



Comparison of Positron Emission Tomography Measurement of Adenosine-Stimulated Absolute Myocardial Blood Flow Versus Relative Myocardial Tracer Content for Physiological Assessment of Coronary Artery Stenosis Severity and Location

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OBJECTIVES This study tests the hypothesis that absolute measurement of adenosine (Ado)-stimulated myocardial blood flow (MBF_{Ado}) is superior to measurement of relative tracer uptake for identification of hemodynamically significant coronary artery disease (CAD).

BACKGROUND Positron emission tomography measurement of absolute myocardial blood flow (MBF) (¹³N-ammonia) with Ado has the capability to more accurately assess hemodynamic severity of CAD than measurement of relative tracer content (TC) (nCi/ml) during Ado, which by definition depends on at least 1 normal zone to which others are compared.

METHODS A total of 27 patients (20 male, 58 ± 11 years, mean ± SD) with known or suspected CAD and 21 normal subjects (13 male, 38 ± 10 years) were studied. Parametric (K1) MBF images and TC sum images were analyzed. A stenosis ≥70% defined significant CAD. The receiver-operator characteristic curve (ROC) analysis area under the curve (AUC) compared MBF and TC results. Cut-point analysis for sensitivity, specificity, and accuracy showed the best MBF criteria for CAD as MBF_{Ado} <1.85 ml/min/g and the best TC as <70% maximum. The myocardial blood flow reserve ratio (MBFR) (optimal <2.0×) also was studied.

RESULTS The ROC analysis of PET parameters showed that MBF_{Ado} was superior to <70% maximum uptake for CAD detection (n = 144 vessels; AUC 0.900 vs. 0.690, respectively, p < 0.0001) and was marginally greater than MBFR (0.856; p = 0.10). For CAD cut-point analysis, MBF_{Ado} accuracy exceeded TC (0.84 vs. 0.72, respectively, p = 0.005), as did sensitivity (0.81 vs. 0.48, respectively; p = 0.001). Specificity of MBF_{Ado} for CAD classification (0.85) was comparable to TC (0.82; p = NS). Sensitivity, specificity, and predictive accuracy for MBFR were 0.62, 0.85, and 0.79, respectively. The difference in specificity was not significant versus MBF_{Ado}. However, MBF_{Ado} was more sensitive than MBFR (p = 0.01). The difference in predictive accuracy was borderline (p = 0.06) in favor of MBF_{Ado}.

CONCLUSIONS Measurement of Ado-stimulated absolute MBF is superior to relative measurement of myocardial tracer retention for identification of CAD and can be accomplished with a single MBF_{Ado} measurement. (J Am Coll Cardiol Img 2009;2:751–8) © 2009 by the American College of Cardiology Foundation

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Prior studies have shown that retention of ^{13}N -ammonia in positron emission tomography (PET) myocardial perfusion scans may not accurately reflect the absolute level of myocardial blood flow (MBF) at the time of tracer injection (1,2). A widely accepted tracer kinetic model for obtaining K1 (1,3,4), a measure of MBF (ml/min/g), identifies back diffusion of the tracer into blood (k2) and incorporation of ^{13}N -ammonia into glutamine (k3) as potential causes of disparity between initial myocardial uptake (i.e., K1) and equilibrium

were in good health, asymptomatic, free of cardiac risk factors, and had not had cardiac catheterization. The Partners Institutional Review Board approved the study.

PET measurements of MBF and image analysis. The PET imaging was performed on a Scanditronix PC4096 (General Electric, Milwaukee, Wisconsin) whole-body tomography machine (1,3,6-11). At baseline, approximately 25 mCi of ^{13}N -ammonia was administered intravenously over 30 s, with dynamic imaging begun just before injection.

Subsequently, radioactivity was allowed to decay for at least 30 min. Next, 2 min after starting an infusion of Ado (Adenoscan, Astellas Pharma US, Deerfield, Illinois) at $140 \mu\text{g}/\text{kg}/\text{min} \times 6 \text{ min}$, dynamic data acquisition was begun, and several seconds later approximately 25 mCi of ^{13}N -ammonia was administered.

