

# Comparison of two software systems for quantification of myocardial blood flow in patients with hypertrophic cardiomyopathy

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**Background.** Quantification of myocardial blood flow (MBF) by positron emission tomography (PET) is important for investigation of angina in hypertrophic cardiomyopathy (HCM). Several software programs exist for MBF quantification, but they have been mostly evaluated in patients (with normal cardiac geometry), referred for evaluation of coronary artery disease (CAD). Software performance has not been evaluated in HCM patients who frequently have hyperdynamic LV function, LV outflow tract (LVOT) obstruction, small LV cavity size, and variation in the degree/location of LV hypertrophy.

**Aim.** We compared results of MBF obtained using PMod, which permits manual segmentation, to those obtained by FDA-approved QPET software which has an automated segmentation algorithm.

**Methods.** <sup>13</sup>N-ammonia PET perfusion data were acquired in list mode at rest and during pharmacologic vasodilation, in 76 HCM patients and 10 non-HCM patients referred for evaluation of CAD (CAD group.) Data were resampled to create static, ECG-gated and 36-frame-dynamic images. Myocardial flow reserve (MFR) and MBF (in ml/min/g) were calculated using QPET and PMod softwares.

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**Results.** All HCM patients had asymmetric septal hypertrophy, and 50% had evidence of LVOT obstruction, whereas non-HCM patients (CAD group) had normal wall thickness and ejection fraction. PMod yielded significantly higher values for global and regional stress-MBF and MFR than for QPET in HCM. Reasonably fair correlation was observed for global rest-MBF, stress-MBF, and MFR using these two softwares (rest-MBF:  $r = 0.78$ ; stress-MBF:  $r = 0.66$ ; MFR:  $r = 0.7$ ) in HCM patients. Agreement between global MBF and MFR values improved when HCM patients with high spillover fractions ( $> 0.65$ ) were excluded from the analysis (rest-MBF:  $r = 0.84$ ; stress-MBF:  $r = 0.72$ ; MFR:  $r = 0.8$ .) Regionally, the highest agreement between PMod and QPET was observed in the LAD territory (rest-MBF:  $r = 0.82$ , Stress-MBF:  $r = 0.68$ ) where spillover fraction was the lowest. Unlike HCM patients, the non-HCM patients (CAD group) demonstrated excellent agreement in MBF/MFR values, obtained by the two softwares, when patients with high spillover fractions were excluded (rest-MBF:  $r = 0.95$ ; stress-MBF:  $r = 0.92$ ; MFR:  $r = 0.95$ ).

**Conclusions.** Anatomic characteristics specific to HCM hearts contribute to lower correlations between MBF/MFR values obtained by PMod and QPET, compared with non-HCM patients. These differences indicate that PMod and QPET cannot be used interchangeably for MBF/MFR analyses in HCM patients. (J Nucl Cardiol 2019;26:1243–53.)

**Key Words:** Hypertrophic cardiomyopathy • myocardial blood flow • N-13 Ammonia PET • quantitative analysis

#### Abbreviations

HCM	Hypertrophic cardiomyopathy
PET	Positron emission tomography
MBF	Myocardial blood flow
MFR	Myocardial flow reserve
LAD	Left anterior descending coronary artery
RCA	Right coronary artery
LCx	Left circumflex coronary artery
LV	Left ventricle
FDA	Food and drug administration
CT	Computerized tomography
MBq	Megabecquerel
mCi	Millicurie
EKG	Electrocardiography
GE	General Electric
ROI	Region of interest
LVOTG	Left ventricular outflow tract gradient
SDS	Summed difference score
LVCD	Left ventricular cavity dilation
LVEF	Left ventricular ejection fraction
SD	Standard deviation

