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ORIGINAL ARTICLE

Non-invasive diagnosis of in stent stenosis by stress 99m technetium tetrofosmin myocardial perfusion imaging

Abdou Elhendy · Arend FL Schinkel · Ron T van Domberg · Jeroen J Bax · Roelf Valkema · Don Poldermans

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Abstract
Background The aim of this study was to assess the accuracy of stress 99m technetium tetrofosmin myocardial perfusion imaging for the diagnosis of in stent stenosis (ISS).
Methods We studied 72 patients who underwent exercise or dobutamine stress 99m technetium tetrofosmin imaging, 0.9±0.5 years after percutaneous coronary interventions in which stents were deployed. Coronary angiography was performed within 3 months of the stress test. ISS was defined as ≥50% stenosis in a coronary segment with previous stenting. Significant coronary artery disease (CAD) was defined as ≥50% stenosis within or outside the stented coronary segment.
Results The stent was deployed in 1 coronary artery in 52 patients, and in 2 coronary arteries in 20 patients (a total of 92 detected in 42 (58%) patients (51 stents). Reversible perfusion abnormalities were present in 34 of patients with ISS (sensitivity=81%, CI 70–94). Regional sensitivity for diagnosis of stenosis per stent was 76% (CI 65–88), specificity was 83% (CI 71–94) and accuracy was 79% (CI 69–85). Reversible perfusion abnormalities were detected in ≥2 vascular distributions in 15 of 22 patients with multi-vessel CAD and in 5 of 50 patients without (sensitivity for identifying multivessel CAD=68%, CI 50–89; specificity=90%, CI 82–98; and accuracy=83%, CI 75–90).
Conclusion Stress 99m technetium tetrofosmin myocardial perfusion imaging is a useful non-invasive technique for the diagnosis of in stent stenosis and extent of CAD in patients with previous percutaneous coronary artery interventions.

Keywords Coronary artery stent · Percutaneous coronary intervention · Myocardial perfusion · Radionuclide imaging

A. Elhendy · A. FL Schinkel · R. T. van Domberg · D. Poldermans
Thoraxcenter, University Hospital Rotterdam, Rotterdam, The Netherlands

A. Elhendy (✉)
982265 Nebraska Medical Center, University of Nebraska Medical Center, Omaha, Nebraska 68198-2265, USA
E-mail: Aelhendy@unmc.edu
Tel.: +1-402-5599268
Fax: +1-402-5598355

J. J. Bax
Leiden University Hospital, Leiden, The Netherlands

R. Valkema
Department of Nuclear Medicine, University Hospital Rotterdam, Rotterdam, The Netherlands

Introduction

Percutaneous coronary intervention (PCI) with stent implantation is an increasingly used technique for restoration of myocardial perfusion and treatment of myocardial ischemia in patients with obstructive coronary artery disease (CAD) [1–2]. The improved

outcome with the use of stents, and the implement of new antiplatelet agents have resulted in a significant increase in the number of percutaneous revascularization procedures over the last decade. As a result, the use of, and indications for, PCI have greatly expanded [1–2]. Nevertheless, in stent stenosis (ISS) remains a major clinical problem [3, 4].

The non-invasive evaluation of CAD after PCI is a clinical challenge. Patients may remain asymptomatic or have atypical symptoms despite restenosis or progression of CAD in other coronary arterial segments. Coronary angiography is not recommended as a routine follow up tool due to the associated risk and the high cost. Exercise electrocardiography has a limited accuracy for detection of restenosis and localization of CAD, particularly due to the high incidence of baseline electrocardiographic abnormalities in this population [4]. Stress radionuclide myocardial perfusion imaging has been used for the diagnosis of restenosis after PCI [4–11]. However, published experience with the diagnostic accuracy of this technique after coronary artery stenting is very limited. The aim of this study was to assess the accuracy of stress 99m technetium tetrofosmin myocardial perfusion imaging for the diagnosis of ISS and evaluation of extent of CAD in patients with previous PCI.

