Noninvasive Diagnosis of Coronary Artery Disease in Patients With Diabetes by Dobutamine Stress Real-Time Myocardial Contrast Perfusion Imaging

ABDOU ELHENDY, MD, PHD
JEANE M. TSUTSUI, MD
EDWARD L. O’LEARY, MD
FENG XIE, MD
ANNA C. MCGRAIN, BSN, RN
THOMAS R. PORTER, MD

OBJECTIVE — The aim of this study was to assess the accuracy of real-time myocardial contrast perfusion imaging (MCPI) during dobutamine stress in the diagnosis and localization of coronary artery disease (CAD) in patients with diabetes. Myocardial contrast echocardiography is a new technique that allows evaluation of myocardial perfusion. Its utility in diabetic patients has not been defined.

RESEARCH DESIGN AND METHODS — Dobutamine-atropine stress test was performed in conjunction with MCPI using Optison or Definity at rest and at peak stress in 128 patients with diabetes and suspected CAD who underwent coronary angiography within 1 month. CAD was defined as ≥50% stenosis in one or more coronary artery. MCPI was considered diagnostic of CAD in the presence of reversible perfusion abnormalities. The normalcy rate of MCPI was additionally determined in 18 asymptomatic nondiabetic patients with low probability.

RESULTS — CAD was detected in 101 (79%) patients by angiography. Reversible perfusion abnormalities were detected in 90 patients with and 13 patients without CAD. The overall sensitivity of MCPI was 89% (95% CI 83–95), specificity 52% (33–71), and accuracy 81% (75–88). Reversible abnormalities were detected in two or more vascular distributions in 44 of 56 patients with multivessel CAD and in 8 of 63 patients without CAD (sensitivity 68%, specificity 87%, positive predictive value 84%, and accuracy 79%). Regional sensitivity was 75% (65–85) for left anterior descending CAD, 71% (60–83) for left circumflex, and 67% (55–78) for right CAD. MCPI was normal in 16 of the 18 patients with low clinical probability of CAD (normalcy rate 89%).

CONCLUSIONS — MCPI is a useful noninvasive technique for the diagnosis and localization of CAD in diabetic patients. The extent of perfusion abnormalities can identify patients with multivessel CAD with a moderate sensitivity and high specificity.

Diabetes Care 28:1662–1667, 2005
Diabetes was defined as a fasting glucose level $\geq 140$ mg/dl or the need for insulin or oral hypoglycemic agents. Hypercholesterolemia was defined as a total cholesterol $\geq 200$ mg/dl or treatment with lipid-lowering medications. Proliferative retinopathy was determined by stereo fundus examination or a history of laser therapy for proliferative disease. Overt nephropathy was defined as an albumin excretion rate $>200$ µg/min on at least two of three timed urine samples and/or a serum creatinine level $>2$ mg/dl, renal failure, or renal transplant. Peripheral neuropathy was considered present if there was decreased or absent deep tendon reflexes or signs of sensory loss. Perioperative risk assessment was achievement of target heart rate (220 $-$ age). Reasons for test termination were achievement of target heart rate, maximal dose of dobutamine and atropine, hypertension (blood pressure $>240/120$ mmHg), symptomatic decrease in systolic blood pressure, symptomatic or sustained nonsinus tachycardia, and ST segment depression $>2$ mm in electrocardiogram leads without resting ST depression, severe angina, and any intolerable adverse effect considered to be the result of dobutamine or atropine. Metoprolol (1-10 mg) was used intravenously to reverse the side effects of dobutamine if these did not revert quickly after termination of the stress test.

**Echocardiographic imaging**

The contrast agents used for the study were perfluorocarbon-containing albumin-coated microbubbles (Optison; Mallinckrodt, St. Louis, MO; GE-Amersham, Princeton, NJ) in 87 patients and lipid-encapsulated perfluoropropane-filled microbubbles (Definity; Bristol-Myers Squibb Medical Imaging, North Billerica, MA) in 41 patients. Imaging was performed using commercially available ultrasound scanners (Philips Sonos 5500, Philips HDI 5000, or Siemens Acuson Sequoia C512) equipped with low-mechanical index real-time pulse sequence schemes. Imaging was performed by the use of pulse inversion Doppler (Philips ATL), Contrast Pulse Sequencing (Siemens Acuson Sequoia), or Power Modulation (Philips Agilent). The equipment was adjusted to achieve maximal nonlinear signal from contrast. Mechanical indexes were set to $\leq 0.3$ and frame rate to $\approx 25$ Hz. Time gain compensation and two-dimensional gain settings were adjusted to suppress signals from the myocardium before contrast injection. Images from apical views (four-chamber, two-chamber, and long-axis views) were obtained and digitized at rest and at maximal stress after the patient achieved $\geq 85\%$ predicted maximum heart rate or a test end point.

