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Software reproducibility of myocardial blood flow and flow reserve quantification in ischemic heart disease: A ^{13}N -ammonia PET study

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Background. We explored agreement in the quantification of myocardial perfusion by cross-comparison of implemented software packages (SPs) in three distinguishable patient profile populations.

Methods. We studied 91 scans of patients divided into 3 subgroups based on their semi-quantitative perfusion findings: patients with normal perfusion, with reversible perfusion defects, and with fixed perfusion defects. Rest myocardial blood flow (MBF), stress MBF, and myocardial flow reserve (MFR) were obtained with QPET, SyngoMBF, and Carimas. Agreement between SPs was considered adequate when a pairwise standardized difference was found to be < 0.20 and its corresponding intraclass correlation coefficient was ≥ 0.75 .

Results. In patients with normal perfusion, two out of three comparisons of global stress MBF quantifications were outside the limits of agreement. In ischemic patients, all comparisons of global stress MBF and MFR were outside the limits of established agreement. In patients with fixed perfusion defects, all SP comparisons of perfusion quantifications were within the limit of agreement. Regionally, agreement of these perfusion estimates was mostly found for the left anterior descending artery vascular territory.

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The authors of this article have provided a PowerPoint file, available for download at SpringerLink, which summarizes the contents of the paper and is free for re-use at meetings and presentations. Search for the article DOI on SpringerLink.com.

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Conclusion. Reversible defects demonstrated the worst agreement in global stress MBF and MFR and discrepancies showed to be regional dependent. Reproducibility between SPs should not be assumed. (J Nucl Cardiol 2019)

Key Words: Myocardial ischemia and infarction • PET • myocardial blood flow • image interpretation • diagnostic and prognostic application • image reconstruction

Abbreviations

MBF	Myocardial blood flow
MFR	Myocardial flow reserve
LAD	Left anterior descending artery
LCx	Left circumflex coronary artery
RCA	Right coronary artery
PET	Positron emission tomography

INTRODUCTION

Myocardial perfusion imaging derived from positron emission tomography (PET) is an established technique that provides useful diagnostic and prognostic information in the study of patients with suspected myocardial ischemia.¹⁻⁴ Beyond visual semi-quantitative analysis, PET offers the possibility to quantify myocardial blood flow (MBF) in absolute terms, both globally and regionally. Stress MBF, rest MBF, and its ratio assigned as myocardial flow reserve (MFR) represent well-accepted and useful non-invasive perfusion parameters in determining the hemodynamic significance of coronary stenoses and/or microvascular dysfunction.^{5,6} Currently, several software packages (SPs) are clinically available for the quantification of MBF and MFR using established perfusion radiotracers (i.e., ⁸²rubidium, ¹³N-ammonia, and ¹⁵O-water).

Considering the clinical utilization of quantitative PET perfusion parameters, it is fundamental that SPs provide reproducible results. Therefore, a number of studies have been conducted in order to evaluate agreement between several SPs demonstrating an overall moderate-to-good agreement.⁷⁻⁹ Those studies, however, have mostly performed in populations deemed as either normal or with a low-to-intermediate likelihood of coronary artery disease (CAD). No exploration of SP agreement in the estimation of quantitative PET myocardial perfusion parameters has been conducted with defined patient groups that include both myocardial ischemia and myocardial infarction.

Hence, the aim of this study was to explore agreement in quantification of myocardial perfusion parameters with ¹³N-ammonia PET by cross-comparison of three clinically implemented SPs (QPET, SyngoMBF, and Carimas) in three distinguishable population profiles, namely, patients with normal perfusion imaging,

patients with reversible perfusion defects, and patients with fixed perfusion defects.

METHODS

Patient Population and Study Design

This is a pilot study, and therefore, we selected at random 91 patient scans from a cohort of 393 patients referred for the assessment of myocardial perfusion to the PET/CT Unit at the National Autonomous University of Mexico in Mexico City between 2012 and 2016. Patients were selected from 3 discernible subgroups based on the reported semi-quantitative perfusion findings: (1) those with normal perfusion, (2) those with reversible perfusion defects (myocardial ischemia), and (3) those fixed perfusion defects (myocardial infarction).

