JACC: CARDIOVASCULAR IMAGING
VOL. 7, NO. 4, 2014

ISSN 1936-878X/$36.00
PUBLISHED BY ELSEVIER INC.
http://dx.doi.org/10.1016/j.jcmg.2014.01.001

Diagnostic Value of PET-Measured Longitudinal Flow Gradient for the Identification of Coronary Artery Disease

Ines Valenta, MD,* Alessandra Quercioli, MD,† Thomas H. Schindler, MD*
Baltimore, Maryland; and Geneva, Switzerland

OBJECTIVES The purpose of this study was to evaluate the diagnostic value of a positron emission tomography (PET)/computed tomography (CT)–determined longitudinal decrease in myocardial blood flow (MBF) gradient during hyperemia and myocardial flow reserve (MFR) for the identification of epicardial stenosis ≥50%.

BACKGROUND Although PET-determined reductions in MFR are increasingly applied to identify epicardial lesions in coronary artery disease (CAD), it may be seen as a suboptimal approach due to the nonspecific origin of decreases in MFR.

METHODS In 24 patients with suspected or known CAD, MBF was measured with ^{13}N-ammonia and PET/CT in ml/g/min at rest, during dipyridamole stimulation, and the corresponding MFR was calculated. MBF was also determined in the mid and mid-distal myocardium of the left ventricle (LV). A decrease in MBF from mid to mid-distal LV myocardium was defined as longitudinal MBF gradient. MBF parameters were determined in the myocardial region with stress-induced perfusion defect and with stenosis ≥50% (territory 1), without defect but with stenosis ≥50% (territory 2), or without stenosis ≥50% (territory 3).

RESULTS In territories 1 and 2 with focal stenosis ≥50%, the severity of epicardial artery stenosis correlated with the Δlongitudinal MBF gradient (stress-rest) ($r = 0.52$; $p < 0.0001$), while this association was less pronounced for corresponding MFR ($r = -0.40$; $p < 0.003$). On a vessel-based analysis, the sensitivity and specificity of the Δlongitudinal MBF gradient in the identification of epicardial lesions was higher than those for MFR (88% vs. 71%, $p \leq 0.044$; and 81% vs. 63%, $p = 0.134$, respectively). Combining both parameters resulted in an optimal sensitivity of 100% and intermediate specificity of 75%. The diagnostic accuracy was highest for the combined analysis than for the Δlongitudinal MBF gradient or MFR alone (94% vs. 86%, $p \leq 0.003$; and 94% vs. 70%, $p \leq 0.0002$).

CONCLUSIONS The combined evaluation of a Δlongitudinal MBF gradient and MFR may evolve as a new promising analytic approach to further optimize the identification of CAD lesions. (J Am Coll Cardiol Img 2014;7:387–96) © 2014 by the American College of Cardiology Foundation

From the *Division of Nuclear Medicine, Department of Radiology, and Division of Cardiology, Department of Medicine, Johns Hopkins University, Baltimore, Maryland; and the †Department of Specialties in Medicine, University Hospitals of Geneva, Geneva, Switzerland. This study was supported by a departmental fund from Johns Hopkins University, with contributions of the Clinical Research Center, University Hospital, and Faculty of Medicine, Geneva; the Louis-Jeantet Foundation; and the Swiss Heart Foundation. Dr. Schindler has received research grant no. 3200B0-122237 from the Swiss National Science Foundation; and has received support from the Gustave and Simone Prévot fund. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received October 18, 2013; revised manuscript received January 5, 2014, accepted January 7, 2014.