After optimization of the settings, a 0.2- to 0.3-ml calibration dose of Optison or 0.1- to 0.15-ml dose of Definity followed by saline flush was given. Setting corrections were made to optimize gain and minimize any tissue nonlinear signals. Imaging began with a similar contrast dose in the apical four-chamber view. A minimum of 15 s of image acquisition was performed following peak myocardial opacification until disappearance of contrast from the myocardium. Imaging was acquired from the apical two-chamber and apical long-axis views using the same method.

Myocardial perfusion was interpreted using the 16-segment model (37) by an independent investigator who was blinded to clinical data. Studies were interpreted as either normal or abnormal in each of the three coronary arterial territories. A reversible perfusion abnormality was defined as a perfusion defect during stress imaging that was not observed at resting imaging. This was considered diagnostic of CAD. A reversible defect was considered present when two contiguous

**Table 1 — Clinical data of the study patients**

<table>
<thead>
<tr>
<th>Clinical parameters</th>
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<tbody>
<tr>
<td>Reasons for referral</td>
<td></td>
</tr>
<tr>
<td>Evaluation of chest pain</td>
<td>57 (45)</td>
</tr>
<tr>
<td>Multiple risk factors</td>
<td>41 (32)</td>
</tr>
<tr>
<td>Perioperative risk assessment</td>
<td>30 (23)</td>
</tr>
<tr>
<td>Type 1 diabetes</td>
<td>26 (20)</td>
</tr>
<tr>
<td>Previous myocardial infarction</td>
<td>28 (22)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>98 (77)</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>83 (65)</td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td>29 (23)</td>
</tr>
<tr>
<td>$\beta$-Blockers</td>
<td>68 (53)</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>35 (27)</td>
</tr>
<tr>
<td>Diabetes management</td>
<td></td>
</tr>
<tr>
<td>Insulin</td>
<td>32 (25)</td>
</tr>
<tr>
<td>Oral hypoglycemic agents</td>
<td>61 (48)</td>
</tr>
<tr>
<td>Both</td>
<td>21 (16)</td>
</tr>
<tr>
<td>Diet only</td>
<td>14 (11)</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>11 (9)</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>12 (9)</td>
</tr>
<tr>
<td>Overt nephropathy</td>
<td>44 (35)</td>
</tr>
<tr>
<td>Previous stroke</td>
<td>8 (6)</td>
</tr>
<tr>
<td>Proliferative retinopathy</td>
<td>11 (9)</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>55 ± 12</td>
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</table>

Data are $n$ (%) or means ± SD.
segment failed to exhibited contrast enhancement during the washout of contrast following the bolus injection, as compared with other segments at the same depth in the same view. Contrast enhancement was additionally compared with the same segment at rest using a side-by-side image analysis. Attenuation from contrast or lung interference was considered present if any segment could not be visualized and was not distinguishable from surrounding tissue. The interobserver agreement on the presence of reversible perfusion defects on MCPI in our laboratory is 92%. The intrareader agreement is 92% (27).

The anterior septum, mid-posterior septum, anterior wall, and adjacent apical segments were assigned to the left anterior descending coronary artery (LAD). The lateral segments were assigned to the left circumflex coronary artery (LCx). The inferior and basal septal segments were assigned to the right coronary artery (RCA). The posterior wall was considered an overlap region and was assigned to either the LCx or RCA distribution. The apical inferior/posterior segments were also considered overlap regions and were assigned to the vascular territory with contiguous abnormalities. MCPI was considered diagnostic for CAD in the presence of reversible perfusion abnormalities. The feasibility for interpretation of stress MCPI in our laboratory is 96% for LAD distribution, 95% for RCA distribution, and 94% for LCx distribution (38).

