Diagnostic Value of ^{13}N-Ammonia Myocardial Perfusion PET: Added Value of Myocardial Flow Reserve

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The ability to obtain quantitative values of flow and myocardial flow reserve (MFR) has been perceived as an important advantage of PET over conventional nuclear myocardial perfusion imaging (MPI). We evaluated the added diagnostic value of MFR over MPI alone as assessed with ^{13}N-ammonia and PET/CT to predict angiographic coronary artery disease (CAD). **Methods:** Seventy-three patients underwent 1-d adenosine stress–rest ^{13}N-ammonia PET/CT MPI, and MFR was calculated. The added value of MFR as an adjunct to MPI for predicting CAD (luminal narrowing $\geq$ 50%) was evaluated using invasive coronary angiography as a standard of reference. **Results:** Per patient, the sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of MPI for detecting significant CAD were 79%, 80%, 91%, 59%, and 79%, respectively. Adding a cutoff of less than 2.0 for global MFR to MPI findings improved the values to 96% ($P < 0.005$), 80%, 93%, 89% ($P < 0.005$), and 92% ($P < 0.005$), respectively. **Conclusion:** The quantification of MFR in ^{13}N-ammonia PET/CT MPI provides a substantial added diagnostic value for detection of CAD. Particularly in patients with normal MPI results, quantification of MFR helps to unmask clinically significant CAD.

Key Words: myocardial flow reserve; ^{13}N-ammonia; positron emission tomography; diagnostic value; myocardial perfusion imaging

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The PET technique confers advantages over SPECT related to improved image resolution and intrinsic attenuation correction (*1*). In addition, in myocardial perfusion imaging (MPI) PET offers quantitative assessment of myocardial blood flow (MBF) at rest and pharmacologic stress allowing calculation of myocardial flow reserve (MFR) (*2*). The latter is an index to evaluate blood circulation from the epicardial coronary arteries down to the microcirculation (*3*), which therefore provides functional information far beyond the epicardial section of the coronary vascular tree. Relative MPI such as SPECT (or PET without quantitative measurement) relies on induction of flow heterogeneities by hyperemic stress, which may sometimes underestimate the extent of coronary artery disease (CAD), as only the most severely underperfused territory may be evidenced (*4*). By contrast, absolute flow and MFR may reveal the true extent of CAD even at an early stage of subclinical atherosclerotic CAD. This possibility is supported by recent results documenting an added prognostic value for MFR over PET MPI alone with either ^{13}N-ammonia (*5*) or ^{82}Rb (*6,7*). Interestingly, MFR remained predictive throughout a 10-y follow-up period (*5*). Although many studies have revealed a reversed correlation of increasing coronary artery lesion narrowing with decreasing hyperemic flow and MFR in the respective myocardial territory (*8–10*), its diagnostic added value over MPI PET has not been assessed systematically.

We evaluated the hypothesis that patients with decreased MFR (<2.0) would have a higher probability of CAD and that, thus, MFR would confer an added diagnostic value over MPI alone to predict angiographically documented CAD (coronary luminal narrowing $\geq$ 50%).

MATERIALS AND METHODS

Study Population

This study included 73 consecutive patients who underwent PET and invasive coronary angiography because of suspected impaired myocardial perfusion. In 21 patients PET was the primary test, followed by invasive coronary angiography because of abnormal PET perfusion findings, whereas the remaining 52 patients underwent PET after invasive coronary angiography. This decision was made by a joint heart team with a noninvasive and an interventional cardiologist, including all data such as clinical, semiquantitative, and quantitative MFR findings. Baseline patient characteristics are given in Table 1.

The need for written informed consent was waived by the institutional review board (local ethics committee) because of the nature of the study, which solely had clinical data collection. The study population was partly shared with the cardiac imaging registry reported elsewhere (*5*).

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TABLE 1
Baseline Patient Characteristics (n = 73)

Characteristic	Value
Mean age ± SD (y)	61 ± 11
Males (%)	73
Cardiovascular risk factors (%)	
Hypertension	62
Hypercholesterolemia	58
Diabetes mellitus	28
Smoking	46
Positive family history	32
Clinical history of CAD (%)	
CAD	38
History of myocardial infarction	21
Previous PCI	26
Typical angina symptoms (CCS class ≥ 2)	58
Dyspnea (NYHA functional class ≥ II)	51
Medication (%)	
Platelet aggregation inhibitors	92
Antiischemic agents	80
Lipid-lowering agents	61

PCI = Percutaneous coronary intervention, 4.3 ± 1.7 y ago; CCS = Canadian Cardiovascular Society; NYHA = New York Heart Association.

