Does quantification of myocardial flow reserve using rubidium-82 positron emission tomography facilitate detection of multivessel coronary artery disease?

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Background. **Relative myocardial perfusion imaging (MPI) is the standard imaging approach for the diagnosis and prognostic work-up of coronary artery disease (CAD). However, this technique may underestimate the extent of disease in patients with 3-vessel CAD. Positron emission tomography (PET) is also able to quantify myocardial blood flow. Rubidium-82 (^{82}Rb) is a valid PET tracer alternative in centers that lack a cyclotron. The aim of this study was to assess whether assessment of myocardial flow reserve (MFR) measured with ^{82}Rb PET is an independent predictor of severe obstructive 3-vessel CAD.**

Methods. **We enrolled a cohort of 120 consecutive patients referred to a dipyridamole ^{82}Rb PET MPI for evaluation of ischemia neither with prior coronary artery bypass graft nor with recent percutaneous coronary intervention that also underwent coronary angiogram within 6 months of the PET study. Patients with and without 3-vessel CAD were compared.**

Results. **Among patients with severe 3-vessel CAD, MFR was globally reduced (<2) in 88% (22/25). On the adjusted logistic Cox model, MFR was an independent predictor of 3-vessel CAD [.5 unit decrease, HR: 2.1, 95% CI (1.2-3.8); $P = .015$]. The incremental value of ^{82}Rb MFR over the SSS was also shown by comparing the adjusted SSS models with and without ^{82}Rb MFR ($P = .005$).**

Conclusion. **^{82}Rb MFR is an independent predictor of 3-vessel CAD and provided added value to relative MPI. Clinical integration of this approach should be considered to enhance detection and risk assessment of patients with known or suspected CAD. (J Nucl Cardiol 2012)**

Key Words: Rubidium-82 PET • myocardial flow reserve • detection of multivessel disease • clinical utility

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INTRODUCTION

Standard relative myocardial perfusion imaging (MPI) is widely used for the assessment of patients with known or suspected coronary artery disease (CAD). This method is based on defining regional reductions in uptake relative to the maximum in the heart. Thus, it sometimes may only identify the territory supplied by the most severe coronary artery stenosis. As such, balanced reductions in myocardial blood flow (MBF), often present in patients with diffuse obstructive 3-vessel CAD, can lead to false negative results. This constitutes one of the principal shortcomings of standard relative MPI; a limitation that applies to both single photon emission tomography and positron emission tomography (PET).[1-8] In recent years, focus has turned toward implementation of methodologies able to provide

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additional information beyond standard relative MPI. As such, there is increasing interest in the wider application of PET and its advantages, including its ability to quantify MBF and myocardial flow reserve (MFR; the ratio of stress MBF/rest MBF) noninvasively and routinely.

It has been proposed that this approach may enhance detection of diffuse severe 3-vessel CAD.[1-3] Small studies have suggested quantitative estimates of tracer retention appeared promising.[6] However, to date, flow quantification per se, has not been evaluated in this regard, nor in the context of other high risk parameters on gated MPI. As such, MFR and MBF have not been widely integrated into clinical practice, although some centers are starting use these parameters clinically. There is limited data supporting incremental diagnostic utility of flow quantification in patients being assessed for myocardial ischemia. Nonetheless, recent data suggest an added prognostic value of MFR measured with ^{13}N-ammonia ($^{13}NH_3$)[9] beyond standard relative MPI. While $^{13}NH_3$ and Oxygen-15 water ($H_2^{15}O$) are well-established tracers used to quantify flow, they both require an on-site cyclotron for their production, hence cannot be broadly distributed. On the other hand, flow quantification using Rubidium-82 (^{82}Rb) PET, has been shown to be feasible, valid and reproducible.[10-13] As a generator product, ^{82}Rb can be distributed widely to sites without an in-house cyclotron. However, the limited data underscore the need for further investigation of the potential clinical value of ^{82}Rb PET flow quantification.

Our objective was to determine whether ^{82}Rb MFR is an independent predictor of 3-vessel CAD. In this way, we aimed to explore one end of the spectrum of coronary disease where flow quantification may be advantageous as a clinical parameter.

METHODS

Patient Population

A cohort of consecutive patients with known or suspected CAD who were referred for a dipyridamole ^{82}Rb PET MPI for the assessment of myocardial ischemia at the University of Ottawa Heart Institute (UOHI), Ottawa, Canada, between January 2008 to 2009 and that also have a recent (<6 months) coronary angiogram were included. All patients provided written informed consent for inclusion in the study.

Patients were excluded if they did not have absolute MBF data available because dynamic acquisition was not acquired or due to other technical factors (n = 4) including: incomplete time-activity curve (TAC) acquisition due to late scan start, or patient motion during the scan resulting in suboptimal fitting of the model to the TAC data.[14] Patients who underwent Dobutamine or exercise PET and/or $^{13}NH_3$ PET were also excluded. Patients with a history of coronary artery bypass graft (CABG) surgery and/or recent (<6 months) percutaneous coronary intervention (PCI) or an inter-current event between PET and the angiogram were excluded from the analysis. For those with more than one ^{82}Rb PET scan during the enrollment period, only the first scan was utilized.

A cohort of 120 patients had known coronary anatomy and met inclusion and exclusion criteria.