PET Acquisition

Scans were performed in a PET/CT scanner (Biograph True Point PET/CT 64-Multislice Scanner; Siemens Medical, Erlangen, Germany). Patients underwent an overnight fast and refrained from caffeine and theophylline 24 hours prior to the study. Dynamic data were acquired at rest and during adenosine stress, as previously described.¹⁰ The 10-minute rest imaging acquisition started with a 740 MBq of ¹³N-ammonia i.v. injection. Pharmacological stress was performed after 30 minutes of the rest acquisition with an i.v. injection of adenosine during a 6-minute period (140 µg·kg·min). A 10-minute stress imaging acquisition started few seconds before the second dose of 740 MBq of ¹³N-ammonia was injected i.v. at the third minute of the pharmacological stress. Static, dynamic, and gated datasets were obtained at rest and stress.¹¹ Dynamic data were obtained during 6 minutes in 16 frames to calculate MBF (13 × 10, 2 × 30, and 1 × 60 seconds). A standard reconstruction (2D attenuation-weighted OSEM) was used with 3 iterations, 14 subsets, and 3D post-filtering with a 5-mm Gaussian kernel filter. Transverse data were reformatted to a 168 × 168 × 47 matrix with 2 mm pixels for each dynamic frame.

Semi-quantitative Myocardial Perfusion Assessment

Perfusion images were analyzed using QPET software. An experienced observer assessed the images of dynamic datasets. Semi-quantification of myocardial perfusion imaging was performed on static images of the 17 segments of the heart and reported as summed stress score (SSS), summed rest score (SRS), and summed difference score (SDS).¹² Scans were considered as normal if SSS was < 4, mildly abnormal if the

SSS was between 4 and 7, moderately abnormal if the SSS was between 8 and 11, and severely abnormal if the SSS > 12.¹⁰ Reversible perfusion defects (with an SDS > 2 but an SRS < 4) were considered those disappearing at rest. Fixed perfusion defects did not disappear at rest (with an SRS ≥ 4). Transmural and non-transmural fixed perfusion defects were assessed as the irreversible absence or irreversible reduced uptake of radiotracer uptake in the myocardial segment, respectively.¹⁰

Software Processing for Quantitative Analysis

A different experienced observer assessed all images in each SP. Global (entire left ventricle) and regional [based on vascular territories: left anterior descending artery (LAD), left circumflex artery (LCx), and right coronary artery (RCA)] absolute perfusion estimates were obtained with every SP. In patients with reversible and fixed perfusion defects, myocardial perfusion quantifications were obtained in each vascular territory regardless of the location of the perfusion defects.

SyngoMBF processing. All images were processed with SyngoMBF VB14 (Siemens Medical Solutions). Dynamic datasets were automatically loaded, centered, and oriented, followed by manual corrections for adjustment of centering and reorientation of axial limits only when needed. Motion was visually assessed in each frame and the automatic correction tool was used when considered necessary. The two-tissue compartment model developed by Hutchins et al was fitted to measure the time-activity curve (TAC) in order to calculate rest MBF, stress MBF, and MFR.¹³

QPET processing. All images were processed with QPET 17 Rev. A (Cedars-Sinai Medical Center). QPET performed automatic orientation, segmentation of the left ventricle, calculation of endocardial and epicardial 3-D surfaces, and detection of the valve plane. Contours of the short and long axis images of the left ventricle were visually assessed and corrected manually when needed. Manual motion correction was used when motion artifacts were visually detected. Determination of absolute rest MBF, stress MBF, MFR, stress spill-over fraction, and rest spill-over fraction of the heart was calculated with the one-tissue compartment model developed by Choi et al.^{14,15}

Carimas processing. All images were processed with Carimas v.2.9.5 (Turku PET Center, Finland). Images were uploaded and automatically oriented. Manual reorientation was performed when necessary. Determination of absolute rest MBF, stress MBF, and MFR of the left ventricle was calculated with the two-tissue compartment model developed by Hutchins et al.¹³

Statistical Methods

Continuous variables are summarized as means and standard deviations or as medians and interquartile ranges as appropriate, while categorical variables are presented as frequencies and percentages. Fisher's tests were used to compare proportions of categorical variables. The ANOVA

test with a post hoc Bonferroni correction for multiple comparisons or the Kruskal–Wallis tests with Wilcoxon Signed Rank tests for post hoc comparisons were used to compare continuous data. A two-tailed *P* value ≤ .05 was considered statistically significant.

