent both ^{82}Rb-PET myocardial perfusion imaging and coronary angiogram. The clinical PET myocardial perfusion imaging showed a mild reversible defect in lateral and inferior walls. The patient also underwent coronary angiography which revealed that there was up to 40% stenosis in the proximal segment of the first diagonal branch of the LAD. The remainder of the LAD and its branches had luminal irregularities consistent with CAV. Similarly, LCx and RCA had the proximal to mid mild luminal irregularities with normal distal flow. The rest MBFs were elevated in LAD and RCA regions with reduced stress MBFs in LAD and LCx regions, and thus a significant reduction in CFRs (Table 4).

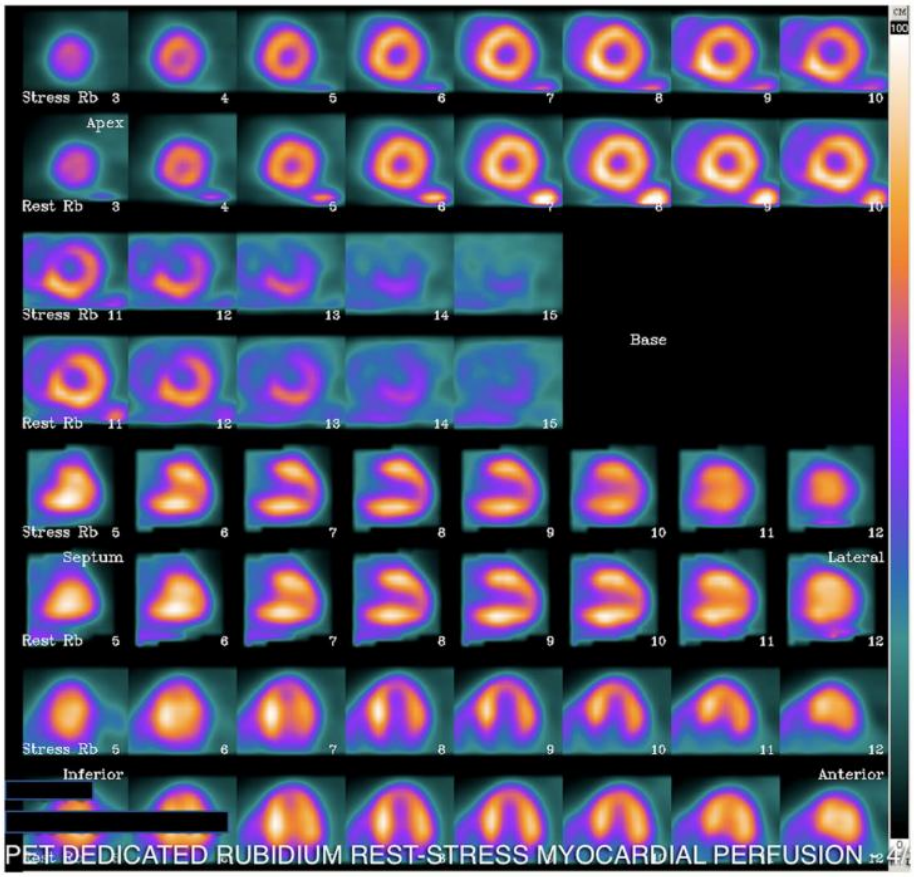

Fig. 4 Case example (Non-CAV): Myocardial perfusion image of a 45 years old male heart transplant patient with congenital dextrocardia and pulmonic stenosis, and ascending aortic aneurysm whose course has been complicated by transplant rejection, underwent rest/stress dynamic ^{82}Rb-PET study. The results showed abnormal perfusion near apical region. However, the coronary angiogram showed no angiographically significant coronary artery disease in all vascular territories

Table 3 Case example of MBF and CFR in a patient with no angiographically significant CAD (NonCAV)

	Rest MBF	Stress MBF	CFR
LAD	0.7122	2.1382	3.002
RCA	0.8757	3.1031	3.543
LCX	0.7199	3.1031	3.543

Table 4 Case example in a patient with angiographically significant coronary artery disease (CAV)

	Rest MBF	Stress MBF	CFR
LAD	1.4436	2.1497	1.488
RCA	2.3249	4.2409	1.823
LCX	1.0195	1.3675	1.341

Discussion

Uniqueness and significant findings of this current study

In the present study, we show that the resting MBF is higher in long-term post-OHT patients who develop CAV compared to those without CAV and the flow reserve is not augmented in the ratio of 2.0 or more due to impaired stress vasodilatory capacity. A number of previous studies have demonstrated that the resting MBF is elevated in OHT patients compared to control group (~ 1 ml/g/min) due to increased resting HR and RPP in the denervated heart [16]. An elevated level of resting heart rate may be due to the lack of sinus node parasympathetic control because of parasympathetic denervation [17]. This could be a driving factor for increased resting MBF.

