Diagnosis of high-risk patients with multivessel coronary artery disease by combined cardiac gated SPET imaging and coronary calcium score

Milan Kamínek[1,3] MD, PhD,
Iva Metelková[1] MD, PhD,
Miroslava Budíková[1] MD, PhD,
Pavel Koranda[1] MD, PhD,
Lenka Henzlova[1] MD,
Martin Havel[1] MD,
Eliška Sovová[2] MD, PhD,
Vladimír Kincl[3] MD, PhD

1. Department of Nuclear Medicine and
2. Department of Internal Medicine-Cardiology, Palacky University and University Hospital, Olomouc,
3. International Clinical Research Centre, Center of Molecular Imaging, Brno, Czech Republic

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Correspondence address:
Vladimír Kincl MD, PhD
International Clinical Research Centre, Center of Molecular Imaging,
St. Anne´s FacultyHospital,
Masaryk University,
Pekařská 53, 656 91 Brno,
Czech Republic,
vladimir.kincl@fnusa.cz

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Abstract

Objective: The added value of coronary artery calcium (CAC) to SPET for identification of multivessel CAD has not been studied yet. The aim of this original study was to investigate CAC as an adjunct to gated single photon emission tomography (GSPET) in the detection of multivessel coronary artery disease (CAD).
Subjects and methods: The study group consisted of 164 prospectively recruited patients without known CAD-123 (75%) men and 60 (37%) women, having diabetes type II, renal insufficiency, left ventricular dilatation and other cardiac problems (arrhythmia, necessity of pharmacological stress test, etc.). The mean age of these patients was 61±12 years (range 34-85 years). All these patients underwent GSPET imaging, CAC score measurement, and coronary angiography. The percentage of ischaemic myocardium, stress and rest left ventricular ejection fraction (LVEF), and transient ischaemic dilation (TID) ratio were measured.
Results: Patients with multivessel CAD had more frequently reversible defects in multiple territories, severe ischaemia ≥10% of the left ventricle, stress worsening of the LVEF ≥5%, TID ratio ≥1.17, and CAC score >1000. In the detection of multivessel CAD, the sensitivity of combined assessment of perfusion, function, and CAC (i.e., multiple and/or ≥10% ischaemia, and/or worsening of the LVEF≥5%, and/or TID ratio ≥1.17, and/or CAC score >1000) was significantly higher than the sensitivity of perfusion alone or perfusion and function alone (81% vs. 55% and 65%, respectively, P<0.05). Sensitivity of only CAC was low (41%). **Conclusion**: Sensitivity of combined assessment of myocardial perfusion, function, and CAC was significantly higher than sensitivity of perfusion alone or perfusion and function alone, suggesting better identification of high-risk patients with CAD.

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Introduction

Gated single-photon emission tomography (GSPET) is a well-established method for myocardial perfusion, function, and viability imaging in patients with suspected or known coronary artery disease (CAD) [1, 2]. The extent, location, and severity of perfusion defects and left ventricular function parameters are important prognostic factors. Patients with a large reversible perfusion defect (left ventricle ischaemia>10%) have greatly benefit from revascularization [1, 3]. In patients with stable angina or silent ischaemia, indications for revascularization are: large area of ischaemia >10% of the left ventricle (LV) or anatomical and/or functional severe CAD (left main stem disease with stenosis >50%, any proximal left anterior descending artery stenosis >50%, two-vessel or three-vessel disease with impaired LV function, single remaining patent coronary artery with stenosis >50%, in all cases with documented ischaemia or fractional flow reserve ≤0.80 for diameter stenosis <90%) [1].

Patients with multivessel CAD are more likely to have an exercise perfusion abnormality compared to patients with single-vessel CAD. After a stress myocardial perfusion SPET test, the presence of multiple vascular perfusion defects suggests multivessel CAD. However, a potential limitation of this imaging is that it measures a relative, rather than an absolute myocardial blood flow. Moreover, once ischemia is induced related to the most severe coronary narrowing, ischemic symptoms may prevent further exercise and the induction of additional perfusion defects. In patients with multivessel CAD, perfusion defects may be evident only in the most ischemic area, whereas the least ischemic area may falsely appear normal.