PET Imaging

Patients refrained from caffeine-containing beverages ≥12 hours and theophylline containing medications for >48 hours before the MPI study, as per ASNC guidelines.[14-16] Antianginal medications were withheld on the morning of the test. After an overnight fast, all patients were positioned in a 3D PET system (GE Discovery Rx/VCT).[17] After a scout scan to confirm proper positioning, a low-dose (~.5 mSv), fast helical (1.5 s) CT scan (120 kpv with axial and angular mA modulation at noise-index = 50) was acquired at normal end-expiration for attenuation correction. Immediately following, 10 MBq/kg of ^{82}Rb was administered intravenously over 30 seconds using an in-house developed ^{82}Rb elution system.[18] A 17 frame, 10 minute, dynamic ^{82}Rb scan was acquired (12 × 10, 2 × 30, 1 × 60, 1 × 120, 1 × 240 second, total = 10 minute) with a parallel list-mode acquisition at rest.

Pharmacological stress testing and imaging. Following rest PET MPI, a dipyridamole stress test was performed (.14 mg/kg/minute over 5 minute). Ten MBq/kg of ^{82}Rb was infused 3 minute after completion of the vasodilator infusion. Stress images were acquired using the identical protocol as the rest MPI. A repeat low-dose CT scan was acquired following the stress images for attenuation correction as described for the rest study.

Image processing. PET images were reconstructed using Fourier rebinning and filtered back-projection with a 12-mm 3D Hann window of the ramp filter. Automatic reorientation of the images into short-axis sections, as well as automatic extraction of mean myocardial and cavity TAC[19] and generation of polar maps of absolute MBF and MFR were performed using our FlowQuant© software (UOHI, Ottawa, Canada).

ECG-gating. The list-mode data from 2.5-10 minute were replayed to reconstruct ECG-gated images (8 bins/cycle). LV ejection fractions were determined using 4DM software (INVIA, Ann Arbor, Michigan).

Data Analysis

^{82}Rb PET static image interpretation. Images were interpreted semi-quantitatively using a standard 17-segment model[20] and a 5-point scoring system blinded to clinical, imaging and flow data. Images were read by an experienced blinded observer; then independently compared to the clinical imaging report. If there were any discrepancies between the two readers, images were then reviewed by a third reader. Further discrepancies were settled by consensus. The global summed stress score (SSS), summed rest score (SRS), and summed difference score (SDS = SSS − SRS) were calculated. A scan was considered abnormal if the SSS was ≥4.[9,21] The left ventricular end diastolic volume (LVEDV), LV end

systolic volume (LVESV), LVEF during rest and stress, and LVEF reserve (stress-rest LVEF)[22,23] were determined. The presence or absence of transient ischemic dilatation (TID) on visual analysis was also noted.

We defined the presence of ''high risk imaging features'' as the presence of *any* of the following: positive ischemic ECG response during dipyridamole infusion, presence of visual TID, reduced LVEF reserve.

^{82}Rb flow quantification. MBF was quantified using a one-tissue compartment model with a flow-dependent extraction correction, as described by Lortie et al.[12] In this study, the washout rate was expressed as $k_2 = K_1/DV$, where DV represents the distribution volume of ^{82}Rb in myocardial tissue. DV was set to a constant value[24] for each scan by fitting the model to the region of highest uptake.

Polar-maps representing rest flow, stress flow, MFR (stress/rest) and myocardial flow difference (MFD) (stress-rest)[6] were generated using FlowQuant©. A global MFR <2.0 was considered abnormal, as previously recommended and applied.[1,9] Flow data were not available for review with the clinical reports of the perfusion scan.

ECG analysis. Stress ECGs were reviewed and interpreted by blinded observers in the same manner as relative MPI noted above and using recommended practice guidelines.[25]

Coronary Angiographic Data

Severe 3-vessel CAD was defined visually as a diameter stenosis of the LM ≥ 50% + proximal or mid segments of RCA ≥ 70%; or, proximal or mid segments of the RCA, LAD, and LCX ≥ 70% stenosis.

Statistical Analysis

Continuous measures are presented as means ± standard deviations (SD). Categorical measures are presented as frequencies with percentages (%) (Table 1).

Table 1. Baseline patient characteristics

Variable	n = 120
Age, mean (±SD)	63 (±12)
Male, n (%)	88 (73)
Hypertension, n (%)	81 (67.5)
Diabetes mellitus, n (%)	37 (31)
Smoking, n (%)	82 (68)
Hypercholesterolemia, n (%)	89 (74)
Family history of CAD, n (%)	59 (49)
Known CAD, n (%)	77 (64)
Angina (CCS ≥ II), n (%)	66 (55)
Dyspnea (NYHA ≥ II), n (%)	34 (28)

CAD, Coronary artery disease; *CCS*, Canadian Cardiovascular Society; *NYHA*, New York Heart Association

For the univariate comparison of patients with and without 3-vessel CAD (Table 2), univariate logistic regressions of this outcome with each variable were performed. Multivariable logistic regression was performed to assess the combined effect of SSS and MFR as continuous variables adjusted for potential confounders. To prevent overfitting of the model, variables were considered with SSS or MFR individually first. Any variables with $P < .1$ included with SSS or MFR in the model were then considered in the development of an initial adjusted model for SSS without MFR resulting in diabetes mellitus (DM), family history of CAD, and age being included with SSS (Table 3). MFR was added to this model in order to illustrate its incremental value. Although the sample size of 120 may be small, it is powered to detect the effect of SSS and MFR on 3-vessel CAD with only these three other variables considered in the adjustment.[26] To show the incremental value of MFR over SSS, the adjusted model with SSS + MFR was compared to the model with SSS only using a likelihood ratio Chi-squared test. The % of information values were calculated using the individual predictors' Wald Chi-squared statistics. The unadjusted model-predicted probabilities of severe 3-vessel CAD were plotted against MFR.