Methods

Patients

We studied 72 patients with previous PCI and successful stent implantation who were referred for evaluation of myocardial ischemia by stress 99m technetium tetrofosmin single photon emission computed tomography (SPECT). All patients underwent quantitative coronary angiography within 3 month of the stress test. The stress test was performed 1 months–3 years (mean=0.9±0.5 years) after stenting. Patients gave an informed consent to undergo the stress test. Revasularization was complete in 62 (86%) patients. The stress test was performed within 6 months after stenting in 28 (39%) patients. The protocol of this study was approved by the Hospital Ethics Committee. Diabetes mellitus was defined as a fasting glucose level ≥140 mg/dl or the need for insulin or oral hypoglycemic agents. Hypercholesterolemia was defined as a total cholesterol ≥200 mg/dl, or treatment with lipid-lowering medications. Hypertension was defined as repeated blood pressure measurements >140/90 mm Hg or intake of antihypertensive medications. Contraindications for the test were severe heart failure, severe valvular heart disease, severe hypertension (blood pressure ≥180/110 mm Hg), hypotension (blood pressure <90/60 mm Hg) and unstable chest pain.

Mean age was 57±10 year. There were 55 men (76%). Risk factors were hypertension in 23 (32%) patients, diabetes in 12 (17%) patients, hypercholesterolemia in 41 (57%) and smoking in 19 (26%) patients. Thirty (42%) patients had a history of previous myocardial infarction, and 7 (10%) patients had a history of heart failure. Thirty six patients (50%) had angina and 11 (15%) patients had atypical chest pain. Medications included beta-blockers in 46 (64%), angiotensin converting enzyme inhibitors in 24 (33%), and calcium channel blockers in 25 (35%) patients.

Stress test protocols

Patients were instructed to discontinue beta blockers, at least 24 h before the stress test, whenever applicable. Other medications were not routinely discontinued. The choice of stress test type was based on ability to exercise. Exercise stress test was performed in 37 patients using a symptom-limited upright bicycle ergometry test with stepwise increment of 20 Watts every minute. Dobutamine-atropine stress testing was performed in 35 patients. Dobutamine was infused intravenously, starting at a dose of 10 μg/kg/min for 3 min, increasing by 10 μg/kg/min every 3 min up to a maximum dose of 40 μg/kg/min. If the test end-point was not reached at a dobutamine dose of 40 μg/kg/min, atropine (up to 1 mg) was given intravenously. Blood pressure, heart rate, and electrocardiography were continuously monitored. Test end-points were achievement of target heart rate (85% of maximum age predicted heart rate), horizontal or downsloping ST-segment depression >2 mm at an interval of 80 ms after the J-point compared with baseline, severe angina, systolic blood pressure fall >40 mm Hg, blood pressure >240/120 mm Hg, and significant cardiac arrhythmia. Metoprolol was available to reverse the side effects if needed. Three electrocardiographic leads were con-

tinuously monitored. Cuff blood pressure measurements and twelve-lead electrocardiography were recorded at rest and every minute during stress and recovery. ST-segment depression was defined as a >1 mm horizontal or downsloping ST-segment depression occurring at 80 ms after the J point [12].

99m Technetium tetrofosmin SPECT imaging

An intravenous dose of 370 MBq of 99m technetium tetrofosmin (Myoview, Amersham, and Buckinghamshire, United Kingdom) was administered approximately 1 min before the termination of the dobutamine or exercise test. For resting studies, 370 MBq of tetrofosmin were injected at least 24 h after the exercise study. Images were acquired with a Gammasonics single-head Rota camera without attenuation or scatter correction, by using a low-energy all-purpose collimator. Thirty-two projections were obtained over a 180° arc, from left posterior oblique to right anterior oblique, with an acquisition time of 45 s per projection. From the three-dimensional data, oblique (short-axis) and sagittal (vertical long-axis) images obtained perpendicular and parallel to the long axis, respectively, were reconstructed. For each study six oblique (short axis) slices from the apex to the base, three sagittal (vertical long axis) slices were defined. Each of the 6 short axis slices was divided into 8 equal segments. The septal part of the 2 basal slices was excluded from analysis because this region corresponds to the fibrous portion of the interventricular septum and normally exhibits reduced uptake. Consequently, a total of 47 segments were identified (3 long axis and 44 short axis). The interpretation of the scan was semiquantitatively performed by visual analysis. Stress and rest tomographic views were reviewed side by side by an experienced observer who was unaware of the patients' clinical or angiographic data. A reversible perfusion defect was defined as a defect on stress images that partially or completely resolved at rest in ≥2 contiguous segments and slices in the 47-segment model [12]. This was considered diagnostic of significant CAD or ISS. A reverse perfusion pattern was not considered diagnostic of significant stenosis [13]. A fixed perfusion defect was defined as a perfusion defect on stress images in 2 or more contiguous segments and slices, which persists at rest in the 47-segment model. For data reporting, 6 major left ventricular myocardial segments were identified: anterior, septal anterior, septal posterior, inferior, posterolateral and apical. The interobserver and intraobserver agreement on presence of reversible perfusion abnormalities in our laboratory are 92% and 94% respectively.