Attenuation-corrected ^{13}N -ammonia images were reconstructed with a filtered back projection algorithm and yielded an output resolution of 7.8 mm in the transverse plane. A region of interest placed over the left ventricular cavity was used to generate the arterial input function for the tracer kinetic model used to compute K1 (1). The K1 values were converted to MBF (ml/min/g) (3).

The K1 images were analyzed in a blinded fashion at base, mid, and distal left ventricular levels (Fig. 1). Regions of interest at each level were placed over myocardial segments of the left anterior descending artery (LAD) (septal, anteroseptal, anterior, anterolateral), left circumflex artery (LCX) (lateral, inferolateral), and right coronary artery (RCA) (inferior and inferoseptal) (3). The same regions of interest were analyzed for the summed images to measure tracer content (TC) (nCi/ml).

Data analysis. DEFINITION OF CAD. Coronary arteriograms were analyzed visually by an experienced invasive cardiologist blinded to PET data. Lumen diameter reduction $\geq 70\%$ defined hemodynamically significant CAD.

TRAINING AND VERIFICATION DATA SETS. The list of patients and subjects was alphabetized, and every other one was assigned to a training group ($n = 24$) to develop optimal criteria for detection of CAD. The best criteria subsequently were applied to the verification set ($n = 24$ remaining patients/subjects). The PET criteria were tested for sensitivity and specificity to determine which performed best (greatest sensitivity-specificity product) for detection of CAD. Based on prior work (1,6), Ado-stimulated myocardial blood flow (MBF_{Ado}) at cutoff points of $<1.65 \text{ ml}/\text{min}/\text{g}$, $<1.85 \text{ ml}/\text{min}/\text{g}$,

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distribution of the tracer. Tracer retention (k3) has been shown by others to be an indicator of myocardial viability (2). Similar considerations apply to ^{82}Rb , whose initial myocardial uptake may differ from retention at later time points depending on myocardial viability (5). Accordingly, the present study was designed to test the hypothesis that absolute measurement of MBF by the PET ^{13}N -ammonia technique is superior to relative measurement of myocardial tracer retention for identification of hemodynamically significant coronary artery disease (CAD) ($\geq 70\%$ lumen diameter stenosis). We also tested the hypothesis that a single measurement of absolute MBF under conditions of adenosine (Ado) stress is adequate for this purpose and thereby eliminates the requirement for a 2-injection study comparing rest and stress MBF, or more commonly, relative tracer distribution.

METHODS

Patient/subject population. Subjects and patients were selected from a database ($N = 157$) studied according to the PET myocardial perfusion protocol used in our laboratory (1,3,6-11). The vast majority of patients have been reported previously in the context of other unrelated studies (1,3,6-11). We selected patients with known or suspected CAD who had had clinically indicated cardiac catheterization within 1 year of the PET study without interval change in their clinical condition ($N = 27$; 20 male, 58 ± 11 years, mean \pm SD). Patients with coronary artery bypass graft or prior myocardial infarction were excluded. Normal volunteers (subjects, $N = 21$; 13 male, 38 ± 10 years)

ABBREVIATIONS AND ACRONYMS

Ado	= adenosine
AUC	= area under the curve
CAD	= coronary artery disease
LAD	= left anterior descending coronary artery
LCX	= left circumflex coronary artery
MBF	= myocardial blood flow
MBF_{Ado}	= adenosine-stimulated myocardial blood flow
MBFR	= myocardial blood flow reserve ratio
MPI	= myocardial perfusion imaging
PET	= positron emission tomography
RCA	= right coronary artery
ROC	= receiver-operator characteristic curve
TC	= tracer content

and <2.00 ml/min/g in 2, 3, or 4 myocardial segments of a given coronary artery were tested (i.e., 9 combinations). The ratio of Ado-stimulated to rest MBF (myocardial blood flow reserve ratio [MBFR]) was tested at cut points of $<2.0\times$, $<2.5\times$, and $<3.0\times$ for 2, 3, or 4 myocardial segments of a given coronary artery (i.e., 9 combinations). Relative TC cutoff criteria of $<70\%$ maximum, $<75\%$ maximum, and $<80\%$ maximum for 2, 3, or 4 segments of a given coronary territory also were tested (i.e., 9 combinations).