Quantitative angiography
Coronary angiography was performed within 1 month (9 ± 7 days [means ± SD]) after the DSE using the Judkins’ technique. Quantitative measurements of coronary artery stenosis were made by an experienced interventional cardiologist blinded to DSE results using a hand-held electronic caliper (Tesa, Renens, Switzerland) (39). Measurements were expressed as the percentage of diameter narrowing using the diameter of the nearest normal-appearing region as a reference. CAD was defined as ≥50% luminal diameter stenosis in one or more major epicardial vessel. Twenty patients had previous coronary artery bypass surgery. In these patients, CAD was defined as ≥50% luminal diameter stenosis of a nongrafted major coronary artery or ≥50% luminal diameter stenosis of the vein or arterial bypass graft.

Statistical analysis
Continuous variables were compared using Student’s t test and are presented as means ± SD. Sensitivity, specificity, and accuracy were calculated using standard definitions and are presented with 95% CIs. Comparison of proportions was made by $\chi^2$ test. A $P$ value <0.05 was considered significant.

RESULTS
Coronary angiography
CAD (≥50% stenosis) was detected in 101 (79%) patients. Among these patients, 36 had single-vessel, 41 had two-vessel, and 24 had three-vessel CAD. The remaining 27 patients had no significant CAD. Coronary artery stenoses involved the LAD in 68 (53%), RCA in 63 (49%), and LCx in 59 (46%) patients.

Dobutamine stress test
The stress test was performed in all patients without serious complications. No death or myocardial infarction occurred during or immediately after the stress test. Dobutamine-atropine induced significant changes in heart rate (76 ± 17 vs. 140 ± 15 bpm), whereas systolic blood pressure did not change (148 ± 30 vs. 148 ± 34 mmHg) from rest to peak stress, respectively. Atropine was administered in 88 (69%) patients with a mean dose of 0.6 ± 0.5 mg. Chest pain occurred in 47 (37%) patients, and ST segment depression (>0.1 mV horizontal or downsloping) occurred in 15 (12%) patients. The target heart rate was achieved in 116 (91%) patients. One patient had nonsustained ventricular tachycardia, and two patients had a brief episode of supraventricular tachycardia. MCPI was feasible in all patients. Myocardial perfusion abnormalities were detected at baseline imaging in 29 (23%) patients. Among these patients, 26 had previous myocardial infarction. Reversible perfusion abnormalities occurred in 103 (80%) patients.

Diagnostic accuracy of MCPI
Reversible myocardial perfusion abnormalities were detected in 90 of 101 patients with and 13 of 27 patients without significant CAD. Sensitivity was 89% (95% CI 83–95), specificity 52% (33–71), and accuracy 81% (75–88).

Conclusions
Identification of diabetic patients at high risk for cardiac events is an important step in the determination of a management strategy. The extent of CAD is a known predictor of cardiac mortality and identifies patients who receive the greatest benefit from revascularization procedures (24, 25). There are limited data regarding the accuracy of stress imaging techniques in the diagnosis of CAD in diabetic patients. Furthermore, data regarding the estimation of extent of CAD in diabetic patients are scarce. Although patients with multivessel CAD often demonstrate abnormalities during stress imaging, these are often detected in a single vascular region with underestimation of the extent of CAD. In general, the sensitivity of DSE for identifying multivessel CAD based on inducible wall motion abnormalities in multivascular regions has ranged from 8 to 71% (40, 41).

In this study we demonstrated that MCPI is a safe method for diagnosis of CAD in 128 patients with diabetes. Re-
versatile perfusion abnormalities during dobutamine stress had a high sensitivity (89%) and accuracy (81%) with a modest specificity for the diagnosis of CAD. The majority of patients (68%) with multivessel CAD were identified based on the presence of reversible perfusion abnormalities in a multivessel distribution. This perfusion pattern provided a specificity of 87% for multivessel CAD. The accuracy was maintained in the three major coronary distributions. These findings suggest that MCPI is a promising technique for evaluating the extent of CAD and identifying diabetic patients who have the largest functional area at risk.

To date, clinical studies of myocardial perfusion in diabetic patients were mainly performed with nuclear techniques. The current study suggests that MCPI potentially could be an alternative echocardiographic method for the evaluation of myocardial perfusion in diabetic patients. In contrast to the nuclear techniques, MCPI does not require ionizing irradiation or a nuclear scanner and provides immediate assessment of perfusion. Stress and rest images are acquired in the same setting with MCPI, whereas they are acquired in two different settings with nuclear imaging.