Quantitative angiography

Coronary angiography was performed within 3 months from the stress test. Referral to angiography was at the discretion of the patient's cardiologist. Quantitative coronary angiography was performed on the stent itself and the stent-related vessel and major branch vessels. The most normal-appearing area within the stented vessel was considered the reference segment representing 0% stenosis. ISS was considered present for stenoses both within or adjacent to the stent and for new lesions in the stented vascular territory >5 mm from the stent [6]. Significant CAD was defined as a diameter stenosis ≥50% in a major epicardial coronary artery, including the stented coronary segment. The anterior, apical, septal and anteroseptal walls were assigned to the left anterior descending coronary artery (LAD). The posterolateral wall was assigned to the left circumflex (LCX) coronary artery and its marginal branches. The inferior wall and basal septal segments were assigned to the right coronary artery (RCA) [12].

Statistical analysis

Continuous variables were presented as mean and standard deviation and were compared using Student's t test. Sensitivity, specificity and accuracy of myocardial perfusion imaging were calculated using standard definitions and were presented with 95% Confidence Intervals (CI). Comparison of proportions was made by χ^2-test. A p value <0.05 was considered significant.

Results

Stress test data

There was a significant increase of heart rate (71±17 vs 132±20 beats/min) and systolic blood pressure (131±21 vs 159±34 mm Hg) from rest to peak stress respectively. ST segment depression occurred in 20

(28%) patients and angina occurred in 34 (47%) patients with stress. The mean achieved workload with exercise was 135±35 watts. The mean maximal dobutamine dose was 33±10 μg/kg/min. Atropine was administered in 18 patients. The target heart rate was achieved in 60 (84%) patients (82% with exercise and 86% with dobutamine).

Coronary angiography

The stent was deployed in 1 coronary artery in 52 patients, and 2 coronary arteries in 20 patients (a total of 92 coronary arteries with stents). Significant CAD was detected in 52 (72%) patients. Among them, 30 had single vessel, 15 had 2 vessel and 7 had 3 vessel CAD. ISS was detected in 42 (58%) patients, and involved 51 (55%) stents.

Diagnostic accuracy of tetrofosmin SPECT

Myocardial perfusion was normal in 13 (18%) patients. Myocardial perfusion abnormalities were fixed in 12 (17%) patients, and reversible in 47 (65%) patients. Among patients with reversible defects, 9 had completely reversible defects and 38 had resting perfusion defects as well. ISS in ≥1 coronary artery was detected in 42 (58%) patients. Reversible perfusion abnormalities were present in 34 of them (sensitivity=81%, CI 70–94). Table 1 presents the regional accuracy for SPECT for diagnosis of ISS based on coronary artery location. The diagnostic accuracy was not different in the 3 major coronary arterial regions. Reversible perfusion abnormalities were detected in 43 of 52 patients with significant CAD and in 4 of 20 patients without (overall sensitivity=83%, 95% CI 72–93, specificity=80%, CI 63–98, and accuracy=82%, 95% CI 73–91). Reversible perfusion abnormalities were detected in ≥2 vascular distributions in 15 of 22 patients with multi-vessel CAD and in 5 of 50 patients without (sensitivity for identifying multivessel CAD by detecting perfusion abnormalities in multivessel distribution=68%, CI 50–89; specificity=90%, CI 82–98; and accuracy=83%, CI 75–90).

Discussion

In this study we demonstrated that stress 99m technetium tetrofosmin myocardial perfusion imaging was a useful method for diagnosis of ISS and evaluation of extent of CAD in 72 patients who were studied at a mean of 0.9 years after PCI with coronary artery stenting. Reversible perfusion abnormalities were detected in 81% patients of patients with ISS. The accuracy was maintained in the 3 coronary arterial distributions. The majority of patients with multivessel CAD were identified by observing perfusion abnormalities in multivessel distribution with an accuracy of 83%. Therefore, stress myocardial perfusion imaging is useful in determining patients with large myocardial regions at risk after stenting and selecting patients for further invasive procedure.