A P value <.05 was considered statistically significant. Statistical calculations were carried out using SAS software (Copyright, SAS Institute Inc. SAS and all other SAS Institute Inc. product or service names are registered trademarks or trademarks of SAS Institute Inc., Cary, NC, USA).

RESULTS

A total of 193 consecutive patients with recent invasive coronary angiogram were considered for inclusion. Among these, 33 were excluded from analysis having had previous CABG; 40 were excluded because of recent PCI. None of the remaining patients had had intercurrent events. Thus, 120 patients with known anatomy were available to include in the analysis. Table 1 shows the baseline patient characteristics.

Comparison of Patients With and Without 3-Vessel CAD

Among 120 patients with coronary anatomy, 25 (21%) patients had severe 3-vessel CAD (Table 2). Compared to patients without 3-vessel CAD, patients with 3-vessel CAD were older, more often had a family history of CAD, had increased SSS, reduced stress EF, and more often had TID. There were trends for more hypertension, known history of CAD, positive ECG and LVEF reserve response. However, ten out of these 25 patients (40%) did not have any high risk imaging features (i.e., positive ECG response, TID, or reduced LVEF reserve); and of note, 9 of these 10 (90%) had reduced MFR. Overall, 88% (22/25) of patients with 3-vessel CAD had globally reduced MFR, stress MBF, and MFD. MFR was significantly reduced in 3-vessel

Table 2. Comparison of patients with and without 3-vessel CAD

Variables	No3V-CAD (n = 95)	3V-CAD (n = 25)	*P*
Age, mean (SD)	61 ± 11	69 ± 10	.003
Male, n (%)	71 (74)	17 (68)	ns
Hypertension, n (%)	60 (63)	21 (84)	.06
Hyperlipidemia, n (%)	70 (74)	19 (76)	ns
Diabetes mellitus, n (%)	26 (27)	11 (44)	ns
Smoking, n (%)	64 (67)	18 (72)	ns
Family history of CAD, n (%)	42 (44)	17 (68)	.04
Known CAD, n (%)	65 (68)	12 (48)	.06
Angina (CCS ≥ II), n (%)	52 (55)	14 (56)	ns
Dyspnea (NYHA ≥ II), n (%)	26 (27)	8 (32)	ns
+ECG response, n (%)	21 (22)	10 (40)	.07
SSS, mean (SD)	7.1 ± 6.6	11.5 ± 7.8	.008
TID, n (%)	12 (13)	8 (32)	.03
Stress LVEF, mean (SD)	57 ± 14	48 ± 16	.005
Stress LVEF < 50%, n (%)	25 (26)	15 (60)	.002
LVEF reserve, mean (SD)	4.8 ± 9	.6 ± 11	.06
LVEF reserve < 0%, n (%)	22 (23)	9 (36)	ns

CAD, Coronary artery disease; *CCS*, Canadian Cardiovascular Society; *ECG*, electrocardiogram; *LVEF*, left ventricular ejection fraction; *LVEF reserve* (stress-rest LVEF); *MI*, myocardial infarction; *ns*, not significant; *NYHA*, New York Heart Association; *PCI*, percutaneous coronary intervention; *SSS*, summed stress score; *TID*, transient ischemic dilatation; *3V*, three vessel

Table 3. Multivariable logistic models for predicting severe 3-vessel CAD

Model	Variable	*P*	% of information	Deviance statistic
Baseline + SSS	Age	<.001	36.9	89.205
	SSS	.002	26.7	
	Family Hx of CAD	.003	24.4	
	DM	.036	11.9	
Baseline + SSS + MFR	Family Hx of CAD	.006	30.4	81.36*
	Age	.012	25	
	MFR	.015	23.8	
	SSS	.11	10.2	
	DM	.104	10.5	

DM, Diabetes mellitus; *Hx*, history; *MFR*, myocardial flow reserve; *SSS*, summed stress score
* Likelihood ratio Chi-squared test $P = .005$

CAD patients compared to those without 3-vessel CAD (1.3 ± .5 vs 2.2 ± .9, $P < .001$) (Figure 1).

Incremental Value of ^{82}Rb MFR over SSS to Predict Severe 3-Vessel CAD

The multivariable analysis to assess the importance of the MFR as an independent predictor of severe 3-vessel CAD controlling for baseline patient characteristics and SSS is summarized in Table 3. In the model without MFR, SSS, DM, age, and family history of CAD were independent predictors of 3-vessel CAD. When ^{82}Rb PET MFR was added into the model, MFR was an independent predictor ($P = .015$) after controlling for the significant covariates age, DM and family history of CAD. Table 3 also notes the significant difference in the deviance statistics for the two models (Likelihood Ratio Chi-squared Test $P = .005$) indicating a better model fit with MFR and an incremental value of MFR to define 3-vessel CAD. Of the remaining variables, the strongest predictors were age, family history, and MFR. This analysis suggests that MFR is a stronger predictor of 3-vessel CAD after