Image Acquisition

^{13}N-ammonia PET data were acquired in a 1-d single-session stress–rest protocol with standard adenosine stimulation (*11*) and intravenous administration of 700–900 MBq of ^{13}N-ammonia into a peripheral vein, followed by a transmission scan for attenuation correction either on a Discovery (LS/RX) PET/CT scanner or on an Advance PET scanner (both GE Healthcare) as previously reported in detail (*5,12,13*).

Data Analysis

The 17-segment model and the semiquantitative scoring system (0 = normal, 1 = mildly abnormal, 2 = moderately abnormal, 3 = severely abnormal, and 4 = complete defect) for detecting severity and extent was used to assess regional ^{13}N-ammonia uptake, as recommended by the American Society of Nuclear Cardiology (*14*). Scans were considered normal if the summed stress score was less than 4, mildly abnormal if the summed stress score was 4–8, and moderately to severely abnormal if the summed stress score was more than 8, as previously described in diagnostic (*15,16*) and prognostic (*17*) PET studies. Image interpretation was performed by 2 experienced nuclear cardiologists, and diverging interpretations were resolved by consensus.

Quantitative MBF was assessed using the PMOD software (version 2.1 to 3.2; PMOD Technologies Ltd.) developed and validated at our institution (*18–20*). Briefly, a spheric region of interest was set into the blood pool of the left ventricle. Blood pool and myocardial time–activity curves were determined from dynamic frames and corrected for radioisotope decay. MBF was assessed by model fitting of the blood pool and myocardial time–activity curves (*21*), correcting for partial volume and spillover, as previously reported (*22*). MFR was determined as the ratio of hyperemic MBF to resting MBF, and a value of less than 2.0 was considered abnormal, as previously suggested (*3*) and supported by prognostic data (*5*). In addition, this cutoff was confirmed by receiver-operating-characteristic curve analysis in the present study. Thus, for the combined interpretation of MPI and MFR, patients with a perfusion defect were classified as having abnormal findings (regardless of MFR), and those with normal MPI findings were reclassified according to MFR as having abnormal (MFR < 2) or definitely normal (MFR ≥ 2) findings. This combined interpretation was explored also for the regional values of the 3 main coronary territories, that is, the right coronary artery, left anterior descending artery, and circumflex artery. A regional true-negative finding was defined as normal perfusion combined with a regional MFR of 2 or more and confirmed by lack of angiographic stenosis in its subtending coronary artery. Conversely, a territory with an MFR of less than 2 or a perfusion defect was classified as true-positive if it was associated with an angiographic coronary lesion, taking into account that standard assumptions about vascular territory distribution in myocardial perfusion analysis may be subject to a substantial morphologic variability of the coronary tree (*23*).

Invasive Coronary Angiography

Invasive coronary angiography was performed by experienced interventional cardiologists according to clinical standards. A coronary stenosis was defined as a luminal narrowing of 50% or more by 2 independent interventional cardiologist observers. In cases of discrepancy, the decision was made by consensus on the basis of visual assessment, reflecting clinical routine in our (*24–26*) and most other catheterization laboratories worldwide (*27*).

Statistical Analysis

Quantitative variables were expressed as mean ± SD, and categoric variables as percentages. SPSS 19.0 software (SPSS) was used for statistical analysis. The MFR cutoff was identified by receiver-operating-characteristic curve analysis. The χ^2 test was used to assess the added value of MFR. A P value of less than 0.05 was considered as statistically significant.

RESULTS

During the enrollment period, 199 patients underwent PET MPI, of which 126 outpatients were not subsequently referred for invasive coronary angiography at our institution. Among these 126 patients without angiography, 54 had an abnormal PET MPI result (47 with fixed defects and 7 with minor ischemia) and 72 a normal PET MPI result. In 22 of the latter patients, MFR was impaired (mean MFR, 1.6 ± 0.3). Invasive coronary angiography was available in 73 patients, who were included in the final analysis.