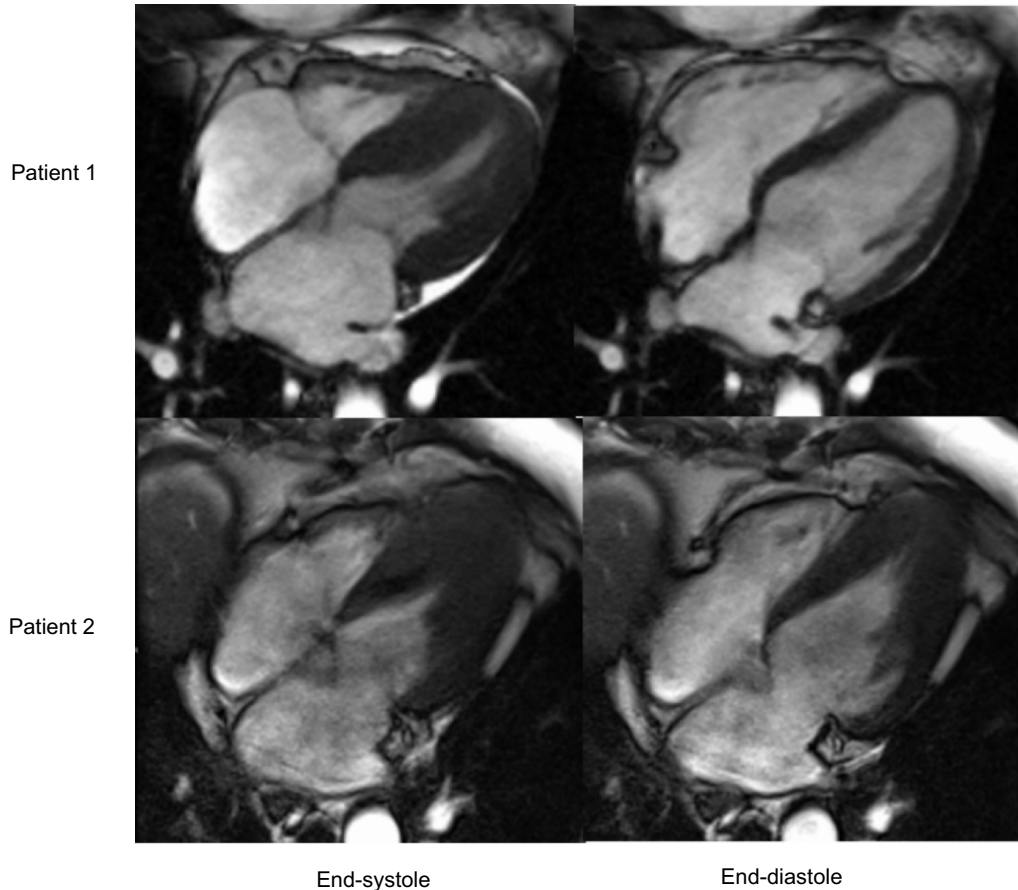
ischemia, heart failure, and death in HCM.<sup>3,4</sup> Hence, there is a need for imaging modalities that permit quantification of myocardial blood flow (MBF) and assessment of myocardial ischemia in HCM patients.

Positron emission tomography (PET) permits noninvasive quantification of myocardial blood flow (MBF) and hence, is an important clinical tool for the investigation of angina in HCM patients.<sup>5</sup> Several methods that implement either a one- or two-compartment model are currently available for measuring myocardial blood flow (MBF). But most of the testing has been performed in patients with normal cardiac geometry, referred for evaluation of coronary artery disease (CAD). It is unknown whether these methods work well in HCM patients, who have LV hypertrophy that can be localized (septum, anterior/lateral/inferior wall, papillary muscles, apex) or generalized.<sup>1</sup> Furthermore, HCM patients tend to have hypercontractility of the LV, resulting in narrowing of the left ventricular outflow tract and/or obliteration of the LV cavity during systole, and reduced LV cavity size during diastole (Figure 1). These anatomic features of HCM hearts can affect segmentation and/or sampling of counts in the blood pool and myocardium to obtain input curves for MBF measurements, using automated tools.<sup>6</sup> Hence, MBF analysis results obtained using manual segmentation could differ from the results obtained using automated segmentation algorithms.

In this study, we examined the agreement between results of MBF and MFR, obtained using PMod (that permits manual segmentation of the heart) and QPET (that has automated segmentation) in HCM patients who underwent <sup>13</sup>N-ammonia PET for clinical indications. Results from HCM patients were compared to a small number of non-HCM patients who underwent <sup>13</sup>N-ammonia PET for assessment of CAD (CAD group.)

#### See related editorial, pp. 1255–1257

Hypertrophic cardiomyopathy (HCM) is the most common genetic cardiovascular disease with a prevalence of  $\sim 1:500$  in the general population.<sup>1</sup> Chest pain at rest and/or exertion due to microvascular dysfunction is a common symptom in HCM patients.<sup>2</sup> Pathologic studies reveal abnormalities in intramural coronary arterioles and relative reduction of capillary density in the setting of increased left ventricular mass, which contribute to the development of microvascular dysfunction, myocardial



**Figure 1.** HCM patient CMR morphology. Cardiac magnetic resonance images of 2 HCM patients showing varying patterns of left ventricular hypertrophy. LV cavity size is reduced in systole as a result of left ventricular hypertrophy and hypercontractility.

## METHODS

### Study Subjects

This study was approved by the Institutional Review Board at Johns Hopkins. Patients enrolled in the HCM Registry at Johns Hopkins were retrospectively studied if they fulfilled the standard diagnostic criteria for HCM (left ventricular hypertrophy in the absence of other causes such as uncontrolled hypertension, valvular disease, amyloidosis) and underwent  $^{13}\text{N}$ -ammonia PET myocardial perfusion imaging. The cohort was composed of 76 consecutive HCM patients without obstructive CAD, and 10 non-HCM patients referred for evaluation of CAD (with spillover fractions  $< 0.65$ ), who underwent  $^{13}\text{NH}_3$ -PET imaging, and had good image quality.