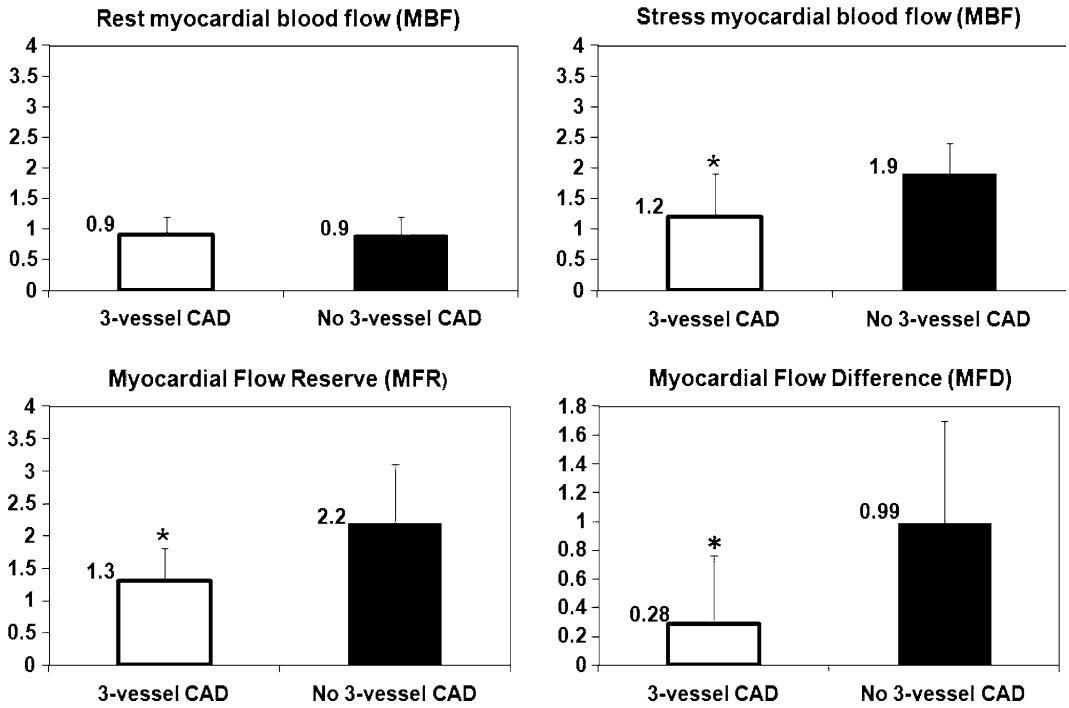

Figure 1. Comparison between patients with and without 3-vessel CAD. There were no statistically significant differences in rest MBF among the 2 groups. However, stress MBF, MFR, and MFD were significantly reduced in patients with 3-vessel CAD (*black asterisks*) ($P < .001$).

considering confounders. A .5 unit reduction in MFR, increases the likelihood of 3-vessel CAD by 2.1 times (95% CI: 1.2-3.8) ($P = .015$). Other parameters such as ECG response, TID, stress LVEF, and LVEF reserve were tested in the model but showed no statistical significance to independently predict 3-vessel CAD when considered with MFR and SSS. Figure 2 demonstrates the unadjusted likelihood of significant obstructive 3-vessel CAD in relation to global MFR. In the setting of preserved global MFR (≥ 2) the probability of severe 3-vessel CAD is low. As global MFR becomes progressively reduced to moderate or severe levels (for example to values of ~ 1.5 or ~ 1.0 respectively), the likelihood of 3-vessel CAD progressively increases (Point estimates for MFR = 2.0, 1.5, and 1.0 from Figure 2 are 11%, 25%, and 48% respectively).

If one considers the sensitivity and specificity of MFR alone for 3-vessel disease at different cut-points of 2.0, 1.5, 1.0, the values are 88.51%, 80.74%, 36.96%, respectively. This indicates that at normal flow reserves the parameter is very sensitive and for severe reductions in flow it is very specific. The *c* statistic is .817 which indicates excellent discrimination with the MFR. The SSS *c* statistic is significantly lower at .679 ($P = .018$). Figure 3 shows the ROC curves for the unadjusted MFR and SSS models. Figures 4 and 5 illustrate patient examples.

DISCUSSION

Our results show that among patients with obstructive 3-vessel CAD, most of them (88%) had reduced ^{82}Rb MFR. This data suggests that a preserved ^{82}Rb MFR makes the presence of 3-vessel CAD very unlikely; while a progressive reduction in ^{82}Rb MFR predicted an increasing likelihood of 3-vessel CAD. ^{82}Rb MFR is a strong predictor of 3-vessel disease and a better predictor than standard relative MPI, as assessed by SSS. Also of note in this study, other high risk imaging parameters were often not present in these high risk patients. This underscores the need for additional ''more sensitive'' parameters to facilitate detection of 3-vessel CAD. This data support that MFR quantified with ^{82}Rb PET is effective adjunct to the detection of 3-vessel CAD. This may yield incremental value beyond relative MPI.