Previous studies of DSE in diabetes

Despite the growing evidence of the clinical utility of DSE, studies of the diagnostic accuracy in diabetic patients are limited by including only a small number of patients. Most of the studies reported a low to modest sensitivity in single-vessel CAD. Bacci et al. (14) evaluated the accuracy of DSE in 35 asymptomatic high-risk type 2 diabetic patients. Significant CAD was defined as 70% lumen reduction and was detected in 19 patients. The sensitivity of DSE was 21%, specificity 94%, and accuracy was 54%. Penfornis et al. (15) compared the efficacy of exercise thallium-201 tomography and DSE in detecting CAD in 26 asymptomatic diabetic patients with three or more risk factors. Predictive positive value was 69% for DSE and 75% for thallium-201 imaging.

Elhendy et al. (23) reported that in 55 diabetic patients with known or suspected CAD, the sensitivity, specificity, and accuracy of DSE were 81, 85, and 82%, respectively. Sensitivity was 60% in patients with single-vessel CAD. Among the 31 patients with multivessel CAD, the sensitivity of DSE based on inducible wall motion abnormalities in multivascular regions was 51%. Hennessy et al. (16) studied 52 diabetic patients with DSE and coronary angiography. The sensitivity, specificity, positive predictive value, and negative predictive value of DSE for detection of CAD were 82, 54, 84, and 50%, respectively.

Studies with stress radionuclide imaging in diabetes

Kumar et al. (12) studied 43 diabetic patients with suspected CAD by exercise thallium imaging. CAD was detected in 24 patients. Sensitivity of thallium imaging was 87.5% and specificity 84%. Kang et al. (13) studied 138 diabetic patients with stress dual-isotope myocardial perfusion imaging and coronary angiography within 6 months. The sensitivity and specificity of perfusion imaging for detecting CAD with the criterion of ≥50% diameter stenosis were 86 and 56%, respectively. The normalcy rate for low likelihood patients was 89% (58 of 65 patients). Paillole et al. (17) determined the accuracy of intravenous dipyridamole myocardial thallium scintigraphy in 59 middle-aged diabetic patients with suspected CAD. Twenty patients had >70% coronary artery stenosis. The sensitivity and specificity for thallium scintigraphy were 80 and 87%, respectively.

Diagnostic accuracy in the three coronary arterial distributions

Previous studies have demonstrated a modest sensitivity for DSE in diagnosing significant CAD in an individual coronary artery, as well as in patients with single-vessel CAD (39,40). In our study, myocardial contrast echocardiography had a good sensitivity and accuracy for the diagnosis of LAD, RCA, and LCx CAD. The

### Table 2—Regional accuracy of myocardial contrast echocardiography for the diagnosis of significant disease in the three major coronary arteries

<table>
<thead>
<tr>
<th>Diagnostic parameter</th>
<th>LAD</th>
<th>LCx</th>
<th>RCA</th>
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<tbody>
<tr>
<td>Sensitivity</td>
<td>75 (65–85)</td>
<td>71 (60–83)</td>
<td>67 (55–78)</td>
</tr>
<tr>
<td>Specificity</td>
<td>73 (62–85)</td>
<td>83 (74–92)</td>
<td>83 (74–92)</td>
</tr>
<tr>
<td>Accuracy</td>
<td>76 (70–82)</td>
<td>77 (70–85)</td>
<td>75 (68–83)</td>
</tr>
<tr>
<td>Data are % (95% CI).</td>
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location of perfusion abnormality was accurate in localizing significant disease in the corresponding coronary artery, with a specificity of 73% for LAD and 83% for both RCA and LCx disease. This information is potentially useful for the physician when deciding which coronary arterial segments may require revascularization, particularly in those with complex angiographic abnormalities.

**Limitations of the study**

Coronary angiography was performed according to the discretion of the treating physician and not per study protocol. Therefore, referral bias may have influenced the results of the study. This may explain the higher prevalence of CAD and the low specificity of MCPI due to possible verification bias in patients with reversible perfusion abnormalities. Another explanation of the low specificity of MCPI could be the presence of artifactual defects in the apical and basal segments due to near field destruction and lung interference. It is possible that impairment of vasodilator reserve may occur in the absence of a major coronary arterial narrowing. This has been particularly observed in diabetes due to impairment of endothelial function (42,43). Although the normalcy rate in this study was 89% in patients with low pretest probability, CAD certainly cannot be excluded in these patients without coronary angiography.

The study consisted of a heterogeneous population with and without symptoms, with possible bias related to referral for stress testing and subsequent angiography. Finally, MCPI requires a high level of experience and is still largely an experimental tool in most stress laboratories. Further studies from other centers are needed to confirm our data before recommending this technique as a standard clinical tool.

**References**