### $^{13}\text{N}$ -Ammonia Myocardial Perfusion Imaging Protocol

All patients underwent cardiac PET/CT scanning using a GE Discovery VCT PET/CT system (GE Healthcare, Waukesha, Wisconsin). Patients were positioned with the assistance of a computed tomographic (CT) topogram, and a low-dose CT

scan was performed for attenuation correction of PET emission data. Motion correction was applied at the time of acquisition to correct misalignment between the PET and the CT. Subsequently, PET images were acquired using a same-day rest/stress protocol as follows: approximately 370 MBq (10 mCi)  $^{13}\text{N}$ -ammonia was bolus injected over 30 s at a constant rate ( $1200 \text{ ml}\cdot\text{h}^{-1}$ ) using a power injector, and a 2-dimensional list-mode PET scan was obtained over 20 min. Approximately 60 min after injection of the rest dose, dipyridamole or regadenoson was administered. Dipyridamole was the drug of choice at the beginning of our PET protocol for HCM patients in 2009, but from June 2011, all HCM patients were administered regadenoson. Dipyridamole ( $0.56 \text{ mg/kg}$ ) was infused over a period of 4 min, followed by a second dose of  $^{13}\text{N}$ -ammonia ( $\sim 370 \text{ MBq}$ ; 10 mCi), 4 min after the end of dipyridamole infusion. Regadenoson ( $0.4 \text{ mg/5 ml}$ ) was injected as a bolus (over 15–20 s), followed by a 5-ml saline flush, and  $^{13}\text{N}$ -ammonia was administered 30 s later. Stress acquisition was begun concomitantly with the second  $^{13}\text{N}$ -ammonia injection, with all other parameters being the same as during rest. Heart rate, blood pressure, and a 12-lead electrocardiogram (EKG) were recorded before, during, and after completion of the stress protocol. List-mode data were

resampled to create static (4-min prescan delay), EKG-gated (eight bins per cardiac cycle), and 36-frame-dynamic ( $20 \times 6$ ,  $5 \times 12$ ,  $4 \times 30$ ,  $5 \times 60$ , and  $2 \times 300$  s) images.<sup>7</sup>

### Myocardial Perfusion Imaging Analysis

Attenuation-corrected PET images were reconstructed incorporating the motion-correction parameters, using an iterative algorithm with postprocessing filtering. The CardIQ Physio package (GE Healthcare) was used for analysis of both EKG-gated and nongated static datasets, including oblique reorientation in the transverse planes, definition of the valve plane, quality control of automated contour detection, and software-derived calculation of EKG-gated-LVEF from the rest and stress datasets.<sup>8</sup>

### Myocardial Blood Flow Analysis

Global and regional MBF values in ml/min/g and MFR (myocardial flow reserve) values were obtained with each commercial tool. LV contours and volume of interest (VOI) for the input function were obtained automatically with minimal operator intervention using QPET (version 2012, Cedars-Sinai, Los Angeles, United States), but manual segmentation was performed using PMod (version 3.4, PMOD Technologies Ltd, Zurich, Switzerland). Both programs used the same modified 2-tissue-compartment model developed by Choi et al without metabolite correction.<sup>9</sup> This model assumed a constant recovery coefficient of 0.75 based on an assumed uniform myocardial wall thickness of 1 cm. Only the first 2 min of the dynamic acquisition were used for curve fitting and to estimate parameters (MBF and spillover), using a weighted least-squares method. Both software programs corrected for spillover from the LV and RV cavities. Mean-MBF was calculated by time-activity curves and analyzed independently by two expert operators (HY, AT.)

### QPET Processing

Left ventricular contours were positioned automatically using a recently described improved QPET algorithm.<sup>10</sup> The LV contour was determined from the summed dynamic image data, skipping the first 2 min using the QPET algorithm<sup>10</sup> which is based on the original quantitative gated SPECT contour detection principles,<sup>11</sup> but takes into consideration, the better valve definition of attenuation-corrected high-resolution PET. The VOI for the LV-input function was automatically placed in the middle of the atrio-ventricular plane and was cylindrical with a 1-cm radius and 2-cm length, with its long axis oriented along the long axis of the heart. Dynamic myocardial samples were obtained from the polar map by analyzing all time frames. Stress-MBF and rest-MBF in ml/min/g were computed for each segment in the polar map. Interpolation was employed, and computation was performed in 17 myocardial segments with equal surface area. Regional flow was computed for each segment. These calculations were then interpolated using a surface-area-weighted bicubic method to determine MBF values for each segment in the

polar map. Myocardial flow reserve (MFR) was computed by dividing each stress polar map value by the rest value in each segment. Global rest-MBF, stress-MBF, and MFR were computed within the entire LV myocardium bounded by the atrio-ventricular valve plane. Regional MBF was obtained by dividing the polar map into three regions (left anterior descending artery, left circumflex coronary artery, and right coronary artery) obtained from the standard 17-segment American Heart Association model using the group option in QPET.