Data reduction and receiver-operator characteristic curve (ROC) analysis. The PET scans had 24 segments (Fig. 1). Tracer uptake during Ado was normalized to the segment with highest concentration (nCi/ml). The PET data were averaged for each vascular territory ($N = 48 \times 3 = 144$ vessels) to obtain a single value for each parameter. The vessels were treated as independent entities for statistical analyses. A subject-wise analysis also was performed for each parameter to determine which best classified all coronary vessels in a given individual.

Statistics. Data are expressed as mean \pm SD. The McNemar test compared the significance of differences between PET parameters for prediction of CAD. Paired and unpaired Student *t* test and chi-square test were used as indicated. ROC curves for detection of CAD were obtained for each PET parameter. The areas under the curve (AUC) were computed by fitting a logistic regression model and were compared using a nonparametric method (12), which takes into account the correlated nature of the data. The method avoids strong assumptions on the distribution of the data. A sample size of 144 arteries provides 80% power to detect a minimum difference of 0.20 AUC units between 2 ROC curves using 2-sided test with 5% type I error (13). Values of $p < 0.05$ were considered statistically significant.

RESULTS

Patient/subject population—training versus verification data sets. Training and verification data sets did not differ significantly regarding age (51 ± 16 vs. 48 ± 17 , respectively; $p = 0.45$), sex (male/female = 16/8 vs. 17/7, respectively; chi-square = 0.0, $p = \text{NS}$), and distribution of known or suspected CAD versus normal subjects (CAD/normal subjects = 14/10 vs. 13/11, respectively; chi-square = 0.0, $p = \text{NS}$) (Table 1). Accordingly, the data sets were combined. Patient/subject clinical and hemodynamic information are

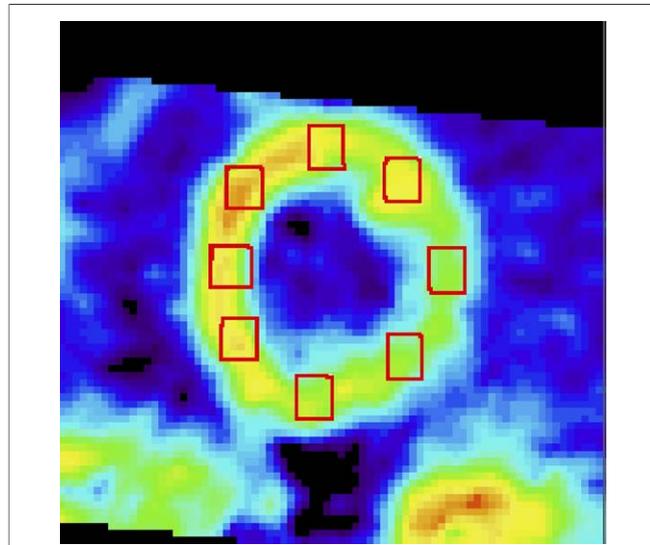


Figure 1. ROI Placement

A short-axis uptake image (base level) with ROIs drawn is shown for a study patient. The ROIs were reproduced at mid and distal LV levels. K1 images were analyzed similarly. LV = left ventricle; ROI = region of interest.

shown in Table 1. None of the normal subjects were taking medications.

ROC analysis. The ROC curves for each PET parameter for all coronary vessels are shown in Figures 2A through 2C. The AUC for MBF_{Ado} (0.900) exceeded that for $<70\%$ maximum tracer uptake (0.690, $p < 0.0001$). The MBF_{Ado} AUC was marginally greater than MBFR (0.856; $p = 0.10$). The MBFR AUC exceeded that of $<70\%$ maximum tracer uptake ($p < 0.005$).

The ROC analysis for the LAD alone is shown in Figures 3A and 3B, and for the LCX and RCA combined in Figures 4A and 4B. The AUC for MBF_{Ado} for LAD (0.922) exceeded that for $<70\%$ maximum tracer uptake (0.709, $p = 0.03$). In contrast, the AUC for MBFR (0.863) did not differ from that of $<70\%$ maximum tracer uptake ($p = 0.15$).

The AUC for MBF_{Ado} for LCX + RCA (Figs. 4A and 4B) exceeded that for $<70\%$ maximum tracer uptake (0.897 vs. 0.738, respectively, $p = 0.02$). The AUC for MBFR (0.864) did not differ from that of $<70\%$ maximum tracer uptake ($p = 0.09$).