To improve the assessment of diagnosis and of prognosis, other indirect hemodynamic indices of CAD, have been used such as transient ischaemic left ventricular di-

latation or worsening by stress left ventricular ejection fraction (LVEF) [4]. Post stress acquisition of cardiac GSPET provides information regarding peak stress perfusion, coupled with myocardial function at the time of acquisition. Gated SPET has the potential to detect postischemic left ventricular stunning because exercise-induced systolic dysfunction continues frequently in patients with more severe and extensive myocardial ischaemia. Yamagishi et al (2002) [5] showed that for detecting multivessel CAD, the sensitivity of the combination of perfusion data and of worsening LVEF by exercise was significantly greater than that of perfusion data alone (43.3% vs. 29.9%; P<0.05).

Consequently, the measurement of coronary artery calcium (CAC) by computed tomography (CT) and by imaging of atherosclerosis by ^{18}F-FDG PET/CT have received considerable attention, with the goal of improving diagnostic assessment and risk stratification [6-9], but the influence of CAC on the diagnostic accuracy in patients with coronary multivessel disesase has not been elucidated yet. Therefore, in the current original study, we examined sensitivity and specificity of GSPET in the detection of CAD, and the added value of the coronary artery calcium (CAC) as an adjunct to GSPET in the detection of multivessel CAD.

Patients and methods

Study population

The study group consisted of 164 prospectively recruited high-risk patients referred to us for cardiac GSPET imaging. They were 123 (75%) men and 60 (37%) women, mean age 61±12 years (range 34-85 years). Sixty patients (37%) had diabetes mellitus type II, 26 (16%) had chronic renal failure treated by dialysis, 41 (25%) had left ventricular dilatation and the rest of the patients had complications during stress-test (arrhythmias, inability to exercise and pharmacological stress needed). All patients underwent GSPET imaging, CAC score measurement, and coronary angiography. Patients with known CAD, after myocardial infarction, and coronary revascularization were excluded. The summed difference score converted to percentage of ischaemic myocardium, stress and rest LVEF, and transient ischaemic dilatation (TID) ratio were automatically measured by 4D-MSPET software. Coronary artery disease was defined as ≥50% stenosis of epicardial coronary arteries or their major branch.

Stress testing

Patients either underwent an exercise test or received intravenous (i.v.) dipyridamole if unable to exercise. The exercise test was performed upright on a bicycle ergometer. Exercise was conducted up to 85% of the age-predicted maximal heart rate or until the onset of angina pectoris, dyspnea or fatigue, dizziness, multifocal or paired ventricular extrasystoles of more than 10/min, ST segment depression (>0.2mV), or a decrease in blood pressure of 10mm Hg below the peak value of the previous level before the test.

Dipyridamole was injected i.v. at a standard dose of 0.56mg per kg of body weight during a 4min period in patients who at a low level exercise could not achieve maximal predicted heart rate. Patients with left bundle branch block underwent dipyridamole stress only

Gated cardiac SPET

Stress imaging was done first with technetium-99m in the radiopharmaceutical of ^{99m}Tc-sestamibi or ^{99m}Tc-tetrofosmin. If the test was completely normal as to the perfusion and left ventricular function, the test was over and no test at rest followed. Patients with abnormal or inconclusive stress images underwent rest study. These patients usually had normal perfusion and an attenuation artefact or had a mild abnormality of left ventricular function. We used either a one day protocol with 300MBq for the first dose and 750MBq for the second dose or a two days protocol with 300MBq.

The gated SPET was performed using a Siemens e.cam camera equipped with a 90° angled dual head, low-energy high-resolution collimators. Images were gated at 8 frames per cardiac cycle. No attenuation correction was applied. The additional at prone position imaging was used in the case of an inferior wall defect, probably caused by attenuation artefact. The summed stress and difference score (SSS, SDS) of myocardial perfusion, the LVEF and end-diastolic/end-systolic volumes (EDV/ESV) were calculated automatically using the 4D-MSPET from the University of Michigan, Ann Arbor, MI, USA software.