Camici and Crea[1] have proposed clinical applications for PET quantification of flow and MFR. Still, the clinical value of these parameters in CAD has not been widely studied. $^{13}NH_3$ and $H_2^{15}O$ have been widely applied for flow quantification, but these tracers are much less accessible due to the requirement for an on-site cyclotron production. ^{82}Rb can be applied in centers without cyclotron capabilities. It should be mentioned that, though, ^{82}Rb has limitations for flow quantification

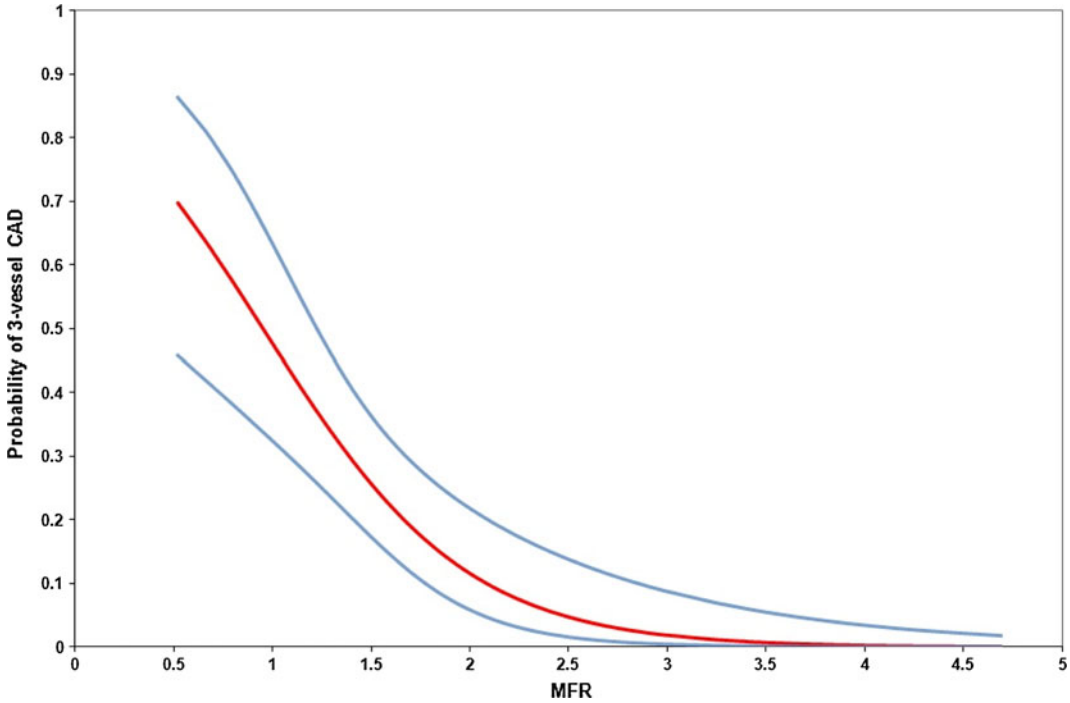

Figure 2. Unadjusted predicted probability (*red line*) and 95% confidence interval (*blue lines*) of severe 3 vessel CAD at various levels of ^{82}Rb PET MFR based on the analysis model. When MFR is preserved, the likelihood of multivessel CAD is low, whereas with reducing MFR the likelihood of 3-vessel CAD increases. *MFR*, Myocardial flow reserve.

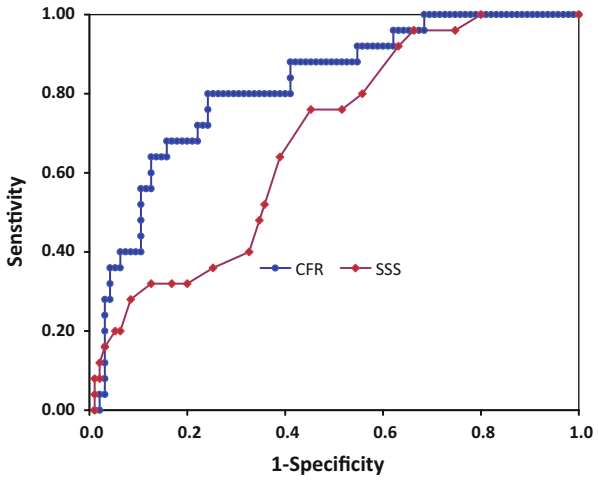

Figure 3. 3-vessel CAD: ROC curves are shown for unadjusted MFR and SSS and are significantly different ($P = .018$).

including its lower extraction fraction, which may affect the precision at hyperemic flow rates; its higher positron range that can reduce image resolution; and its short half life (76 seconds) for imaging perfusion and function in patients with decreased LV function. Until recent years, quantitative approaches with ^{82}Rb have been limited. However, owing to continued improvements in technology, several groups have now demonstrated that quantitative ^{82}Rb PET in humans is feasible, accurate, and reproducible[11-13] and has been validated against microspheres in animal models of CAD.[10] Also, routine list-mode acquisition and simultaneous flow quantification with other traditional MPI parameters is possible, which facilitates quantitative analysis.[2,3] Previous research studies have suggested the potential for quantitative estimation of myocardial perfusion using ^{82}Rb retention measurements,[6] but were small cohorts. In contrast to the current study, the prior study included fewer patients without 3-vessel CAD; did not employ absolute flow quantification per se but rather estimated perfusion by measuring tracer retention; did not use PET/CT and did not consider LV function nor other high risk parameters.