### PMod Processing

After loading the DICOM files, PMod automatically generated blood pool and myocardial images from dynamic uptake series by averaging respective frames, from 0 to 36 s for blood pool, and from 2 to 20 min for myocardium. Then, standard reorientation of the heart was performed. The VOI of the LV contour was generated using the EPI/ENDO method with manual adjustment. The VOI for input function was positioned in the same location as for QPET processing (Figure 2). A previously validated tracer kinetic model was fit to the tissue time-activity curves, providing values of regional and global MBF ( $\text{mL} \cdot \text{min}^{-1} \cdot \text{g}^{-1}$ ). PMod generated a series of polar maps and parameters including MBF at stress, MBF at rest and MFR. The characteristics of QPET and PMod are listed in Supplementary Table 1.

### Transient left Ventricular Cavity Dilatation Following Vasodilator Stress

The PET-LVCD-index was obtained by dividing the LV volume during peak vasodilator stress by the LV volume at rest. HCM patients with an index  $> 1.13$  were considered to have LVCD.<sup>8</sup>

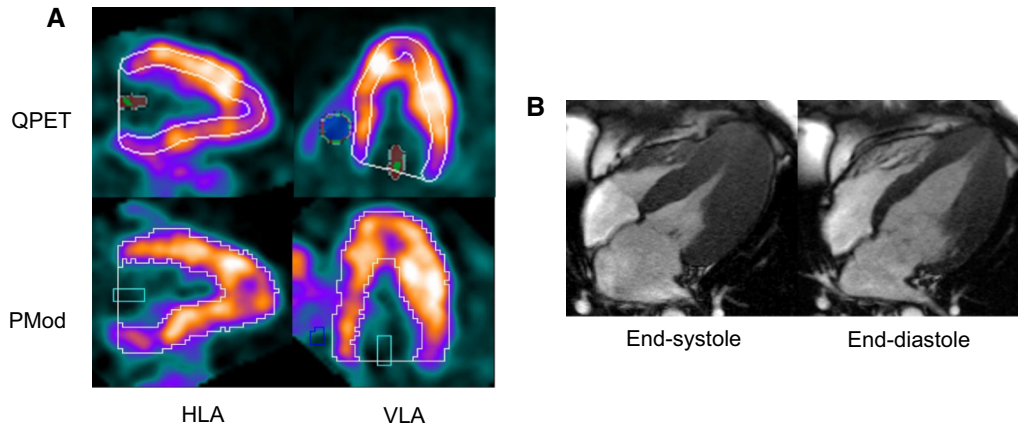
### Statistical Analysis

We used SPSS 23.0 (IBM Corp, Somers, NY) for statistical analysis. Variables are presented as mean  $\pm$  standard deviation. Comparison of stress-MBF, rest-MBF, and MFR obtained using QPET and PMod was performed using the paired *t* test. A comparison of values obtained between these two methods was evaluated using Pearson correlation or Bland-Altman analysis. Interobserver variability was assessed using Pearson correlation. A value of  $p < .05$  was considered statistically significant.

## RESULTS

### Patient Characteristics

We studied 76 patients with a clinical diagnosis of HCM. All HCM patients had evidence of asymmetric septal hypertrophy; approximately 50% of HCM patients had evidence of left ventricular outflow tract



**Figure 2.** Segmentation of PET images using QPET and PMod. **A** Representative images of LV segmentation of PET images in an HCM patient, with maximum wall thickness of 3.4 cm, using PMod and QPET softwares. The VOI for LV-input function was placed in atrio-ventricular valve plane, with its long axis oriented along the long axis of the heart. The RV-VOI was placed in right ventricle in the horizontal long axis, in order to correct for spillover in the septum. *HLA* horizontal long axis, *VLA* vertical long axis. **B** CMR image of the same patient showing left ventricular hypertrophy.

obstruction—Table 1. All non-HCM patients had normal wall thickness and LVEF.

### Global MBF Analysis in HCM

PMod yielded higher values for global stress-MBF and MFR than QPET (Table 2), which resulted in a higher number of HCM patients being classified as having normal stress-MBF ( $\geq 1.8 \text{ mL}\cdot\text{min}^{-1}\cdot\text{g}^{-1}$ ) and MFR ( $\geq 2.0$ ) values<sup>12</sup> by PMod, when compared to QPET (Supplemental Table 2). Next, we examined correlations between SDS scores (which have been validated extensively<sup>13,14</sup>) and MBF values obtained by QPET and PMod in HCM patients (with  $\text{SDS} \geq 2$ ) in an attempt to assess which software performed better in HCM. We detected a statistically significant inverse correlation only between MFR values obtained by PMod, and SDS in HCM patients (Supplemental Table 3, Figure 4).

Since high spillover fractions can result in unreliable data, we used the cutoff of 0.65 established by Slomka et al,<sup>15</sup> as an indicator of extremely high spillover. PMod resulted in markedly higher values of global stress-MBF in HCM patients with high spillover fractions, which led to higher global stress-MBF values in the population as a whole (Table 2). However, when patients with high spillover fractions were excluded, QPET resulted in higher MFR values than PMod.

