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Computed tomography myocardial perfusion imaging with transesophageal atrial pacing stress test in patients with borderline stenoses in the coronary arteries: a comparison with fractional flow reserve

Aim To evaluate the diagnostic accuracy of cardiac perfusion computed tomography (PCT) with transesophageal electrocardiostimulation (TE ECS) for detection of ischemia in patients with borderline coronary stenosis (50–75%) compared to measurements of fractional flow reserve (FFR).

Material and methods The study included 25 patients with borderline (50–75%) coronary stenosis as per data of computed tomography angiography (CTA) or coronary angiography (CAG). Later the patients underwent invasive measurement of FFR and cardiac PCT on a 320-row detector tomograph in combination with the TE ECS stress test. FFR values <0.8 indicated the hemodynamic significance of stenosis. Myocardial perfusion was evaluated visually based on consensus of two experts.

Results All patients completed the study protocol. Cardiac pacing duration was 6 min for all patients. Four patients required intravenous administration of atropine sulphate. PCT with TE ECS detected significant for FFR stenoses with sensitivity, specificity, and predictive value of a positive result and predictive value for a negative result of 47, 90, 87, and 53%, respectively.

Conclusion PCT with TE ECS in combination with CTA can be considered as an informative method for simultaneous evaluation of the condition of coronary arteries and detection of myocardial ischemia. This method is particularly relevant for assessing the hemodynamic significance of borderline coronary stenoses.

Keywords Acute coronary syndrome; computed tomography; perfusion computed tomography; borderline stenosis; transesophageal electrocardiostimulation; fractional flow reserve

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Coronary computed tomography angiogram (CTA) is widely used to detect atherosclerotic changes in coronary arteries. According to current clinical guidelines, coronary CTA is the diagnostic technique of choice in patients with suspected non-ST-segment elevation acute coronary syndrome (NSTE-ACS) and coronary heart disease (CHD) with low to medium probability [1, 2]. Prospective clinical studies have shown that coronary CTA is associated in patients with suspected CHD with better clinical outcomes compared to diagnostic tests used to identify myocardial ischemia alone [3, 4]. Coronary CTA is limited by the impossibility of performing functional assessment of the identified stenotic lesions. Additional stress tests with myocardial imaging, i.e., echocardiography, single-photon emission computed tomography (SPECT), magnetic resonance imaging (MRI), are often needed to determine the hemodynamic significance of stenosis and indications for myocardial revascularization. Perfusion computed tomography (PCT) is a method used to identify myocardial ischemia [5].

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Stress tests, such as exercise, pharmaceuticals, or transesophageal pacing (TEP), are used to assess myocardial perfusion or transient ischemia. TEP is a safe and effective stress test for patients who are unable to exercise [6]. In TEP, heart rate (HR) recovers immediately after the stimulation is ceased, and induced myocardial ischemia usually continues for no more than a minute, which can be manifested by ST segment depression in several electrocardiogram (ECG) complexes after TEP is discontinued. Thus, TEP can be used during PCT.

The obvious benefit of using PCT is the possibility of assessing simultaneously coronary anatomy and the functional significance of stenosis. This technique is of the most interest in patients with suspected ACS who have borderline stenosis (50–75%) shown by coronary CTA. The study also included patients with confirmed acute myocardial infarction (AMI) with borderline stenosis in non-infarct-related arteries detected during coronary angiography (CAG).

Invasive measurement of fractional flow reserve (FFR) is the gold standard in determining the functional significance of stenosis [7]. It reflects the gradient between the mean coronary pressure proximal to the stenosis site and the mean aortic pressure. The threshold FFR value is 0.8 [8]. Many studies have demonstrated that the FFR-oriented approach to revascularization was associated with a reduced risk of cardiovascular complications, including AMI and death [9]. Thus, the FFR measurement was used as a reference technique in our study to evaluate the diagnostic capabilities of PCT more accurately and objectively.

Table 1. Clinical characteristics of patients / with acute coronary syndrome (n=19) and acute myocardial infarction (n=6)

Parameter	Patients with NSTE-ACS and AMI	
	n	%
Total number of patients	25	100
Mean age, years	63 ± 7.8	
Sex, M/F	17/8	68/32
Postinfarction cardiosclerosis	9	36
Hypertension	19	76
Hypercholesterolemia	16	64
Diabetes mellitus	4	16
Smoking	12	48
History of CVA	1	4
Burdened family history	10	40

NSTE-ACS, non-ST-segment elevation acute coronary syndrome; AMI, acute myocardial infarction; CVA, cerebrovascular accident.