As shown in an earlier study, quantification of MBF and CFR can provide improved detection and gradation of CAV severity over standard myocardial perfusion assessment [18]. This unique patient cohort demonstrated lower CFR indicative of distributed microvascular disease. The uniqueness of our study is that we have demonstrated the capability of assessing CAV in late-stage post-OHT patients by measuring MBF and CFR noninvasively using dynamic ^{82}Rb-PET.

Since there were no significant difference in the stress MBFs between CAV and nonCAV patients, one may argue that the reduced CFR in patients with CAV might be the result of increased rest MBF alone. However, there were significant differences in RPP-normalized MBFs at stress

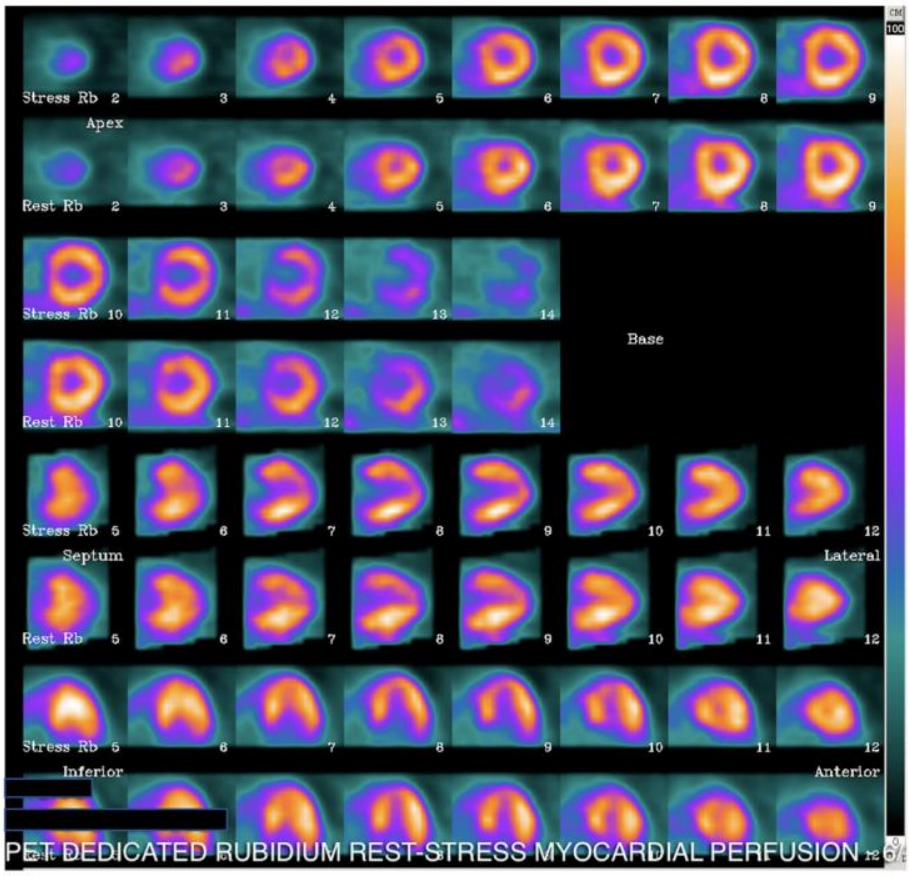

Fig. 5 Case example (CAV): myocardial perfusion image of an 81 years old heart transplant patient with a history of hypertension and on chronic immunosuppression, underwent rest/stress dynamic ^{82}Rb-PET study. The results showed mild perfusion abnormalities in the lateral and inferior walls. The coronary angiogram showed 40% stenosis in the first diagonal branch of the LAD with luminal irregularities in all three vascular territories

between CAV and NonCAV patients, while RPP-normalized MBFs at rest were not significantly different despite elevated rest flow compared to non-OHT patients [6]. This strongly suggests that the contribution to the reduction in the CFR is coming from both the elevated resting MBF and blunted response to stress due to lack of vasodilatory reserve. It was also suggested that a late term OHT rejection was associated with microvascular injury leading to a dramatic progression to severe CAV [19, 20]. We speculate that owing to the injuries to epicardial coronary subsystem of resistance vessels and endothelial damage at the time of transplant may be the cause of late term CAV-related flow abnormalities.

