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Fractional Flow Reserve of Infarct-Related Arteries Identifies Reversible Defects on Noninvasive Myocardial Perfusion Imaging Early After Myocardial Infarction

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OBJECTIVES We hypothesized that fractional flow reserve (FFR) of an infarct-related artery (IRA) early after myocardial infarction (MI) identifies inducible ischemia on noninvasive imaging.

BACKGROUND Early after MI, IRAs frequently have angiographically indeterminant lesions. Whether FFR can detect reversible perfusion defects early after MI when dynamic microvascular abnormalities are present is not known.

METHODS Rest and dipyridamole (DP)-stress ^{99m}Tc sestamibi single-photon emission computed tomography (SPECT) were performed in 48 patients 3.7 ± 1.3 days after MI, with 23 patients undergoing concurrent myocardial contrast echocardiography (MCE). Angiography, FFR, and percutaneous coronary intervention (PCI) of the IRA (as necessary) were subsequently performed. Follow-up SPECT was performed 11 weeks after PCI to identify true reversibility on baseline SPECT.

RESULTS The sensitivity, specificity, positive and negative predictive value, and concordance of FFR ≤0.75 for detecting reversibility on SPECT were 88%, 50%, 68%, 89%, and 71% (chi-square <0.001), respectively; which improved to 88%, 93%, 88%, 93%, and 91% (chi-square <0.001), respectively, for the detection of true reversibility. The corresponding values of FFR ≤0.75 for detecting reversibility on DP-MCE were 90%, 100%, 100%, 75%, and 93% (chi-square <0.001), respectively, and on either SPECT or MCE were 88%, 93%, 91%, 91%, and 91% (chi-square <0.001), respectively. The optimal FFR value for discriminating inducible ischemia on noninvasive imaging was 0.78.

CONCLUSIONS Fractional flow reserve of the IRA accurately identifies reversibility on noninvasive imaging early after MI. These findings support the utility of FFR early after MI. (J Am Coll Cardiol 2006;47:2187–93) © 2006 by the American College of Cardiology Foundation

Risk stratification after myocardial infarction (MI) may be performed either noninvasively (1–3) or angiographically (4,5). The latter provides only anatomic information, and stenoses of the infarct-related artery (IRA) often appear indeterminate.

Fractional flow reserve (FFR) has been developed as an invasive physiologic index of lesion severity and, if validated in this setting, would allow combined anatomic and physiologic evaluation of IRAs to determine suitability for revascularization. Although a FFR ≤0.75 correlates well with noninvasive determinants of ischemia in normal myocardium and late after MI (6,7), it is not known whether FFR has utility early after MI, a period characterized by microvascular injury and increases in microvascular resistance as well as dynamic flow changes.

We hypothesized that a FFR ≤0.75 of the IRA early after stabilized MI will correlate with inducible ischemia on noninvasive imaging. Although dipyridamole (DP)-stress ^{99m}Tc-sestamibi single-photon emission computed tomography (SPECT) is frequently used for early post-infarction risk stratification, it may underestimate reversibility early after MI. We therefore also compared FFR to DP myocardial contrast echocardiography (MCE), which offers better spatial resolution than SPECT.

METHODS

Study population. The Human Investigation Committee at the University of Virginia approved the protocol, and all patients consented to participate in the study. Patients referred for angiography two days after non–ST-segment elevation myocardial infarction (STEMI) and three days after STEMI were enrolled. The diagnosis of MI was supported by typical ischemic chest pain and/or a troponin I (TnI) ≥5 with electrocardiographic changes of ischemia. Exclusion criteria were: 1) prior MI within the infarction bed; 2) ongoing

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Abbreviations and Acronyms

DP = dipyridamole
DS = diameter stenosis
FFR = fractional flow reserve
IRA = infarct-related artery
MCE = myocardial contrast echocardiography
MI = myocardial infarction
NPV = negative predictive value
NS = not specified
PCI = percutaneous coronary intervention
PI = pulsing intervals
PPV = positive predictive value
QCA = quantitative coronary angiography
SDS = segmental difference score
SPECT = single-photon emission computed tomography
SRS = segmental rest score
SSS = segmental stress score
STEMI = ST-segment elevation myocardial infarction
TnI = troponin I

ischemia or hemodynamic instability; 3) prior bypass of the index artery; 4) contraindication to DP or FFR; 5) complex three-vessel or left main disease; or 6) occlusion of or inability to determine the IRA lesion.