We observed fair agreement between QPET and PMod for global rest-MBF, stress-MBF, and MFR using PMod and QPET (Figure 3A, B; Table 2). Correlations

**Table 1.** Clinical characteristics ( $n = 76$ )

Characteristics	Values
Age (years)	58 ± 14
Male <i>n</i> (%)	39 (51)
Nonobstructive HCM, <i>n</i> (%)	38
Latent obstructive HCM, <i>n</i> (%)	16
Obstructive HCM, <i>n</i> (%)	22
Hypertension, <i>n</i> (%)	36 (47)
Diabetes, <i>n</i> (%)	8 (10)
Medications	
Beta blockers, <i>n</i> (%)	55 (72)
Calcium channel blockers, <i>n</i> (%)	17 (22)
ACE-I/ARB, <i>n</i> (%)	18 (23)
Echocardiography	
Maximum wall thickness (cm)	2.04 ± 0.4
Rest LVOTG (mmHg)	22 ± 25
Stress LVOTG (mmHg)	52 ± 59
PET	
SDS	6 ± 5
Stress LVEF(%)	47 ± 11
Rest LVEF(%)	56 ± 11
LVCD ratio	1.13 ± 0.14

ACE-I/ARB angiotensin converting enzyme inhibitor/angiotensin receptor blocker, PET Positron emission tomography, LVOTG left ventricular outflow tract gradient, SDS summed difference score, LVEF left ventricular ejection fraction, SDS summed difference score, LVCD transient left ventricular cavity dilation



between global rest-MBF, stress-MBF, and MFR improved when HCM patients whose data contained high spillover fractions were excluded from the analysis (Figure 3C, D; Table 2). With regard to spillover, we found no difference in spillover fraction values (PMod:  $0.34 \pm 0.23$ , QPET  $0.31 \pm 0.06$ ,  $p = .25$ ), and modest agreement between PMod and QPET for spillover fractions in HCM patients ( $r = 0.64$ ,  $p < .001$ ) (Figure 4).

### Regional MBF Analysis in HCM

PMod yielded higher values for stress-MBF and MFR for the LAD, LCx, and RCA territories, when compared to QPET, but rest-MBF values were similar in the 3 coronary territories (Table 3). The best correlations between QPET and PMod were obtained in the LAD territory, where spillover fraction was the lowest (Table 3). The range for spillover fractions was 0.09-0.69 for the LAD territory, 0.17-0.72 for the LCx territory, and 0.14-0.67 for the RCA territory.

Next, we compared rest-MBF, stress-MBF, and MFR values between PMod and QPET in the hypertrophied and non-hypertrophied regions (identified by echocardiography/CMR), after excluding patients with high spillover fractions. Higher values for stress-MBF and MFR were obtained using PMod, in both non-hypertrophied and hypertrophied walls, but rest-MBF was similar in non-hypertrophied and hypertrophied walls. The best correlations between the two softwares

**Figure 3.** Correlation and Bland-Altman plots for MBF analysis using QPET and PMod software. **A, B.** Correlation analysis and Bland-Altman plots for stress-MBF, rest-MBF, and MFR in entire HCM cohort ( $n = 76$ ). Y-axes in Bland-Altman plots represent difference between PMod and QPET values, and X-axes represent the mean of PMod and QPET values in HCM patients. **C, D.** Correlation analysis and Bland-Altman plots for QPET and PMod, for stress-MBF, rest-MBF, and MFR values in HCM patients ( $n = 53$ ) after excluding patients with high spillover fractions.

were obtained for rest-MBF in both hypertrophied and non-hypertrophied walls (Table 4).

### Global MBF Analysis in non-HCM Patients

In order to assess whether cardiac anatomic characteristics specific to HCM influence MBF analysis obtained by QPET and PMod, we examined agreement between QPET and PMod in 10 non-HCM patients referred for evaluation of CAD, after excluding patients with spillover fractions  $> 0.65$ . Excellent agreement was observed between QPET and PMod in the 10 non-HCM patients, in contrast to modest agreement in the HCM cohort. (Supplementary Table 4).

### Interobserver Variability

Interobserver agreement was excellent for global MBF and MFR values obtained by QPET and PMod in HCM patients (Supplemental Table 5).