The ROC analysis of PET parameters in subjects on ($n = 19$) versus off ($n = 29$) beta-blockers was performed. Patients on beta-blockers were older (59 ± 12 years vs. 43 ± 14 years, respectively, $p < 0.001$), and were more likely to have CAD (chi-square = 12.3, $p < 0.005$) and hypertension (chi-square = 10.5, $p < 0.005$) versus individuals who were not, 72% of whom were normal subjects. The group not on beta-blockers had lower systolic arte-

rial pressure (119 ± 13 mm Hg vs. 138 ± 17 mm Hg, respectively, $p < 0.001$) but identical resting heart rate (64 ± 11 beats/min vs. 64 ± 12 beats/min, respectively). Thus, the beta-blocker group had slightly higher rate-pressure product (mm Hg/min) than those not taking beta-blockers ($8,817 \pm 2,209$ vs. $7,563 \pm 1,436$, respectively, $p = 0.04$),

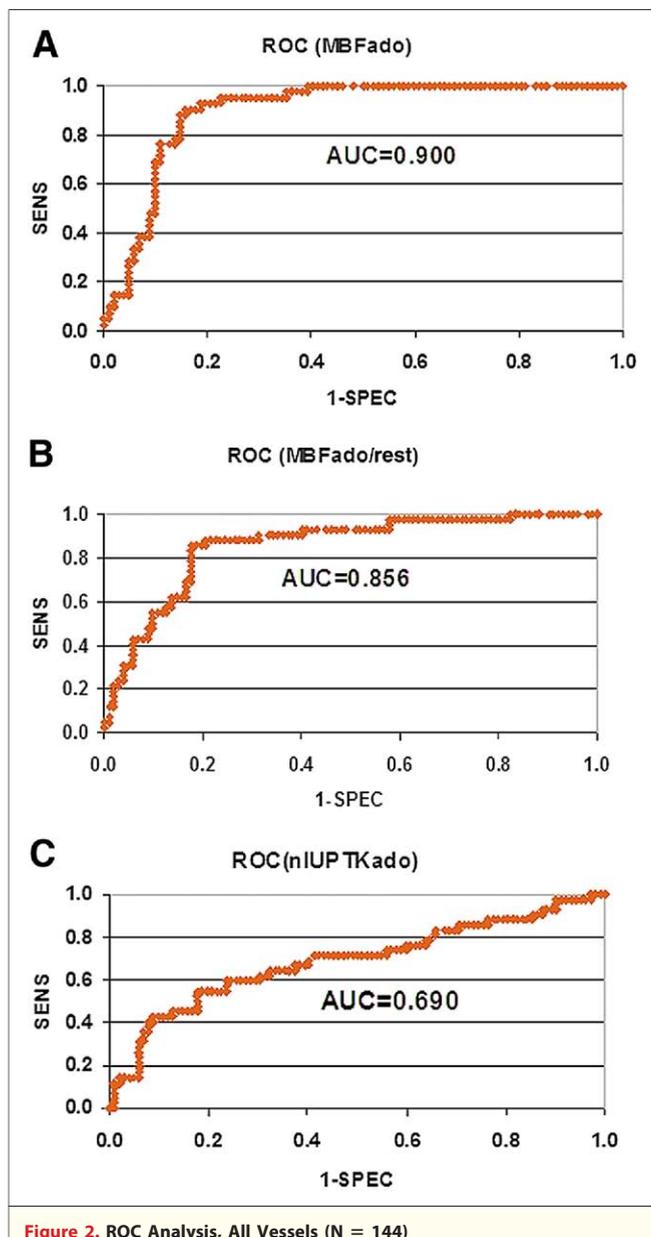


Figure 2. ROC Analysis, All Vessels (N = 144)

The ROC curves for PET parameters tested for all coronary vessels are shown. (A) MBFado; (B) MBFR (MBFado/rest); (C) normalized tracer uptake (nIUPTKado). The AUC for MBFado exceeded nIUPTKado ($p < 0.0001$). The MBFado did not differ from MBFR ($p = 0.10$). AUC = area under the curve; MBFado = adenosine-stimulated myocardial blood flow; MBFR = myocardial blood flow reserve ratio; PET = positron emission tomography; ROC = receiver-operator characteristic curve; SENS = sensitivity; SPEC = specificity.