More recently, the use of $^{13}NH_3$ PET to measure MFR in patients with known or suspected CAD has been evaluated. Tio et al[27] demonstrated that among patients with significant LV dysfunction (mean LVEF = 36%), those with MFR <1.49 had worse survival. However, this was a sicker population than the current study. In another study, Herzog et al[9] demonstrated an incremental prognostic value of MFR <2.0 (the value used in the current study to define abnormal MFR) to predict adverse outcomes over standard relative MPI. However

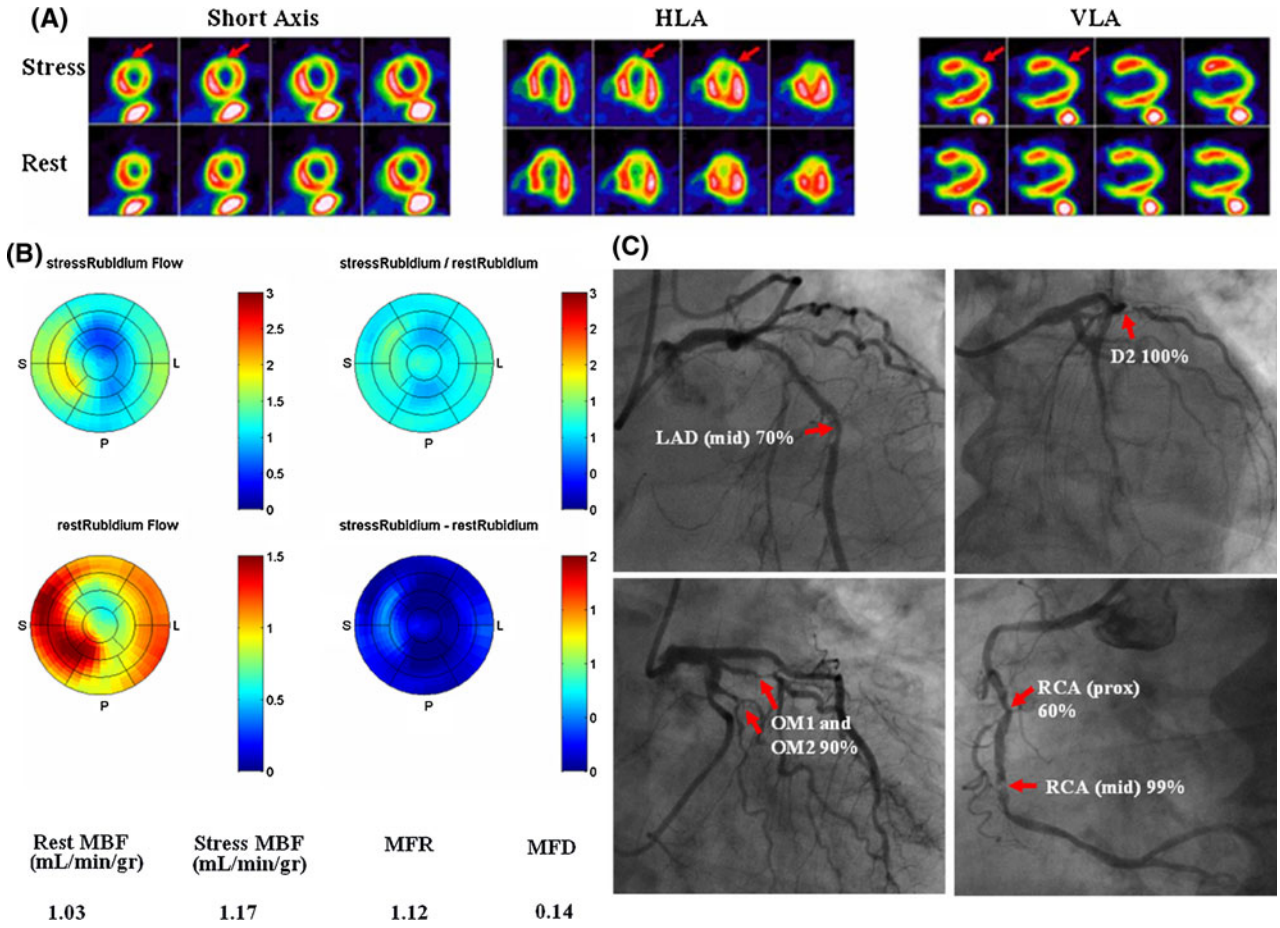

Figure 4. Clinical example. A 70-year-old female with multiple CAD risk factors and dyspnea with exertion: (**A**) dypiridamole ^{82}Rb PET MPI static images demonstrate a small area of mild ischemia in the LAD territory (*red arrows*); (**B**) 17-segment model polar maps of rest MBF (*lower left*; color display scale 0-1.5 ml/min/g), stress MBF (*upper left*; scale: 0-3.0 ml/min/g), MFR (*upper right*; scale: 0-3.0), and MFD (*lower right*; scale: 0-2.0) which demonstrate severe global impairments, absolute values displayed in the table below; (**C**) coronary angiogram reveals significant obstructive 3-vessel CAD (*arrows* point out significant stenosis). *HLA*, Horizontal long axis; *SA*, short axis; *VLA*, vertical long axis; *MBF*, myocardial blood flow; *MFR*, myocardial flow reserve; *MFD*, myocardial flow difference.

both of these studies used $^{13}NH_3$, which is not as practical for widespread use as ^{82}Rb. Kajander et al,[28] demonstrated the role of flow quantification using in 104 patients with moderate pre-test likelihood of CAD. ^{15}O-Water is used in some European centers but is not widely used in North America.