CAC scoring

CAC score was examined by the PET/CT scanner (Biograph 16, Siemens, Germany) using standard software based on Agatston method (with a cut-off >130 Hounsfield units). CAC score >1000 was defined as an extensive calcification with a high risk of future cardiac events [9].

Statistical analysis

All continuous data were expressed as means±standard deviation (MD±SD) and non-continuous variables were expressed as percentages. Continuous variables were compared using the nonparametric Mann-Whitney test because the normality of data was violated. Differences between proportions were compared using the $\chi 2$ test. Probability values <0.05 were considered significant.

Results

After visual assessment of the perfusion GSPET images, their sensitivity, specificity, positive and negative predictive values for the detection of CAD were: 88% (98/111), 74% (39/53), 88% (98/112), and 75% (39/52), respectively. We observed significantly lower sensitivity in patients with single-vessel disease as compared with patients having two-vessel or three-vessel disease (76% vs. 94% and 95%, respectively, P<0.05). However, only 38 (51%) of 74 patients with multivessel CAD had reversible defects in multiple territories, and only 30 (41%) had CAC score >1000. Patients with multivessel CAD had more frequently severe ischaemia, stress worsening of the LVEF, and CAC score >1000 (Table 1). In the detection of multivessel CAD, the sensitivity of combined assessment of myocardial perfusion, of function, and CAC

was significantly higher than that of perfusion and function of perfusion alone (Table 2, P<0.05). We observed no significant difference between patients with diabetes type II and other group of patients (with a renal insufficiency, left ventricular dilatation, arrhythmia, or necessity of pharmacological stress test).

Discussion

The relationship between CAC measurements and myocardial perfusion is still under investigation. At one study [8], authors evaluated 136 patients without known CAD by a semi-quantitative rubidium-82 PET myocardial perfusion study and CAC scoring. With increasing CAC score, there was on a per patient basis, a modest stepwise decline in coronary flow reserve: 1.8±0.5vs1.7±0.5vs 1.5±0.4 with P=0.048 and with total CAC score on a per vessel basis of 0, 1-400 and >400, respectively. Because of the expansion of the GSPET/CT and PET-CT scanners, CAC scoring has become more available. Using modern dual-source CT systems, some researchers [10] described very low radiation burden of CAC with the effective dose to be reduced to 0.3mSv.

The decision of whether and when myocardial perfusion imaging using GSPET or PET should be coupled with CAC scoring is becoming increasingly relevant to CAD studies. In another study [8], authors evaluated 695 consecutive patients with intermediate risk of CAD using PET. Among patients with normal myocardial perfusion imaging and CAC score, the authors found a lower annual cardiac event rate than in those with a CAC score ≥1000 (2.6% versus 12.3%, respectively). Likewise, in patients with ischaemia and CAC score <1000, the annual event rate was lower than among patients with a CAC score ≥1000 (8.2% versus 22.1%). These researchers showed the additional importance of CAC scoring for coronary events prediction. The role of CAC for CAD identification with stenosis of a coronary artery >50% has also been reported [11]. Our study is focused on the identification of multivessel CAD. This may be problematic, especially in diabetic type II patients with balanced triple vessel disease, where relative myocardial perfusion is weak. In our study, patients had an intermediate pre-test likelihood of CAD, however, the prevalence of diabetic patients was relatively high (37%). In our previous study [2], diabetes mellitus type II was an independent predictor of major adverse cardiac events in patients with normal SPET (1.3 vs. 0.5% per year, P<0.001). Therefore, we recommend the diagnostic use of both GSPET imaging and CAC scoring as a method of choice in the evaluation of CAD in diabetic patients. Moreover, current study extends this recommendation to patients with a renal insufficiency, left ventricular dilatation and other cardiac problems (arrhythmia, necessity of pharmacological stress test, etc.).

In conclusion, combined perfusion, function and CAC score in patients with multivessel CAD can help identifying high-risk patients.

