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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

Mohammad M. Hajjiri, MD,* Marcia B. Leavitt, BA,* Hui Zheng, PHD,†
Amy E. Spooner, MD,* Alan J. Fischman MD, PHD,‡ Henry Gewirtz, MD*
Boston, Massachusetts

OBJECTIVES This study tests the hypothesis that absolute measurement of adenosine (Ado)-stimulated myocardial blood flow (MBFado) 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) (^{13}N-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 MBFado <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 MBFado 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, MBFado 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 MBFado 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 MBFado. However, MBFado was more sensitive than MBFR (p = 0.01). The difference in predictive accuracy was borderline (p = 0.06) in favor of MBFado.

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 MBFado measurement. (J Am Coll Cardiol Img 2009;2:751–8) © 2009 by the American College of Cardiology Foundation

From the *Cardiology Division, Department of Medicine, and †Biostatistics Center, Massachusetts General Hospital, Harvard Medical School; and the ‡Department of Nuclear Medicine, Shriner Burns Hospital, Boston, Massachusetts. Supported in part by unrestricted grants from Astellas Pharma US to Dr. Gewirtz.

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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 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) (≥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.

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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
MBFado = 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

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 ± SD). Patients with coronary artery bypass graft or prior myocardial infarction were excluded. Normal volunteers (subjects, N = 21; 13 male, 38 ± 10 years) 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 μg/kg/min × 6 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 ≥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 (MBFado) at cutoff points of <1.65 ml/min/g, <1.85 ml/min/g,