**Table 2.** Comparison of global MBF and MFR obtained by QPET and PMod

Measure	N	QPET	PMod	r	p value <sup>†</sup>
Cohort A					
Stress-MBF (ml/min/g)	76	2.1 ± 0.70	2.7 ± 1.2*	0.66	< .001
Rest-MBF (ml/min/g)	76	0.9 ± 0.25	0.8 ± 0.2	0.78	< .001
MFR	76	2.5 ± 0.8	3.4 ± 1.4*	0.70	< .001
Cohort B					
Stress-MBF (ml/min/g)	53	2.3 ± 0.7	2.0 ± 0.6	0.72	< .001
Rest-MBF (ml/min/g)	53	0.8 ± 0.2	0.9 ± 0.2	0.84	< .001
MFR	53	2.9 ± 1.1	2.4 ± 0.7*	0.80	< .001
Cohort C					
Stress-MBF (ml/min/g)	23	2.4 ± 0.7	3.7 ± 1.4*	0.73	< .001
Rest-MBF (ml/min/g)	23	0.9 ± 0.2	0.8 ± 0.2	0.61	.002
MFR	23	2.8 ± 1.0	4.3 ± 1.5*	0.62	.002

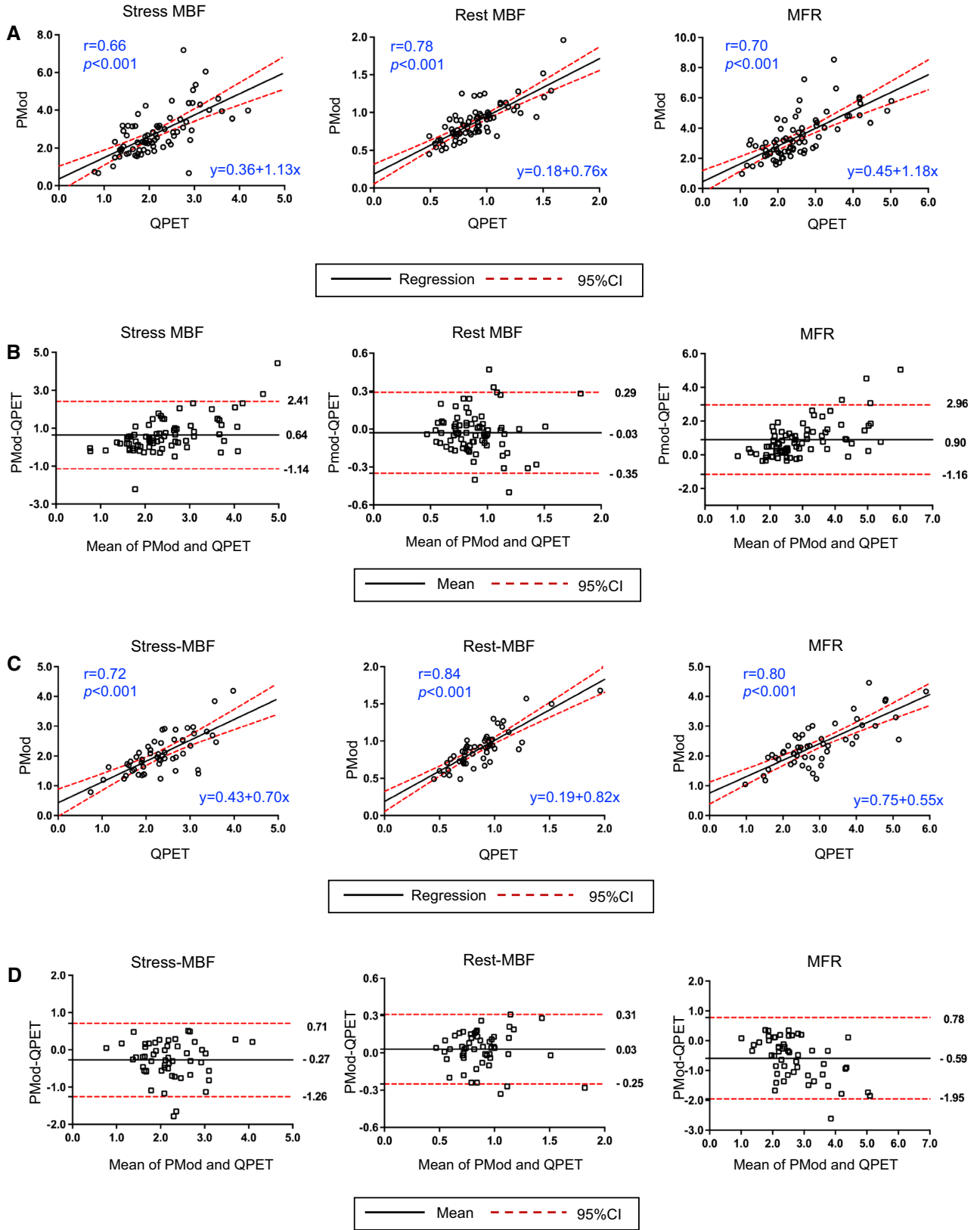
A Obtained from the entire HCM cohort

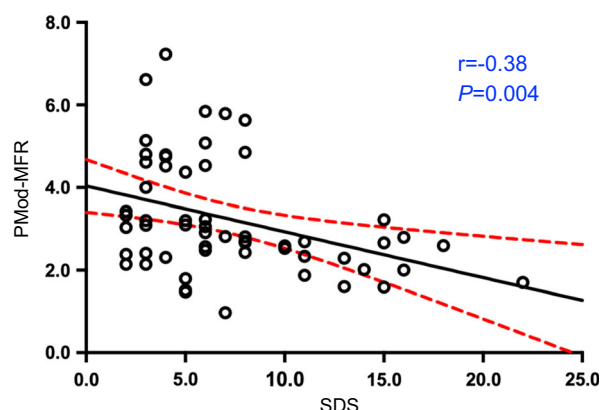
B HCM cohort after excluding patients with high spillover fraction (using threshold  $< 0.65$ )