Table 1. Patient/Subject Clinical Characteristics and Hemodynamic Parameters

N (male/female)	48 (33/15)
Mean age \pm SD (range) (yrs)	49 ± 15 (23–81)
Cardiac catheterization	27
Coronary anatomy	
3-vessel disease	7
2-vessel disease	9
1-vessel disease	3
All patent*	8
Medications	
ACEI/ARB	15
Beta-blockers	19
HMG-CoA reductase inhibitor	8
CCB	5
Oral nitrates	15
Electrocardiogram†	
Normal	25
NSSTW	22
IVCD/LBBB	5
Hemodynamic parameters (mean \pm SD, N = 48)	
Rest	
HR (beats/min)	64 ± 11
SAP (mm Hg)	127 ± 17
RPP (mm Hg/min)	$8,059 \pm 1,866$
Adenosine	
HR (beats/min)	88 ± 24 ‡
SAP (mm Hg)	123 ± 19
RPP (mm Hg/min)	$10,818 \pm 3,612$ ‡

*Five patients with atypical chest pain, 1 with dilated cardiomyopathy, 2 with patent stents. †Four patients had both NSSTW and IVCD/LBBB. ‡ $p < 0.001$ versus rest.

ACEI/ARB = angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; CCB = calcium channel blocker; HMG-CoA = 3-hydroxy-3-methylglutaryl-coenzyme A; HR = heart rate; IVCD/LBBB = intraventricular conduction delay/left bundle branch block; NSSTW = nonspecific ST/T wave abnormalities; RPP = rate-pressure product; SAP = systolic arterial pressure.

although rest MBF did not differ (0.86 ± 16 vs. 0.76 ± 06 , respectively, $p = \text{NS}$).

In subjects on beta-blockers, the AUC for MBFado (0.839) exceeded that for MBFR (0.720, $p < 0.05$) as well as $<70\%$ maximum tracer uptake (0.645, $p = 0.03$). In individuals off beta-blockers, the AUC for MBFado (0.925) did not differ from that of MBFR (0.932) but exceeded that for $<70\%$ maximum tracer uptake (0.699, $p < 0.005$).

Optimal MBF and tracer retention cut-point analysis.

The best MBFado cut-point was <1.85 ml/min/g. The best MBFR was $<2.0\times$. Thus, sensitivity, specificity, and predictive accuracy for MBFado were 0.81, 0.85, and 0.84, respectively versus 0.62, 0.85, and 0.79 for MBFR. The difference in specificity was not significant. However, MBFado was more sensitive than MBFR ($p = 0.01$), whereas the

difference in overall predictive accuracy was borderline ($p = 0.06$).

The best ^{13}N -ammonia retention criterion was $<70\%$ maximum. Thus, sensitivity, specificity, and predictive accuracy for ^{13}N -ammonia retention criteria were 0.48, 0.82, and 0.72, respectively.

Comparison of optimal MBF versus ^{13}N -ammonia retention criteria for CAD detection. In a subject-wise analysis requiring all 3 coronary vessels to be correctly classified, MBFado exceeded tracer uptake $<70\%$ maximum (10 of 10 discordant pairs correct by MBFado ($p < 0.005$)). The MBFado also classed 2.52 ± 0.71 coronary arteries per individual correctly vs. 2.17 ± 0.86 by tracer uptake ($p < 0.005$).

Detection of CAD was better by MBFado versus tracer uptake $<70\%$ maximum (25 of 33 discordant pairs, 76%, $p = 0.005$). Accordingly, the predictive accuracy (true positive + true negative/all tests) of MBFado (0.84) for detection of CAD exceeded that of tracer uptake $<70\%$ maximum (0.72) and the McNemar test result, by definition, identical to that for detection of CAD. The specificity of MBFado (0.85) did not differ significantly versus tracer uptake $<70\%$ maximum (0.82). However, sensitivity of MBFado (0.81) exceeded that of tracer uptake $<70\%$ maximum (0.48; 15 of 16 discordant pairs, 94% correct by MBFado, $p = 0.001$).