A linear mixed model for repeated measures was used to measure agreement of the three SPs. The calculated metrics of pairwise agreement were the intraclass correlation coefficient (ICC) for single measures and the standardized difference between values. Agreement between SPs was considered adequate when a pairwise standardized difference was found to be < 0.20 and its corresponding ICC was ≥ 0.75. The cutoff value of acceptable 20% difference was based on previous studies.^{16,17} The criteria for ICC were based on previous literature.¹⁸ Biplots were then utilized to depict the obtained results among all comparisons between SPs stratified by group and quantitative perfusion parameter (rest MBF, stress MBF, and MFR) as previously reported.⁸ The X-axis in the biplots represents the pairwise differences standardized for the median across all SPs, while the Y-axis represents the value of 1 minus the corresponding pairwise ICC. The resulting *area of agreement* is depicted in green in the biplots figures.

All statistical analyses were performed for both the global and regional perfusion estimations using SPSS v.23 and SAS v.9.2.

RESULTS

Baseline characteristics of patients with normal perfusion, reversible perfusion defects, and fixed perfusion defects as well as their allocation and further characterization are shown in Table 1 and Figure 1. Semi-quantitative visual grades are shown in the online supplementary material 1.

Mean rest MBF, stress MBF, and MFR estimations are shown in Table 2. Stress and rest spill-over fractions are reported in the online supplementary material 2. The biplots depicting performed comparisons of global quantifications are shown in Figure 2 and will be described for the considered patient groups in the next paragraphs. The biplots depicting performed comparisons of regional quantifications are shown in the supplementary material 3 and will be described for the considered patient groups in the next paragraphs. The corresponding numerical results of the biplots can be consulted in the online supplementary material 4.

Patients with Normal Perfusion

Global assessment. Globally, the comparisons of rest MBF and MFR estimates between all SPs resulted in differences and ICCs found within the established limits of adequate agreement (difference < 20% and ICC ≥ 0.75). In contrast, only the comparison of stress MBF between Carimas and SyngoMBF was found within this area of agreement.

Table 1. Baseline characteristics of patients.

	All patients n = 91 (100%)	Patients with normal perfusion n = 34 (37%)	Patients with reversible defects n = 33 (36%)	Patients with fixed defects n = 24 (26%)	P values
Age	64 ± 11	66 ± 10	63 ± 13	62 ± 9	.32
Male gender	52 (57)	14 (41)	18 (55)	20 (83)	.01
Hypertension	68 (75)	24 (71)	26 (79)	18 (75)	.74
Diabetes mellitus type 2	11 (12)	1 (3)	5 (15)	5 (21)	.10
Dyslipidemia	57 (63)	25 (74)	19 (58)	13 (54)	.24
Smoker	41 (45)	14 (41)	12 (36)	15 (63)	.12
Body mass index	28 ± 4	28 ± 4	28 ± 4	27 ± 4	.74
Known coronary artery disease	8 (9)	2 (6)	2 (6)	4 (17)	.28
Prior revascularization	20 (22)	1 (3)	5 (15)	14 (58)	< .01

Values are mean ± standard deviation, n (%)

Figure 1. Included patients.

Regional assessment. A greater spread of agreement parameters was found in the biplots at the regional level analysis. For the comparisons concerning rest MBF, only the comparisons between QPET and SyngoMBF were found within the area of agreement for every vessel territory (LAD, LCx, and RCA). Regarding stress MBF, all regional comparisons between Carimas and SyngoMBF fell within the area of agreement, while the other SP comparisons (Carimas vs QPET and QPET vs SyngoMBF) were found outside of such area. Among the regional cross-comparisons of MFR estimates

between SPs, all that concerned the RCA territory fell consistently outside the area of agreement.