Invasive coronary angiography revealed CAD in 53 patients (73% prevalence), of which 13 had 1-vessel, 21 had 2-vessel, and 19 had 3-vessel disease. ^{13}N-ammonia uptake was normal in 27 patients and abnormal in 46 patients, yielding a sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of visual PET MPI for detecting angiographic CAD of 79%, 80%, 91%, 59%, and 79%, respectively. By use of a receiver-operating-characteristic curve for global MFR, a value of less than 2.0 was confirmed as the optimal cutoff for best predicting CAD in invasive coronary angiography in patients with normal PET MPI results (area under the curve, 0.92 ± 0.06, with a 95% confidence interval of 0.80–1.00; $P < 0.001$). Adding a global MFR of less than 2.0 as

a criterion for CAD appropriately reclassified 9 patients with normal MPI results as having abnormal results, as was confirmed by invasive coronary angiography. This criterion improved sensitivity, specificity, positive predictive value, negative predictive value, and accuracy to 96% ($P < 0.005$), 80%, 93%, 89% ($P < 0.005$), and 92% ($P < 0.005$), respectively (Fig. 1). The per-vessel analysis in those patients with regional MFR available ($n = 47$) revealed a sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of 73%, 49%, 67%, 57%, and 63%, respectively. These values improved significantly to 91%, 71%, 81%, 86%, and 83%, respectively ($P < 0.001$), after regional MFR was added.

DISCUSSION

For almost 2 decades, the ability of PET MPI to quantify MBF has been suggested as having potential added value over visual analysis alone. However, although numerous reports have documented an inverse relationship between the severity of coronary luminal narrowing and MFR, no data on an added diagnostic value of MFR as assessed by ^{13}N-ammonia and PET are available.

To our knowledge, our results are the first to document an added clinical diagnostic value for MFR over MPI alone to detect angiographic CAD. This added value is particularly evidenced by the fact that 33% of patients with normal MPI findings were correctly reclassified as having abnormal findings when MFR information was added (Fig. 2). It is known that decreased perfusion tracer uptake in MPI is based on induction of flow heterogeneities due to flow-limiting epicardial coronary lesions, whereas segments with the quantitatively highest tracer uptake are considered the reference region with supposedly normal perfusion. The latter territory, however, may also be subtended by a diseased coronary artery, decreasing the sensitivity of MPI and explaining why, in one study, only 29% of patients with 3-vessel disease had defects in all 3 coronary territories (*4*). In this context, it is not surprising that the addition of quantified MFR based on absolute MBF values substantially improves the sensitivity of PET MPI while preserving specificity. A cutoff of less than 2 for abnormal MFR findings has been suggested throughout the literature and has recently been shown to be clinically meaningful when outcome is used as a standard of reference (*5*). Therefore, in the present study this cutoff for MFR was applied. This decision was supported by receiver-operating-characteristic curve analysis using invasive coronary angiography as the anatomic reference, which confirmed its validity.

Adding MFR to MPI reclassified a third of all normal MPI findings. As a result, accuracy increased significantly after the addition of MFR from 79% to 92% ($P < 0.005$), mainly because of an increase in sensitivity from 79% to 96%, that is, from the lower end to clearly above the range of sensitivities reported in a recent metaanalysis (*28*). Of note, adding functional data improved agreement with anatomic angiographic findings, whereas invasive functional data such as fractional flow reserve (*29*) were not assessed in the present study. This finding could at least in part be due to the fact that global MFR reflects coronary disease beyond the epicardial section of the coronary tree involving the microcirculation (Fig. 2), including endothelial dysfunction, supporting recent findings in patients with diabetes mellitus (*30*) and helping to explain the increased sensitivity in detecting CAD when global MFR is used as an adjunct to PET MPI. In fact, the use of global MFR appears to be most appropriate when the aspect of microcirculatory dysfunction is included, which is often associated with CAD. Furthermore, for practical reasons, the implementation of global MFR seems preferable over regional MFR because the reproducibility and the repeatability of global MFR is considerably superior to that of regional MFR (*31,32*). This observation is based not only on technical issues and count statistics of small sample sizes but also on biologic variability, as a profound spatial heterogeneity