Conventional methods

Invasive methods such as SCA [3, 21] is generally good for identifying focal, eccentric narrowing of the vessel lumen [22] rather than diffuse longitudinal lesions as seen in CAV. IVUS [23–25] is considered to be superior to SCA for identifying early diffuse disease that are not picked up by the conventional SCA. Although SCA lacks sensitivity for early stage diagnosis of CAV due to vascular remodeling, it is still considered to be the established method for late-stage surveillance and monitoring of transplant vasculopathy as stated in the ISHLT 2010 consensus report [15]. Monitoring OHT patients with IVUS, in addition to coronary angiography, can increase the sensitivity for the detection of CAV [26, 27]. However, both of these invasive procedures are performed with the injection of intravenous contrast agent, and has shown to increase complications for high risks subgroups such as OHT patients [28, 29]. In addition to invasive methods, noninvasive dobutamine stress echocardiography (DSE) is also utilized to assess CAV [30].

Regional defects assessed by clinical SPECT/PET

There might be several confounding factors such as collateralization and cross-talks between regional segments that influence a correlation between flow and perfusion distribution regionally. There is a significant correlation between ischemia-induced left ventricular dysfunction and coronary blood flow during stress leading to a diminished CFR [31, 32]. In the case of subendocardial ischemia, more likely the subtended supplying vessels would have a reduced myocardial blood flow. In our study, 8 patients had demonstrated evidence of myocardial perfusion abnormalities at the time

of PET studies either in a clinical SPECT MPI or a dynamic ^{82}Rb-PET study assessed clinically, of which 5 patients had abnormal tracer distribution with defects of mild intensities while 3 with defects of severe intensities. In Table 5, we show the correlation of regional defects with MBF and CFR. Of 8 patients, 4 had CAV in SCA with reduced CFR globally, a conspicuous demonstration of diffuse nature of the disease.

Effect of RPP

RPP is a sensitive measure for myocardial oxygen utilization in the normal heart. There is a significant correlation between myocardial oxygen utilization and heart rate, and systolic blood pressure. In the transplanted heart, the extent of sympathetic reinnervation varies from patient to patient [33]. Generally, sympathetic reinnervation favors to a variable extent the anterior wall of the LV and thus introduces additional heterogeneity to MBF-RPP relationship [34] and thus fails to account for more fundamental alteration in the regulation of MBF with respect to the need of oxygen. For OHT patients with beta-blocker administration and immunosuppression drug like calcineurin inhibitors, the heart rate as well as resting blood pressure can be significantly elevated due to denervation. These factors might have caused the wide variability in our MBF results. In this study, the RPP normalized mean stress MBF and CFR were lower for CAV patients compared to nonCAV patients. There was a strong correlations between MBFs and RPP at rest while no statistically significant correlations were observed at stress in both CAV and NonCAV patients group, indicating of complete decoupling of vascular resistance [35].

Suitability of regadenoson to induce stress

In our recent study [6], we addressed the suitability of regadenoson to induce stress in a group of OHT patients using ^{13} N-ammonia PET and showed its safety and efficacy to generate the maximal hyperemia in OHT patients. Previous work also demonstrated the safe utilization of regadenoson as a vasodilator in this patient population [36]. In non-OHT patients, regadenoson shows quick vasodilatory response without having weight-based dosing or requirement of infusion. It can achieve maximal hyperemia within a minute after injection with short-lived hyperemic response [37]. Despite of hypersensitivity of the denervated sinus and atrioventricular nodes to adenosine and elevated risks of sinus arrest in OHT patients [38], our study did not observe any adverse side effects during the regadenoson-induced hyperemia. Unlike in non-OHT patients, as reported earlier [39], regadenoson can achieve only up to 80% of maximal hyperemia compared to dipyridamole, but there is no such comparative study in OHT patients.