Patients with Reversible Perfusion Defects

Global assessment. All global comparisons of rest MBF were found within the limits of agreement. In contrast, all comparisons of stress MBF and MFR were outside the limits of established agreement.

Regional assessment. Rest MBF agreement was adequate among the three SPs in all vascular territories, with exception of the RCA territory among quantifications of Carimas vs QPET (difference of 24% and ICC of 0.70). Most of the stress MBF and MFR comparisons were outside the predefined limit of agreement in each one of the vascular territories.

Patients with Fixed Perfusion Defects

Global assessment. All SP comparisons concerning rest MBF, stress MBF, and MFR showed to be within the limit of agreement in patients with fixed perfusion defects.

Regional assessment. Regionally, rest MBF showed agreement between the three SP in all three vascular territories, with exception of the LCx comparison between Carimas vs QPET. Regarding stress MBF quantifications, only the comparisons of the LAD territory were constantly within the limits of the agreement area. We observed different comparisons of MFR falling outside of the limit of agreement area in each of the vascular territories.

Table 2. Absolute rest MBF, stress MBF, and MFR quantified with different software packages.

	All patients n = 91	Normal perfusion n = 34	Reversible defects n = 33	Fixed defects n = 24
SyngoMBF (Hutchins et al)				
Rest MBF (mL·g·min)				
Total	0.89 ± 0.30	0.95 ± 0.23	0.96 ± 0.36	0.72 ± 0.22
LAD	0.88 ± 0.31	0.95 ± 0.23	0.95 ± 0.36	0.69 ± 0.26
LCx	0.93 ± 0.29	0.97 ± 0.23	1.00 ± 0.37	0.79 ± 0.20
RCA	0.88 ± 0.31	0.94 ± 0.23	0.94 ± 0.39	0.71 ± 0.21
Stress MBF (mL·g·min)				
Total	2.49 ± 0.75	2.79 ± 0.63	2.69 ± 0.65	1.79 ± 0.62
LAD	2.50 ± 0.81	2.82 ± 0.64	2.71 ± 0.67	1.76 ± 0.73
LCx	2.60 ± 0.78	2.90 ± 0.67	2.80 ± 0.71	1.91 ± 0.58
RCA	2.34 ± 0.78	2.60 ± 0.64	2.51 ± 0.71	1.72 ± 0.72
MFR				
Total	2.91 ± 0.80	3.05 ± 0.76	3.01 ± 0.89	2.58 ± 0.67
LAD	3.00 ± 0.86	3.12 ± 0.82	3.10 ± 0.94	2.69 ± 0.73
LCx	2.85 ± 0.92	3.09 ± 0.75	2.92 ± 1.01	2.41 ± 0.87
RCA	2.77 ± 0.85	2.86 ± 0.76	2.90 ± 0.97	2.45 ± 0.74
QPET (Choi et al)				
Rest MBF (mL g min)				
Total	0.84 ± 0.31	0.92 ± 0.31	0.86 ± 0.31	0.69 ± 0.25
LAD	0.82 ± 0.31	0.91 ± 0.31	0.85 ± 0.30	0.66 ± 0.26
LCx	0.91 ± 0.32	0.99 ± 0.32	0.93 ± 0.34	0.78 ± 0.27
RCA	0.76 ± 0.31	0.84 ± 0.31	0.78 ± 0.33	0.63 ± 0.26
Stress MBF (mL·g·min)				
Total	2.16 ± 0.73	2.45 ± 0.75	2.27 ± 0.63	1.60 ± 0.53
LAD	2.23 ± 0.78	2.55 ± 0.73	2.37 ± 0.64	1.60 ± 0.67
LCx	2.31 ± 0.71	2.63 ± 0.69	2.37 ± 0.68	1.78 ± 0.47
RCA	1.85 ± 0.72	2.08 ± 0.75	1.93 ± 0.66	1.44 ± 0.59
MFR				
Total	2.71 ± 0.76	2.84 ± 0.82	2.79 ± 0.73	2.44 ± 0.67
LAD	2.83 ± 0.84	2.95 ± 0.90	2.94 ± 0.80	2.50 ± 0.75
LCx	2.67 ± 0.75	2.80 ± 0.75	2.71 ± 0.75	2.43 ± 0.74
RCA	2.53 ± 0.79	2.63 ± 0.89	2.56 ± 0.76	2.35 ± 0.71
Carimas (Hutchins et al)				
Rest MBF (mL·g·min)				
Total	0.89 ± 0.33	0.98 ± 0.23	0.93 ± 0.43	0.70 ± 0.23
LAD	0.87 ± 0.33	0.97 ± 0.23	0.91 ± 0.41	0.69 ± 0.28
LCx	0.96 ± 0.35	1.01 ± 0.26	1.01 ± 0.47	0.82 ± 0.19
RCA	0.97 ± 0.41	1.09 ± 0.34	1.01 ± 0.50	0.73 ± 0.24
Stress MBF (mL·g·min)				
Total	2.32 ± 0.83	2.72 ± 0.70	2.43 ± 0.78	1.61 ± 0.60
LAD	2.23 ± 0.85	2.61 ± 0.72	2.36 ± 0.79	1.51 ± 0.65
LCx	2.48 ± 0.85	2.89 ± 0.74	2.57 ± 0.82	1.78 ± 0.55
RCA	2.52 ± 0.93	2.95 ± 0.81	2.59 ± 0.87	1.83 ± 0.80
MFR				
Total	2.73 ± 0.85	2.86 ± 0.82	2.83 ± 0.92	2.40 ± 0.72
LAD	2.69 ± 0.96	2.77 ± 0.91	2.82 ± 1.01	2.41 ± 0.94
LCx	2.71 ± 0.85	2.96 ± 0.80	2.77 ± 0.90	2.26 ± 0.70