Detection of LAD stenoses by MBFado was more sensitive than that of tracer uptake $<70\%$ maximum (8 of 8 discordant pairs, $p < 0.02$). Specificity and accuracy did not differ. Because the LCX and RCA territories overlap and clinically carry a better prognosis in terms of ischemia or infarct vis-à-vis the LAD, they were combined to compare MBFado and tracer uptake criteria for detection of CAD. The MBFado specificity did not differ significantly from that of $<70\%$ maximum tracer uptake. The MBFado sensitivity was marginally greater than that for $<70\%$ maximum tracer uptake (7 of 8 discordant pairs, 78%, $p = 0.08$). Accuracy for MBFado exceeded that of $<70\%$ maximum tracer uptake (17 of 23 discordant pairs, 74%, $p < 0.04$).

DISCUSSION

This study tests the hypotheses that: 1) measurement of Ado-stimulated absolute MBF is superior to that of quantitative measurement of relative myocardial tracer retention for identification of CAD; and 2) a single measurement of MBFado would prove adequate for this purpose. The data obtained support both hypotheses.

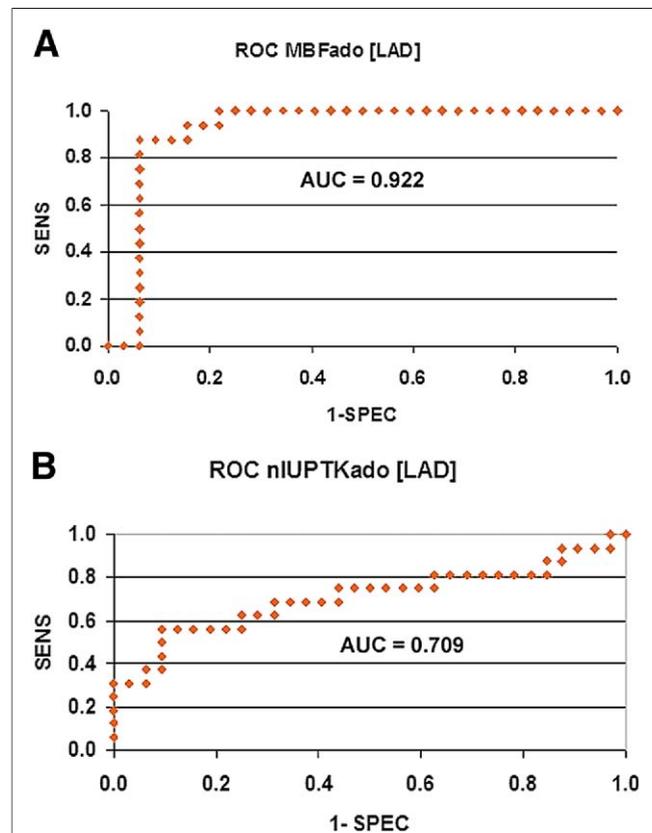
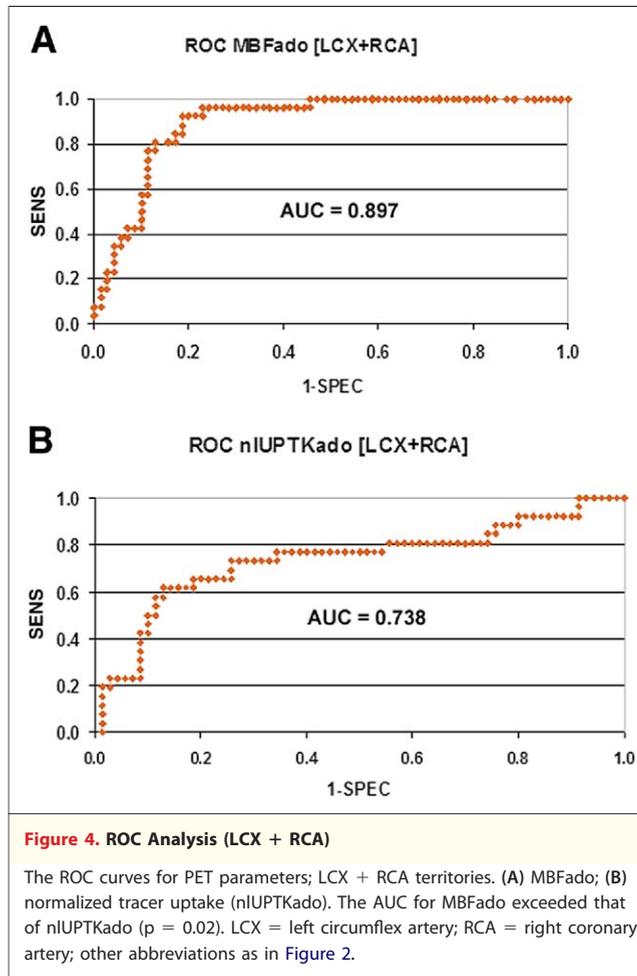