Clinical Implications

MFR quantified with ^{82}Rb PET in the evaluation of multivessel CAD. Previously, it has been demonstrated that perfusion defects diagnostic of multivessel CAD are apparent in only one third of these patients.[5] Berman et al[4] observed that approximately 40% of patients with ≥50% LM stenosis have low-risk scan findings based on standard relative MPI alone. Dorbala et al[22] showed that an increase of LVEF reserve ≥5% yields a high negative predictive value to exclude 3-vessel CAD. These studies emphasize the importance of considering data beyond relative MPI. The current study extends this further to the consideration of MFR as a potential parameter to enhance detection of 3-vessel disease. Recently, there has been a renewed interest in translation of quantitative flow and MFR using PET from the research realm to routine clinical practice. With the increasing availability of PET, there is growing potential for wide application of this measurement.

Our results demonstrate that in a cohort of patients referred for evaluation of ischemia and coronary anatomy, patients with 3-vessel CAD had significantly reduced ^{82}Rb MFR compared to those without. The degree of MFR impairment parallels the severity of

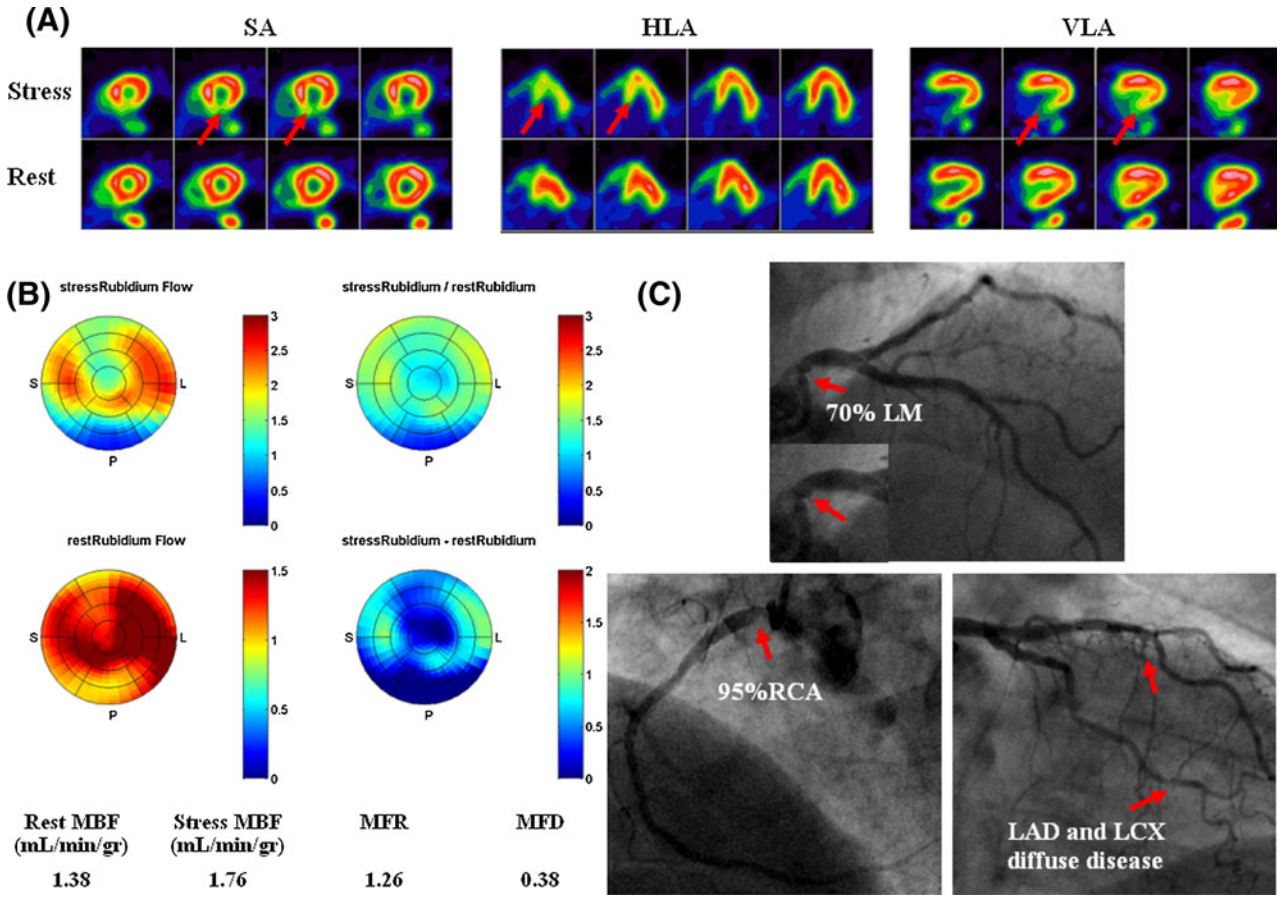

Figure 5. Representative case of a recruited patient. A 70-year-old male with hypertension, PVD, renal insufficiency, worsening angina with exertion: (**A**) dipyridamole ^{82}Rb PET MPI static images demonstrate moderate ischemia in the RCA territory (*red arrows*); (**B**) 17-segment model polar maps of rest flow (*lower left*; color display scale 0-1.5 ml/min/g), stress flow (*upper left*; scale: 0-3.0 ml/min/g), MFR (*upper right*; scale: 0-3.0) and MFD (*lower right*; scale: 0-2.0) with several global reduction in MFR; (**C**) coronary anatomy showed severe LM stenosis and critical ostial RCA with diffuse CAD in LAD and LCX (*arrows* point out significant stenosis). Relative MPI underestimated CAD in LM territory. *HLA*, Horizontal long axis; *SA*, short axis, *VLA*, vertical long axis; *MBF*, myocardial blood flow; *MFR*, myocardial flow reserve; *MFD*, myocardial flow difference.