Table 2 continued

	All patients n = 91	Normal perfusion n = 34	Reversible defects n = 33	Fixed defects n = 24
RCA	2.77 ± 0.92	2.86 ± 0.94	2.81 ± 0.99	2.58 ± 0.78

Values are mean ± standard deviation

Figure 2. Biplots results from SP cross-comparison of global myocardial perfusion quantifications (green box represents area of agreement).

DISCUSSION

This study evaluated the agreement of three clinically available SPs (QPET, SyngoMBF, and Carimas) for the quantification of PET myocardial perfusion in patients groups with normal perfusion imaging, with reversible perfusion defects, and with fixed perfusion defects.

Our results have shown that global PET myocardial perfusion quantifications frequently have an adequate agreement between the three considered SPs; however, some aspects need to be notified. Adequate global SP agreement was commonly found in patients with normal perfusion and with fixed perfusion defects. In those two groups of patients, rest MBF and MFR quantifications were most consistent. Inadequate global SP agreement was commonly found in patients with reversible perfusion defects, especially in stress MBF and MFR. Meanwhile, suboptimal agreement between SPs was more frequently documented in the regional assessment than in the global assessment, especially in stress MBF and MFR quantifications of patients with reversible defects as well as in stress MBF of patients with normal perfusion. Agreement of these perfusion estimates was mostly found for regional estimations of the LAD

vascular territory. On the contrary, several comparisons that showed suboptimal agreement were provided especially by the RCA territory but also by the LCx territory.

Previous studies have already analyzed the reproducibility of SPs for the quantification of myocardial perfusion. Slomka et al reported the reproducibility ^{13}N -ammonia with different SPs in patients with low likelihood of CAD and patients with ischemia.⁷ In that study, a similar MFR was reported for each vascular territory among SPs, with some quantification discrepancies in the RCA territory due to a high spill-over fraction. Additionally, studies with $^{82}\text{rubidium}$ and ^{15}O -water have shown an adequate agreement and reproducibility between SPs.^{8,9,19–21} Nesterov et al reported consistent global MBF values in patients with suspected or known CAD when using the same kinetic model for $^{82}\text{rubidium}$; however, different kinetic models produced different values of global perfusion quantifications that worsened in the regional analysis.⁸ Harms et al reported comparable MBF values among SPs using ^{15}O -water, while MFR was considered less reliable than MBF.⁹ Similar to those studies, our results indicate that global myocardial perfusion quantifications may often have an adequate agreement among different SPs with some

discrepancies. In contrast with the previous studies, we report a lower agreement and reproducibility, especially in patients with reversible defects. Only a recent study of Yalcin et al has also reported significant differences of MBF and MFR between SPs in patients with hypertrophic cardiomyopathy.²²