***Table 1**. Gated SPET/CT and CAC parameters in patients with and without multivessel CAD*

	Single-vessel CAD(n=37)	Multivessel CAD (n=74)	P value
Perfusion defects in multiple territories	4(11%)	38(51%)	P = NS
Large area of ischaemia (≥10% LV)	12(32%)	28(38%)	P<0.05
Stress worsening of the LVEF ≥5%	13(35%)	31(42%)	P<0.05
TID ratio ≥1.17	9(24%)	19(26%)	P = NS
CAC score >1000	8(22%)	21(28%)	P<0.05

CAD=coronary artery disease, LVEF=left ventricular ejection fraction, TID=transient ischaemic dilatation, CAC=coronary artery calcium, LV=left ventricular

***Table 2**. Gated SPET/CT and CAC in the detection of high-risk patients with multivessel CAD*

	Sensitivity (%)	P value
Perfusion defect in multiple territories and/or ≥10% ischemia	55 (41/74)	
Perfusion+function (worsening LVEF ≥5%, and/or TID ratio ≥1.17)	65 (48/74)	P = NS*
Perfusion+function+CAC (CAC score >1000)	81 (60/74)	P <0.05**

*CAD=coronary artery disease, LVEF=left ventricular ejection fraction, TID=transient ischaemic dilatation, CAC=coronary artery calcium, * vs. perfusion alone, **vs. perfusion or perfusion and function alone*

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The authors declare that they have no conflicts of interest.

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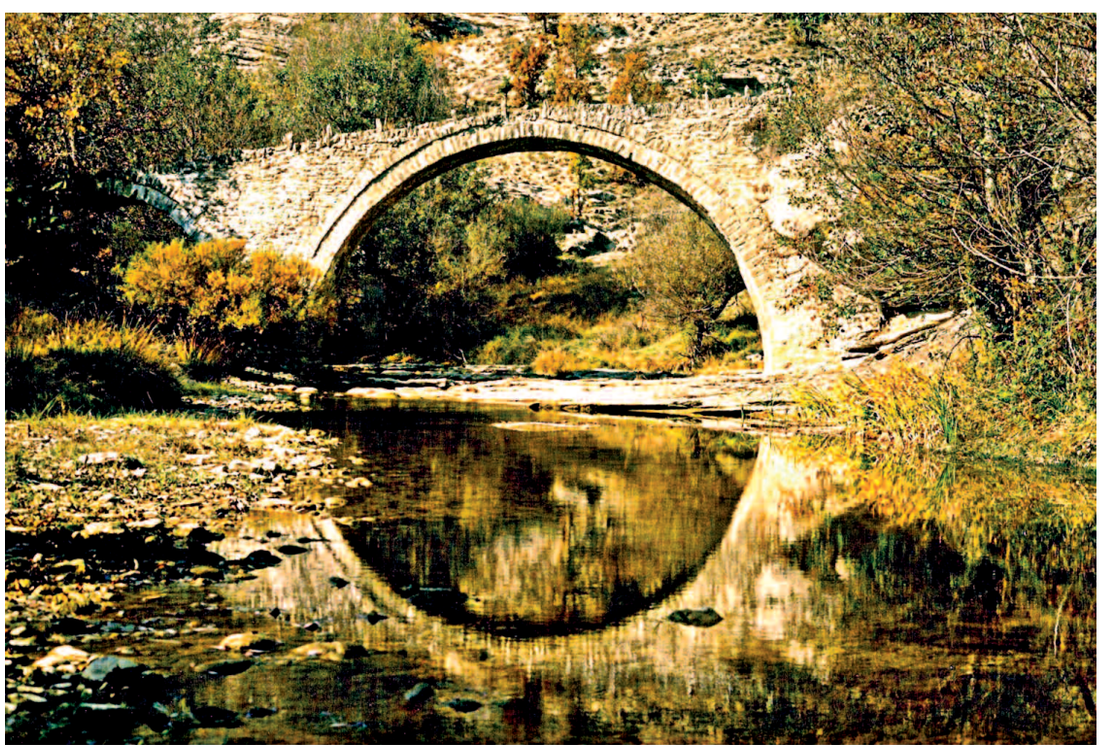

The bridge of Chrysavgi, 9m height and 25m width, at Pentalofos, Kozani, Macedonia, Greece, built in 1854 by a captain of the revolutionary Greek army against the Turkish occupation.