Previous studies

Studies that specifically addressed the diagnostic accuracy of stress radionuclide imaging in patients with previous coronary stenting are very scarce and involved a small number of coronary arteries with ISS. Milavetz et al. studied 33 patients who underwent stress SPECT imaging and follow up coronary angiography. There were 22 stents with ≥50% stenosis [6]. Sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of SPECT were 95%, 73%, 88%, 89%, and 88% respectively. Kosa et al. studied 82 patients, who underwent 93 rest or stress SPECT studies using 201 thallium and 99m sestamibi 210±129 days after

Table 1 Regional accuracy of stress 99m technetium tetrofosmin myocardial perfusion imaging for the diagnosis of in stent stenosis

Stented Coronary Artery	Sensitivity	Specificity	Accuracy
LAD	15/19 (79%, 61–97)	14/17 (82%, 64–95)	29/36 (81%, 68–94)
RCA	13/17 (79%, 65–94)	10/12 (76%, 56–97)	23/29 (83%, 62–97)
LCX	11/15 (73%, 51–96)	10/12 (83%, 62–97)	21/27 (78%, 62–94)
All stents	39/51 (76%, 65–88)	34/41 (83%, 71–94)	73/92 (79%, 69–85)

Diagnostic parameters are presented as % with corresponding 95% confidence interval. LAD=left anterior descending, LCX=left circumflex, RCA=right coronary artery

revascularization [5]. Coronary angiography revealed a stenosis of >50% diameter in the region of the stent in 19 arteries. Fifteen vascular territories with restenosed stents showed stress-induced perfusion abnormalities (sensitivity=79%), while 62/80 territories without restenosis did not (specificity=78%). Giedd et al. pooled data from 8 studies, in which stress radionuclide tomography and coronary angiography were performed within 2 to 48 months of PCI mostly without stenting [4]. The overall sensitivity and specificity of radionuclide imaging for detecting myocardial ischemia were both 79% and were roughly equivalent in all three vascular territories.

To our knowledge, this is the first study to assess the accuracy of 99m technetium tetrofosmin imaging in evaluation of ISS. The study assessed the accuracy of myocardial perfusion imaging in detecting ISS in a larger number of stents compared to previous studies with different isotopes. It is to be noted that the absence of perfusion abnormalities in some patients with >50% stenosis does not necessarily mean a limitation of myocardial perfusion imaging. In contrast, it may suggest that a given stenosis may not be of sufficient functional severity to induce abnormalities of perfusion during stress. Studies from our center [12] and by Zellweger et al. [14] have shown an excellent outcome after a normal stress myocardial perfusion imaging in patients with previous PCI, suggesting that myocardial perfusion may remain a significant predictor of outcome, regardless of the degree of anatomical abnormality.

Limitations of the study

Coronary angiography was performed according to the discretion of the treating physician and not per study protocol. Therefore, verification bias related to performing coronary angiography in patients with abnormal test may have influenced the results. This may in part explain the relatively high incidence of ISS in this study. The population was heterogeneous with a wide time range after PCI and included patients with and without symptoms. We used dobutamine and not vasodilator stress in patients unable to exercise. Preferring vasodilator stress to dobutamine for myocardial perfusion imaging was based on earlier studies demonstrating better flow heterogeneity with dipyridamole than dobutamine [15]. These studies utilized small dose of dobutamine without addition of atropine and do not represent the state of art protocol of the dobutamine stress. Recent studies have shown that the flow heterogeneity obtained by high dose dobutamine-atropine stress is equal to that obtained by dipyridamole [16]. Bin et al. demonstrated that in coronary arterial beds with a noncritical stenosis, the increases in myocardial blood flow and velocity and capillary derecruitment are similar for both dobutamine and adenosine [17]. Therefore, there is no literature supported evidence to suggest a superiority of vasodilator over dobutamine stress [18].

Conclusion

Stress 99m technetium tetrofosmin myocardial perfusion imaging is a useful non-invasive technique for the diagnosis of ISS and extent of CAD in patients with previous PCI. Therefore, the technique can assist the physician in selecting patients for invasive procedures.

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