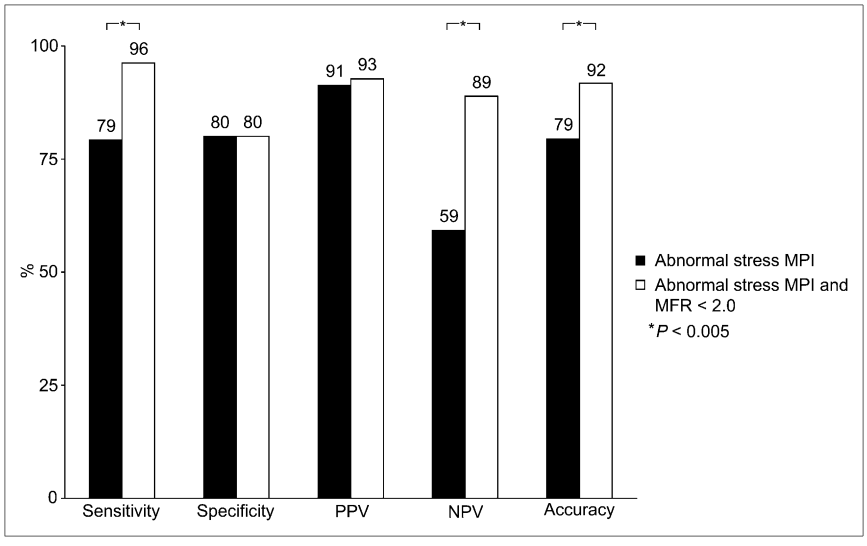

FIGURE 1. Added value of MFR over MPI alone to detect CAD. Adding MFR significantly improves accuracy of PET for detecting CAD ($P < 0.005$). Invasive coronary angiography served as standard of reference.

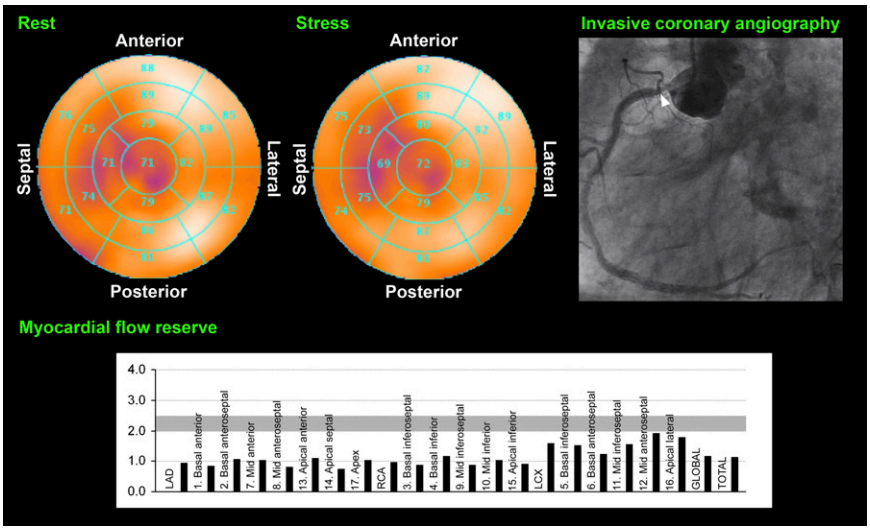

FIGURE 2. Normal PET MPI in CAD. Cardiac ^{13}N-ammonia PET shows normal MPI at rest and at adenosine-stress but abnormal MFR, indicating global myocardial underperfusion. Invasive coronary angiogram reveals significant right coronary artery stenosis (arrowhead). LAD = left anterior descending artery; RCA = right coronary artery; LCX = left circumflex artery.

has been observed in regional MBF at rest and in response to vasodilator stress (*33,34*). The anatomic variability of the coronary tree is another source that might contribute to the lower per-segment performance, as the accuracy measurements are based on assumptions of standard myocardial distribution territories which—unfortunately—correspond in only 50%–60% with the real anatomic coronary tree (*23*). Nevertheless, even in the segmental analysis, the addition of MFR yields a significant increase in accuracy, based mainly on a substantial increase in specificity and negative predictive value.

Noninvasive evaluation of ischemia is typically recommended in patients with an intermediate probability of CAD. The fact that CAD prevalence was 73% may therefore be perceived as a potential limitation of the present study, as such a high prevalence usually tends to yield a lower negative predictive value. This notion, however, would also hold true after adding the MFR information. The fact that negative predictive value increased substantially from 59% to 89% after MFR was implemented underlines its strong clinical validity. Furthermore, the present study offers diagnostic data but was not designed to report prognostic information. Future studies should be designed to evaluate the impact of a PET-guided choice of treatment strategy on outcome.

CONCLUSION

The quantification of MFR in ^{13}N-ammonia PET/CT MPI provides a substantial added diagnostic value for detection of CAD. Particularly in patients with normal MPI findings, quantification of MFR helps to unmask clinically significant CAD.

DISCLOSURE STATEMENT

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