underlying anatomic disease. Previous data suggests that quantitative estimations of perfusion using ^{82}Rb retention measurements may be useful in defining severe obstructive multivessel disease.[6] The present study extends this work to MBF and MFR quantification using 3D mode PET/CT combined with MPI and gated measurements of LV function. In the current study 40% of patients with 3-vessel CAD had none of the generally accepted high risk findings (ischemic ECG changes, TID, and LVEF reserve <0%). Among those without these findings, 90% had impaired MFR. It has been recognized that high risk parameters provide high specificity to diagnose multivessel CAD but rather low sensitivity.[29,30] MFR using ^{82}Rb PET appears to be a more sensitive tool. Thus, while high risk parameters may point to multivessel disease,[22,29] when they are absent, MFR may be very useful at identifying such patients with 88% sensitivity in our study.

In the multivariable analysis, MFR demonstrated independent predictive value for 3-vessel CAD (Table 3). Adding MFR to the model improved the fit of the model supporting the added value of this approach and that MFR was a more effective tool than SSS for predicting 3-vessel CAD.

Also, a preserved MFR makes the presence of 3-vessel CAD very unlikely, while a progressive reduction in MFR predicts an increasing likelihood of 3-vessel CAD. Although other factors are known to adversely affect MFR (ie, microvascular disease due to risk factors, left ventricular hypertrophy, hypertension,

among others),[1,31] the current study suggests that when MFR is severely impaired, the diagnosis of 3-vessel CAD should be considered. These data support the added value of MFR with ^{82}Rb PET MPI. Integration of MFR with clinical imaging could help optimize the detection of 3-vessel obstructive CAD.

The current study used only perfusion imaging and flow quantification so did not incorporate any anatomical or coronary artery calcification (CAC) data with the PET imaging. Various researchers are exploring the use of MBF in combination with CT data (CAC or angiography) using hybrid PET/CT devices,[32] True integration of coronary anatomic and functional information in a single setting may be attractive and provide an in-depth insight of the level of CAD. Specifically, it may help to differentiate whether a reduction in MFR is due to 3-vessel CAD vs microvascular disease as may occur in the presence of cardiovascular risk factors.[28] However, whether or not a single study or a stepwise approach is the most cost effective strategy for functional and anatomic evaluation requires further evaluation.

Study Limitations

As with other studies comparing MPI to coronary anatomy, there may be a referral bias in patients for invasive coronary angiography following standard relative PET MPI (but this was not the case for MFR as this was not available at the time of clinical interpretation and not used to decide management). The sample size of this patient cohort with recent angiography is modest. While this study was large enough to demonstrate the incremental value of MFR to a model which included SSS and selected baseline parameters, it is possible that a larger study may have further unveiled the added value with other imaging parameters such as TID and LVEF which were not significant in this study. Therefore, the association of MFR with 3-vessel CAD in the adjusted model should be confirmed in a larger prospective trial.

A significant percentage of our population had known CAD and symptoms which could have increased the likelihood of obstructive CAD. Additional prospective studies assessing the role of MFR in patients without known CAD are under way.

This study focused on global rather than regional MFR. Regional flow measurements have demonstrated diagnostic value and can be linked to specific coronary stensosis[28,33] but there can be wider variability compared to relative MPI data.[6] Global MFR has been shown to provide prognostic value[9] but regional flow has not. Global MFR measurement enables the detection of early diffuse microvascular disease as well as severe 3-vessel disease, the latter being the focus of the current study. These two areas are where standard relative MPI and regional measurements may have important limitations. In addition, regional flow evaluation is often segmental rather than patient based whereas global flow is by definition patient based. In light of these considerations, the current study focused on global flow measurements.

MFR was not used in clinical interpretation which helped to reduce bias but this fact and the sample size did not enable analysis of the role of MFR in guiding intervention or therapy. Future studies should address this potential role of MFR measurements.

Finally, it is important to consider some drawbacks of quantitative analysis. The results of this study indicate that this method at a cut-point of MFR < 2.0 is sensitive but less specific for 3-vessel CAD. This is likely because there are a number of factors that could affect MFR measurements including concomitant conditions that may impair vascular reactivity. As such, from a clinical perspective, flow quantification should not be considered in isolation. Instead, its role will likely be to compliment data obtained from standard relative perfusion and functional imaging parameters. As flow reserve reduces, the clinician should consider that 3-vessel disease may be present with increasing likelihood. When it is severely reduced, 3-vessel disease becomes more likely. However, when MFR is normal, the likelihood of 3-vessel disease is low.

CONCLUSIONS

Impaired MFR quantified with ^{82}Rb PET is an independent predictor of severe 3-vessel CAD and more effective than standard relative MPI in this regard. A preserved ^{82}Rb MFR makes the presence of 3-vessel CAD unlikely. Conversely, with progressive reductions in MFR the likelihood of 3-vessel CAD increases. Integration of quantitative flow analysis with standard relative ^{82}Rb PET MPI could help to improve detection of 3-vessel CAD. Whether this approach can assist in risk stratification requires further study.

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Conflict of interest

RdK, JR, and RK receive revenue shares from the sale of FlowQuant, the analysis software used in the study. RB, RdK,

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