Relation between OHT and mortality

In a recent study on the evaluation of the all-cause mortality rate of OHT patients [40], the mortality rate associated with lower values of blood flow normalized to rate-pressure product and CFR were increased several fold compared to normal CFR values. Unlike traditional CFR threshold of 2.0, this study used the threshold value of 1.5 between hemodynamic normal and abnormal, which can further increase the correlation between mortality rate and CFR reduction. A similar study showed an association of CAV severity with cardiovascular events following OHT [12].

Limitations

A small sample size, longer time between PET and SCA, wider variability in post-OHT time and wider variability in MBF are notable limitations of this study. The classification based on CAV grade (6 patients had angiographically significant mild CAV (ISHLT CAV grade 1) while only one patient had moderate CAV (ISHLT CAV grade 2)) may provide a gray zone for classification between normal and abnormal patients group and may produce an error in the

Table 5 Regional defects assessed by clinical SPECT/PET

Defects assessed by clinical SPECT/PET	Flow (LAD)			Flow (RCA)			Flow (LCX)			Flow (global)			SCA
Regional location—degree of ischemia	Stress	Rest	CFR	Stress	Rest	CFR	Stress	Rest	CFR	Stress	Rest	CFR	
Anterior and lateral walls (LAD + LCX)—mild	2.88	0.88	3.27	3.62	0.77	4.70	1.71	0.51	3.31	2.78	0.74	3.71	NonCAV
Lateral wall (LCX)—mild	3.44	1.35	2.55	1.97	1.50	1.31	2.28	0.83	2.74	2.67	1.24	2.15	NonCAV
Distal inferolateral wall (RCA + LCX) —severe	2.56	2.25	1.14	2.94	2.14	1.37	1.82	1.40	1.29	2.43	1.91	1.27	CAV
Basal inferolateral wall (RCA + LCX)—severe	2.50	1.95	1.28	2.55	1.75	1.45	2.02	1.70	1.18	2.37	1.82	1.30	CAV
Apical wall (LAD)—mild	2.13	0.71	3	3.10	0.87	3.54	1.54	0.71	2.15	2.26	0.76	2.97	NonCAV
Inferior wall (RCA)—mild	2.14	1.44	1.49	4.24	2.32	1.82	1.36	1.01	1.34	2.55	1.59	1.6	CAV
Anterior wall and apex (LAD)—severe	1.44	1.30	1.11	1.42	0.63	2.25	1.14	0.57	1.98	1.35	0.89	1.51	CAV
Lateral wall (LCX)—mild	2.52	1.20	2.1	4.24	0.89	4.74	2.29	1.11	2.06	2.98	1.08	2.75	NonCAV

interpretation of the results. In contradiction to recent published works [7, 8] that have shown a reduced stress MBF and thus a reduced CFR for patients with CAV, our study shows a blunted response to stress with elevated rest MBF and thus a reduced CFR for CAV patients.

CFR and RPP may be affected by patient's age and are considered to be the predictor of cardiovascular events [41]. In particular, patients with elevated risk factors associated to epicardial coronary artery disease and coronary microvascular dysfunction have shown an age-dependent reduction in CFR [42]. In another study, there was a significant increase in resting MBF and a reduction in CFR above a certain age (> 60 years) [43]. In our study, there is a significant difference in age between CAV and NonCAV patients group ($P = 0.047$) that might have contributed to the difference in RPP and CFR values. Due to a small patient population we were not able to differentiate how much contribution that age had played in the interpretation of our results. Moreover, it is a retrospective study and the selection biases might have played some role for the study design. Our patient's selection criteria were based on the duration between PET and SCA for all OHT patients irrespective of their cardiovascular outcomes that resulted in a disproportional population balance with n = 7 for CAV and n = 13 for NonCAV patient groups.

The microvascular injury, that may lead to a dramatic progression to severe CAV in long-term OHT [20], implies reduced vasodilatory response reflected in the reduced values of CFR. However, we did not perform an IVUS study to match CAV to CFR. We believe this would be a valuable future study.

Conclusions

Quantitative MBF and CFR assessed with PET imaging may have potential to detect diffuse arterial lesions affecting both the epicardial coronary arteries as well as the microvasculature following OHT. This study demonstrates the benefit of noninvasive methods of quantitative measurements of MBF and CFR for assessing CAV in long-term OHT patients. High resting MBF and blunted response to stress due to lack of vasodilatory reserve may be a noninvasive predictor of long-term CAV development in OHT and can be assessed noninvasively using dynamic ^{82}Rb-PET.

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Compliance with ethical standards

Conflict of interest The authors have no conflict of interest.

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