C Obtained from HCM patient sub-group with high spillover fraction (threshold  $\geq 0.65$ ;  $n = 23$ )

\* $p < .01$ , compared with QPET

<sup>†</sup>p value for Pearson's correlation (r)





**Figure 4.** Relationship between SDS and MFR obtained using PMod. A statistically significant inverse correlation ( $r = -0.38$ ,  $p = .004$ ) was present between SDS and MFR values obtained using PMod in HCM patients with  $\text{SDS} \geq 2$  ( $n = 57$ ). Solid line represents the regression line, and dashed lines represent the 95% confidence interval.

## DISCUSSION

Quantification of hyperemic MBF and MFR by PET permits noninvasive assessment of microvascular function and inducible ischemia in HCM patients with angina and arrhythmias. Previous studies have demonstrated that HCM patients who lack obstructive epicardial disease often demonstrate blunting of hyperemic MBF, but preservation of rest-MBF.<sup>16,17</sup> Most importantly, HCM patients who have reduction in hyperemic MBF during pharmacologic vasodilatation have been demonstrated to have an increased propensity to develop adverse LV remodeling, heart failure, and death.<sup>18</sup> Hence, tools that can reliably compute global and regional blood flow in HCM are needed.<sup>5,19</sup>

New PET/CT systems permit acquisition in list mode and reformatting of data into dynamic, static, or gated frames as required. These advances aid clinical practice,<sup>20</sup> but in order to be utilized for clinical decision-making, the reference limits for different methods need to be determined. This has been accomplished by Slomka et al for patients with normal cardiac geometry, referred for evaluation of obstructive CAD,<sup>15</sup> but very limited comparative data are available in the HCM patient population.

## Differences in MBF Values Using PMod and QPET in HCM

In this study, we compared global and regional MBF values obtained by QPET and Pmod in HCM patients, utilizing the same two-compartment model. The UCLA model (Choi) that was used for MBF analysis by QPET and PMod assumes a constant recovery coefficient of 0.75, based on an assumed uniform myocardial wall thickness of 1 cm. While this assumption is likely to be inaccurate, particularly for HCM patients who have variability in the degree and location of hypertrophy, it should (in principle) be consistent between software implementations. The aim of our study was to test this assumption and any other differences in software implementations.

Bland-Altman plots revealed modest agreement between the two software programs in HCM patients, but excellent agreement in a small cohort of non-HCM patients, who were referred for evaluation of CAD. This result suggests that cardiac anatomic characteristics specific to HCM patients contribute to differences in MBF values observed using these two softwares.

**Table 3.** Comparison of regional MBF and MFR obtained by QPET and PMod ( $n = 76$ )

Segment	Measure	QPET	PMod	<i>r</i>	<i>p</i> value <sup>†</sup>
LAD	Stress-MBF (ml/min/g)	2.1 ± 0.7	2.7 ± 1.0*	0.68	< .001
	Rest-MBF (ml/min/g)	0.9 ± 0.2	0.8 ± 0.2	0.82	< .001
	MFR	2.5 ± 1.0	3.1 ± 1.2*	0.66	< .001
LCx	Stress-MBF (ml/min/g)	2.3 ± 0.8	3.7 ± 1.7*	0.47	< .001
	Rest-MBF (ml/min/g)	0.9 ± 0.2	0.9 ± 0.3	0.53	< .001
	MFR	2.5 ± 0.8	4.2 ± 2.2*	0.52	< .001
RCA	Stress-MBF (ml/min/g)	1.9 ± 0.7	2.7 ± 1.1*	0.60	< .001
	Rest-MBF (ml/min/g)	0.8 ± 0.3	0.8 ± 0.3	0.64	< .001
	MFR	2.3 ± 0.8	3.2 ± 1.2*	0.62	< .001

LAD left anterior descending artery, LCx left circumflex artery, RCA right coronary artery

\* $p < .01$  compared with QPET

<sup>†</sup> $p$  value for Pearson's correlation ( $r$ )



**Table 4.** Comparison of QPET and PMod in hypertrophied and non-hypertrophied walls after excluding patients with high spillover ( $n = 50$ )