Catheterization and angiography. Biplane left ventriculography was performed in right and left anterior oblique views. The infarct risk area was identified by two blinded investigators and defined as the number of segments on ventriculography supplied by the culprit lesion divided by a total of 14 segments (corresponding to the SPECT program).

A single observer performed quantitative coronary angiography (QCA) offline using a computer-assisted program (DICOM, Heartlab Inc., Westerly, Rhode Island) as previously described (8). The luminal diameter proximal and distal to the stenosis (reference diameter) and minimal luminal diameter were determined for all lesions. The percent diameter stenosis (DS) was calculated as the ratio of the minimal luminal diameter to reference diameter.

Determination of FFR. Following angiography, FFR was determined using a 0.014-inch sensor-tipped high-fidelity pressure wire (RADI Medical, Uppsala, Sweden) as previously described (8). Heparin (50 U/kg) was administered intravenously. Simultaneous distal coronary and aortic pressures were recorded at baseline and during hyperemia (induced by intracoronary adenosine-30 μg in the right coronary artery and 40 to 60 μg in the left coronary artery). The FFR was calculated as the ratio of the mean distal intracoronary pressure to mean aortic pressure at the time of peak hyperemia. The FFR measurements were repeated after percutaneous coronary intervention (PCI) in 37 of 43 patients.

Percutaneous intervention. Percutaneous coronary intervention was performed at the discretion of the clinician and interventionalist. All patients received glycoprotein IIb/IIIa inhibitors and intracoronary stents.

Noninvasive imaging. PROTOCOL. Rest-DP stress ^{99m}Tc-sestamibi SPECT and MCE were performed concurrently within 24 h of angiography and FFR determination. One hour after injection of 240 to 300 MBq of ^{99m}Tc-sestamibi at rest, SPECT imaging was performed using a Picker Prism 3000 triple-headed gamma camera (Picker, Cleveland, Ohio), followed by resting MCE. Three hours later, 0.56 $mg \cdot kg^{-1}$ of dipyridamole was administered over 4 min, followed by an intravenous injection of 750 to 900 MBq of ^{99m}Tc-sestamibi. Immediately following the administration of ^{99m}Tc-sestamibi, MCE was repeated. One hour later, stress SPECT images were obtained. Continuous monitoring of the electrocardiogram and vital signs were obtained during stress. Repeat rest-DP SPECT studies were performed three months following PCI.

^{99m}Tc-SESTAMIBI SPECT. Quantitative determination of segmental ^{99m}Tc-sestamibi uptake was performed using the University of Virginia program (14 segments per patient) (9). Two observers interpreted SPECT studies. Discordant interpretations were resolved by consensus. Individual segments were classified as being normal or abnormal. Abnormal stress perfusion defects were further classified as mild or severe. The abnormal stress images were compared with corresponding rest images and considered reversible, partially reversible, or fixed based on improved tracer uptake at rest. The SPECT reversibility was defined as at least one reversible or partially reversible segment in the infarct risk area.

For semiquantitative analysis, a segmental stress score (SSS) was derived from the stress images by allocating normal segments a score of 0, mild defect a score of 2, and severe defects a score of 4. Segmental rest scores (SRS) were allocated as follows: fixed defects: SRS = SSS; normal rest perfusion: SRS = 0; partially reversible mild/moderate defects: SRS = 1; partially reversible severe defects: SRS = 2. Segmental difference score (SDS), a semiquantitative marker of reversibility, was defined as the numeric difference between the stress and rest scores.

True negative SPECT was defined as a normal or fixed defect when the initial stress images were paired with post-PCI rest images (in order to adjust for known early post-MI reduced rest tracer uptake rendering reversible defects fixed). True positive SPECT was defined as reversible SPECT images (utilizing post-PCI rest images) that became fixed or normal after revascularization.

To investigate the ability of FFR to detect noninvasive ischemia in different degrees on infarction, we divided 21 patients with true noninvasive ischemia on SPECT or MCE into three groups based on TnI level: TnI <10 ng/dl, small MI; TnI 10 to 100 ng/dl, moderate MI; TnI >100 ng/dl, large MI.

MCE. For MCE, Definity (Bristol-Myers Squibb Medical Imaging, Billerica, Massachusetts) was diluted in saline and infused (AS50, Baxter, Deerfield, Illinois) at 90 to 120 ml^{h-1}. Digital cine loops of regional function and myocar-