There may be several explanations for the quantification inconsistencies between SPs. For instance, SPs have different methods of reorientation, contour detection, segmentation of vascular territories, and sampling of the left ventricle blood pool TAC.²³ Other technical differences among SPs are shown in the supplementary material 5. Likewise, SPs may process motion of the left ventricle during acquisition differently (automatically or manually). That cardiac, respiratory, and patient motion produces misregistration mainly in the lateral and inferior wall (LCx and RCA vascular territories), which has shown to become worse during stress acquisition.^{24–26} Inconsistencies could in addition arise from different compartmental models being used. In comparison to the Hutchins model, Choi accounts for partial volume and spill-over effects.^{13,14} Consequently, the reported high spill-over fraction in the RCA territory could explain why we registered the largest agreement inconsistencies in the RCA territory flow estimates.^{22,27,28} This high spill-over fraction is worsened by the motion of the inferior wall of the left ventricle, a vascular territory of the RCA. In the current study, interestingly, patients with fixed defects had a better agreement than patients with reversible defects as well as patients with normal myocardial perfusion, the latter being a group that may include patients with some degree of microvascular dysfunction. Hence, our results may suggest that quantification of MBF is less reliable in the boundaries of normal and ischemic tissue. This observation is consistent with the study of Du et al, which reported that myocardial perfusion estimates are less accurate in patients with myocardial perfusion defects due to partial volume effects.²⁹ Those partial volume effects (spill-in and spill-out of activity) translate into mixing TACs of different kinds of tissues and produce less contrast between ischemic and non-ischemic tissues.²⁹

These interpretations are of major relevance when considering that MFR and stress MBF represent commonly used parameters for diagnosis of myocardial ischemia and infarction. Stress MBF has been previously proposed as a slightly better clinical perfusion parameter in CAD evaluation, yet our results indicate that agreement between SPs may not always be adequate. Furthermore, it has been previously proposed that MFR may correct for systematic differences because of its nature as a ratio, but our results suggest that agreement is not constant. Especially,

clinicians must realize that agreement might be inadequate in patients with myocardial ischemia, which may be of importance in patients with near-normal perfusion quantifications or those who undergo follow-up scans with different scanners. It can thus be suggested that adequate stress MBF and MFR thresholds should be established for each SP for the diagnosis of ischemia/infarction in patients referred due to with suspected impaired myocardial perfusion, preferably based on a universal database.

This study has some limitations. It is of retrospective design with selected patients and relatively small sample size. Moreover, we could not consider a reference standard in order to determine the differential performance of every SP. Future research should focus on determining the sources and the clinical impact of differences in SP quantifications in the continuum of ischemic heart disease, including whether if differences among SPs may be consistent. It is also recommended to determine whether our results can be extrapolated to other SPs that calculate MBF assuming other compartment models and other tracers. Further studies should also be performed to validate techniques that can enhance PET resolution, improve contour detection, correct for partial volume effects, and reconstruct perfusion images despite cardiac motion, such as cardiac motion frozen.^{29,30}

CONCLUSIONS

Agreement of global myocardial perfusion quantifications between SPs was often adequate. However, reversible defects demonstrated the worst agreement in global stress MBF and MFR and discrepancies showed to be regional dependent. Careful interpretations of PET myocardial perfusion quantification provided by different SPs are therefore warranted, especially when findings are compatible with myocardial ischemia.

NEW KNOWLEDGE GAINED

The present study, which includes not only patients with normal myocardial perfusion but also patients with ischemia and myocardial infarction, suggests that reproducibility between SPs should not be assumed.

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Disclosure

The authors report that they have no relevant relationships to disclose.

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