Segment	Measure	QPET	PMod	<i>r</i>	<i>p</i> value <sup>†</sup>
Hypertrophied wall	Stress-MBF (ml/min/g)	2.0 ± 0.6	2.3 ± 0.8*	0.72	< .001
	Rest-MBF (ml/min/g)	0.9 ± 0.2	0.8 ± 0.2	0.79	< .001
	MFR	2.3 ± 0.8	2.8 ± 1.0*	0.72	< .001
Non-hypertrophied wall	Stress-MBF (ml/min/g)	2.1 ± 0.7	2.5 ± 0.9*	0.61	< .001
	Rest-MBF (ml/min/g)	0.9 ± 0.2	0.8 ± 0.3	0.79	< .001
	MFR	2.4 ± 0.9	3.1 ± 1.4*	0.67	< .001

\* $p < .01$  compared with QPET

<sup>†</sup> $p$  value for Pearson's correlation (*r*)

### High Spillover Fractions in HCM

The prevalence of high spillover fractions was higher in the HCM cohort when compared to CAD patients evaluated by Slomka et al<sup>15</sup> (30% in HCM, vs 7% in CAD.<sup>15</sup>) High spillover in HCM could be related to LV hypertrophy, small LV cavity size, and hypercontractility resulting in inclusion of signal from myocardium in the image-derived input function. This would subsequently lead to bad fits of the kinetic modeling curves and result in high spillover fractions. Another possible contributor to high spillover is motion during the PET acquisition, which was not corrected.

In our study, QPET yielded higher global stress-MBF and MFR values when patients with high spillover fractions were excluded. Since VOIs generated by PMod (which permits manual segmentation) would be larger than corresponding QPET-VOIs, the mean-MBF values resulting from PMod would be lower than those generated by QPET, which are thinner. For thinner VOIs, partial volume underestimation would not be as significant, and consequently, the mean-MBF values would be higher while using QPET, compared with PMod.

In practical terms, the high spillover fraction remains a limitation for clinical analysis because it leads to variability in MBF results. Although there is no better spillover correction method in the modeling to avoid such discrepancies, a high spillover fraction provided by quantitative software should raise concern about an overestimation of the calculated MBF value. We found no differences in spillover fractions between PMod and QPET in HCM patients, suggesting that differences in spillover fractions do not underlie differences in MBF values obtained using PMod and QPET, in HCM patients. Another interesting observation was higher correlation between MBF values obtained by QPET and PMod in the RCA territory than in the LCx territory, despite the fact that the RCA territory had the

highest prevalence of spillover fractions  $\geq 0.65$ . This result, and persistence of a modest agreement in global and regional MBF/MFR values after excluding patients with high spillover fractions, led us to conclude that high spillover is not the only reason for the modest agreement in MBF/MFR values in HCM patients.

### Left Ventricular Hypertrophy and MBF

We observed higher correlations in stress-MBF using PMod and QPET, in hypertrophied walls, when compared to non-hypertrophied walls—this could be due to less partial volume effects in hypertrophied walls, when compared to non-hypertrophied walls.

### CAD Patients Demonstrate Better Agreement in MBF Analyses than HCM

The study by Slomka et al<sup>15</sup> demonstrated excellent correlation between QPET and PMod in CAD patients. Our results in non-HCM patients were similar to those obtained by Slomka et al<sup>15</sup>. The modest agreement in MBF values obtained in the HCM cohort are likely related to the cardiac anatomic characteristics, namely, variability in degree and location of LV hypertrophy, small LV cavity size, and hypercontractility of HCM hearts.

### LIMITATIONS

This is a retrospective study comparing two software programs with several limitations. First, we did not have a phantom or a gold standard for quantification of myocardial blood flow using the software systems. Hence, we are unable to conclude with certainty, whether one software system is more accurate than the other for quantifying MBF in HCM patients. But based on our results of a significant inverse correlation only between PMod-MFR

and SDS, we speculate that PMod may perform better than QPET in HCM patients. Second, since stress-MBF  $\geq 1.8$  mL/min/g and MFR  $\geq 2.0$  are commonly used as a cutoff to distinguish normal or abnormal myocardial hyperemic flow increases,<sup>12</sup> QPET may have overestimated the number of HCM patients with abnormal hyperemic flows. Prospective studies need to be designed in order to ascertain whether MBF/MFR thresholds validated in non-HCM patients are applicable in the HCM patient population.

### NEW KNOWLEDGE GAINED

The present work compared two software systems for MBF assessment in HCM patients who have abnormal geometry of the LV, variable LV wall thickness, and hypercontractility. Our results indicate that these two software programs cannot be used interchangeably in HCM patients. The observed differences in global and regional MBF values obtained by PMod and QPET could be attributed to cardiac anatomic characteristics specific to HCM, often leading to high spillover fractions and variations in estimated parameters.

### CONCLUSIONS

PMod and QPET yield significant differences in stress-MBF values and modest agreement between MBF values in HCM patients. Hence, these two software systems cannot be used interchangeably for MBF analyses in HCM patients. Additional studies are needed to establish normal reference ranges for HCM patients, using clinical software programs.

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### Disclosure

*All authors declare that they have no conflict of interest.*

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