Figure 3. ROC Analysis, LAD Only

The ROC curves are shown for PET parameters; LAD territory. (A) MBFado; (B) normalized tracer uptake (nIUPTKado). The AUC for MBFado exceeded that of nIUPTKado ($p = 0.03$). LAD = left anterior descending coronary artery; other abbreviations as in Figure 2.

The ROC analysis showed that MBFado exceeded $<70\%$ maximum uptake with Ado stress ($p < 0.0001$) (Figs. 2A to 2C); MBFado also showed marginally greater AUC versus MBFR ($p = 0.10$) (Figs. 2A to 2C). The ROC analysis for CAD in the LAD alone and in the combined LCX + RCA distributions showed that MBFado exceeded $<70\%$ maximum uptake in both the LAD distribution ($p = 0.03$) (Figs. 3A to 3B) and in the combined LCX + RCA distributions ($p = 0.02$) (Figs. 4A and 4B).

The best cut-point for CAD detection by MBFado exceeded $<70\%$ maximum uptake for classification of all 3 major coronary arteries in a subject-wise analysis ($p < 0.005$), correct classification of all coronary vessels ($p = 0.005$), and thus predictive accuracy. Although sensitivity for detection of CAD in the LAD distribution was superior by MBFado vs. $<70\%$ maximum uptake ($p < 0.02$), specificity and overall accuracy did not differ. However, accuracy for detection of CAD in the



combined LCX + RCA territories by MBFado exceeded that of <70% maximum uptake ($p < 0.04$). Sensitivity of MBFado was marginally better than <70% maximum uptake ($p = 0.08$). Specificity did not differ between the two.

A single measurement of MBFado was more sensitive, equally specific, and modestly although not significantly better for accuracy in detection of CAD versus MBFR. Although MBFR with a cutoff of <2.0-fold increase has been used to detect CAD (14), such measurements are quite sensitive to the level of rest MBF. Thus, ratios >2 may result when rest MBF is relatively reduced (Fig. 5). Accordingly, MBFado likely is superior to MBFR for CAD detection.

Measurement of MBFado may be thought of as the noninvasive equivalent of the invasive fractional flow reserve measurement (15). A fractional flow reserve <0.75 is a reliable indicator of flow-limiting CAD (15), and because of compensatory microvascular dilation distal to the stenosis at rest (16–18), reflects failure of MBF to augment sufficiently to prevent a decline in distal coronary pressure with intracoronary Ado. The measurement also is not influenced by beta-blockers (19), another similarity to MBFado (see the following text). Accordingly, measurement of absolute MBF with PET, especially with ^{18}F -fluorine labeled tracers (20), offers the prospect of improved detection of CAD with a substantially simplified clinical protocol.

Both MBFado and MBFR may be abnormal in the presence of diffuse microvascular disease absent CAD and will be reduced in proportion to the

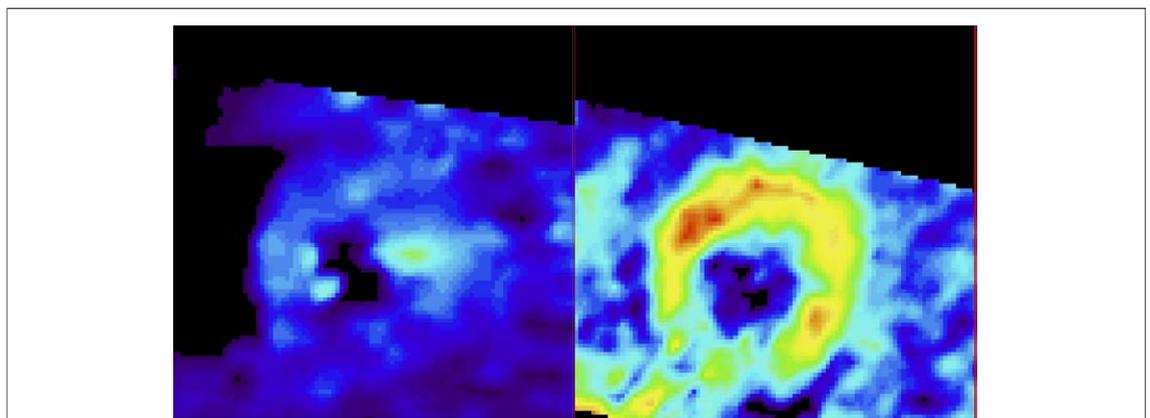


Figure 5. Patient Example (K1 vs. Uptake Images)