JACC: CARDIOVASCULAR IMAGING, VOL. 7, NO. 4, 2014
APRIL 2014:387–96

Assessment of left ventricular (LV) myocardial blood flow (MBF) at rest, during pharmacologically stimulated hyperemia, and the resulting myocardial flow reserve (MFR) with positron emission tomography (PET) or PET/computed tomography (CT) is increasingly applied to assess the flow-limiting effects of single lesions in multivessel coronary artery disease (CAD) (1–4). Such noninvasively-obtained information on hyperemic MBF and MFR has also been demonstrated to carry important prognostic information in patients with and without clinically-manifest CAD (5–7). Reductions in MFR in CAD patients, however, may be interpreted not only as a consequence of flow-limiting effects of epicardial stenosis, if present, but also in the context of microvascular dysfunction (3,7). Due to the relatively low specificity of reduced MFR (7,8), a clear identification of flow-limiting effects of epicardial lesions in the individual CAD patient sometimes may remain uncertain. In this direction, PET flow measurements of an abnormal decrease in MBF from the base to the apex of the LV during hyperemic flows, a so-called flow gradient, has been suggested to provide more detailed information on structural and functional alterations of epicardial artery in cardiovascular risk individuals (9–12). This proximal-to-distal flow gradient has been attributed to fluid dynamic consequences of CAD-induced diffuse luminal narrowing or to functional alterations of the epicardial coronary conduit vessels (9,10,13). As the longitudinal MBF gradient is assumed to be related predominantly to increases in epicardial resistance during hyperemic flows (12,13), it may provide more specific information on flow-limiting effects of epicardial stenosis than the conventional interpretation of MFR alone. According to this, we aimed to determine the diagnostic value of a PET/CT-determined longitudinal decrease in MBF (MBF gradient) during hyperemia and MFR for the identification of epicardial stenosis ≥50% in CAD patients.

ABBREVIATIONS AND ACRONYMS

CAD = coronary artery disease
CT = computed tomography
CVR = coronary vascular resistance
LAD = left anterior descending
LCx = left circumflex
LV = left ventricular
MBF = myocardial blood flow
MFR = myocardial flow reserve
PET = positron emission tomography
RCA = right coronary artery
ROC = receiver-operating characteristic
RPP = rate-pressure product
SDS = summed difference score
SSS = summed stress score

METHODS

Patient population. The study population comprised 24 patients (18 men, 6 women; mean age 67 ± 10 years) with stress-induced regional myocardial perfusion defects on ^{13}N-ammonia PET/CT images. Within 20 days of PET perfusion imaging, these patients underwent invasive coronary angiography (Table 1). Quantitative coronary angiography was performed to assess the severity of epicardial lesions identified during invasive coronary angiography. Patients were considered for study purposes, if coronary artery lesions of ≥50% diameter stenosis were located in the proximal part of the left anterior descending (LAD) (segments 12 to 13), left circumflex (LCx) (segments 18 to 19), and right coronary artery (RCA) (segments 1 to 3) according to the American College of Cardiology/American Heart Association guidelines (14). All CAD patients had normal wall motion on angiographic evaluation. In addition, 34 healthy individuals without known cardiovascular risk factors and normal stress-rest ^{13}N-ammonia PET/CT perfusion imaging served as a control group (Table 1). Cardiovascular risk factors included the presence of arterial hypertension, smoking, type 2 diabetes mellitus, hypercholesterolemia, or family history of CAD. Patients with evidence of left ventricular hypertrophy on echocardiography were excluded from study analysis. Vasoactive medications such as calcium-channel blockers, angiotensin-converting enzyme inhibitors, statins, as well as beta-blockers, and diuretics were discontinued at least 24 h before PET flow study. All study participants refrained from caffeine-containing beverages for ≥24 h and from smoking for ≥12 h prior to the PET study. The study was approved by the University Hospitals of Geneva Institutional Review Board (No. 07-184), and each participant signed the approved informed consent form.

PET/CT flow investigations. Myocardial perfusion and MBF, measured in ml/min/g, were assessed with ^{13}N-ammonia PET/CT, serial PET image acquisition (64-slice Biograph, HiRez TruePoint PET-CT scanner, Siemens Medical Solutions, Erlangen, Germany), and a 2-compartment tracer kinetic model, as described in detail previously (12). Pharmacologic vasodilation to stimulate hyperemic MBF increases was performed with standard infusion of dipyridamole (140 μg/kg/min). Myocardial perfusion at rest and during pharmacologic vasodilation was analyzed visually on reoriented short- and long-axis myocardial slices and semiquantitatively on the corresponding polar map from the last static 18-min transaxial PET image. For the semiquantitative analysis of the PET perfusion images, a 17-segment model and a 5-point grading system by 2 expert observers were applied (12). Summed stress score (SSS), summed rest score, and summed difference score (SDS) were calculated. An SSS <4 was considered normal, 4 to 8 mildly abnormal, 9 to 13 moderately abnormal, and >13 severely