Shown are short-axis, K1 (left), and uptake (right) images obtained during adenosine (Patient A.B.-3VD, on beta-blocker). The MBFado was true positive for all coronary vessels (RCA = 0.57, LCX = 0.99, LAD = 1.13 ml/min/g). Relative uptake was false negative for the LAD (uptake 75% maximum). Moreover, visual interpretation of the uptake image indicates LAD territory is best, and so by definition normal. The MBFR for the LAD ($2.5\times$; MBFrest = 0.45) also is false negative. Note in each image that brighter colors indicate, respectively, higher values of K1 (left) or tracer content (right). LAD = left anterior descending coronary artery; other abbreviations as in Figure 4.

severity of it (7,21,22). However, MBFR will be of no more value than MBFado in making the distinction and, as noted previously, may be misleading. Thus, determination of optimal MBFado criteria for detection of microvascular disease without CAD, observed by ourselves (7) and others (23-25), will require additional quantitative PET studies of MBFado because it was not investigated in this report.

Beta-blockers played only a limited role in the outcome of the present study. As anticipated, MBFado was not impacted by the presence or absence of beta-blocker (AUCs did not differ significantly), a result consistent with microsphere data showing no effect of beta-blockade on the hyperemic response to a specific A2A receptor agonist (26). Further, for subjects on beta-blockers, the AUC for MBFado (0.839) exceeded that for MBFR (0.720, $p < 0.05$). Thus, when rest MBF is at usual levels (approximately 0.75 to 1.00 ml/min/g), MBFR is driven by MBFado, adds little additional information, and may at times be misleading (Fig. 5). Finally, the seemingly paradoxical finding that patients taking beta-blockers had a somewhat higher rate-pressure product and MBF than individuals who were not is accounted for by differences in age and health status, especially hypertension, between the groups. Nonetheless, differences in rest MBF were modest (12%) and not statistically significant, with absolute levels in the expected range for hemodynamic conditions of the study.

The applicability of these data to PET ^{15}O -water and ^{82}Rb myocardial perfusion imaging (MPI) is uncertain. The ^{82}Rb retention in the myocardium varies with time (5). Regions with scar lose ^{82}Rb more rapidly versus viable myocardium (5). Because early (15 to 110 s) and late (120 to 360 s) distributions may differ (5), results of relative analysis will vary with data acquisition timing. Accordingly, results of the present study concerning relative uptake analysis likely are applicable to clinical PET ^{82}Rb MPI. Absolute

measurement of MBF with ^{82}Rb PET (27), however, could provide quantitative results similar to those reported herein. PET ^{15}O -water measurement of absolute MBF is comparable to that of ^{13}N -ammonia (28). Thus, MBFado with ^{15}O -water should be comparable to ^{13}N -ammonia for CAD detection.

Study limitations. The study sample size and composition are reasonable (21 patients with CAD, 5 with atypical chest pain and normal coronary arteries, 1 with dilated cardiomyopathy, and 21 normal subjects). Thus, the incidence of CAD was 44%, an excellent one with intermediate pre-test probability of CAD (29) despite small sample size. However, because the study was retrospective, it suffers from all of the limitations of retrospective analysis. In addition, inclusion of subjects known to be normal may cause positive bias for estimates of sensitivity, specificity, and accuracy for PET parameters, a limitation however, that applies to each and does not change the major conclusions of the study.

CONCLUSIONS

The results of this study show that absolute measurement of MBFado by PET ^{13}N -ammonia is superior to that of relative measurement of myocardial TC for identification of CAD. Accordingly, quantitative MBFado measurement has the potential to greatly simplify clinical PET MPI for evaluation of patients with known or suspected CAD.

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