Objective

Determine diagnostic accuracy of myocardial PCT with TEP in detecting ischemia in patients with borderline (50–75%) coronary stenosis compared to the FFR measurements.

Material and methods

The study included 25 patients admitted to the intensive care and resuscitation units. Patients with suspected ACS and borderline (50–75%) coronary stenosis detected by coronary CTA (n=19) and AMI patients with borderline stenosis in non-infarct-related arteries (n=6) were subsequently subjected to invasive FFR and PCT with a 320-slice scanner in combination with the TEP stress test

The suspected ACS group included patients with negative troponin tests and no ischemic changes in ECG. AMI was diagnosed under the criteria of the Fourth Universal Definition of MI dated 2018 [10]. This included detection of a rise and/or fall of cTn with at least one value above the 99th percentile and with at least one of the following: symptoms of acute myocardial ischemia; new ischemic electrocardiographic (ECG) changes; development of pathological Q waves; imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischemic etiology.

Exclusion criteria were the presence of more than one >50% stenotic lesions per artery, new focal lesion or post-MI scar in the artery bed of interest, renal failure (glomerular filtration rate less than 50 mL/min), history of allergy to iodine-containing drugs, pregnancy and breastfeeding, severe concomitant diseases affecting the prognosis independently, contraindications to TEP, and claustrophobia.

Clinical characteristics of patients included in the study are given in Table 1.

Coronary CTA

Coronary CTA was carried out using a scanner with a 320 slice detector. During one 0.275 sec X-ray tube rotation, a total of 640 tomographic slices 0.5 mm thick were simultaneously made, with the intravenous administration of 50–70 mg (depending on patient weight) of a contrast agent (350–370 mg iodine/mL). The X-ray tube voltage was 100 kV with body mass index (BMI) <25 kg/m^2 (120 kV with BMI ≥25 kg/m^2). When the thoracic topography was performed, the area of interest was marked from 1 cm above the aortic root and to the diaphragm level. The contrast agent was administered intravenously at a rate of 5 mL/sec using an automatic syringe. The arterial phase of the investigation began automatically when the peak concentration of the contrast agent was reached in the lumen of the aortic root. Prospective ECG gating was used in the R – R range of 75–95%. Oral or intravenous beta-blocker was used in BP >65 bpm.

PCT protocol

The protocol included two phases of the investigation: Coronary CTA accompanied by the TEP stress test (stress phase) and at rest, with the same tomographic parameters and contrast agent doses. Patients included in the study based on coronary CT angiographic findings were subjected only to the stress phase of PCT, and resting myocardial perfusion was evaluated on the baseline CT images. The TEP stress test was performed using a transesophageal pacemaker Ezotest DMS. The investigation was performed on an empty stomach (no meals within 3–4 hours before). Antianginal agents, including beta-blockers, were discontinued 48 hours before the investigation. Patients with AMI were investigated on days 7–10 of the disease.

Stress phase

At the beginning of the investigation, topography was performed in the lateral and frontal views, used as the boundaries of the investigational area (from the trachea bifurcation to the lower heart border). Then, the stress test started while the patient was lying on a CT table monitored for the parameters of the 12-lead ECG and blood pressure (BP). TEP was initiated at the rate of 20 impulses per minute less than the submaximum HR calculated using the formula:

$$0.75\times(220 - \text{patient's age}).$$

The pacing rate was increased discreetly every minute without stopping stimulation by 10 ppm for 3 minutes until the submaximal HR was reached, one minute at each step. If atrioventricular block grade 2 developed the Wenckebach periods, 1 mg of atropine sulfate was administered intravenously. The last step of stimulation was performed at the maximum HR for 3 minutes. Total stimulation time was 6 minutes. The contrast agent was automatically injected through a peripheral venous catheter at the end of the 6th minute of stimulation, and when its peak concentration was reached in the aortic root projection, stimulation was immediately discontinued, and coronary CTA was performed.

Rest phase

The resting investigation was carried out 20 minutes after the stress phase. Oral or intravenous beta-blocker was used in BP >65 bpm. The mean effective dose was 11.2±4.6 mSv.

Analysis of the coronary CTA findings

Coronary CT angiograms were analyzed by a skilled expert. The extent of stenosis in each coronary segment was assessed visually. Patients with one lesion of 50-75% and no other ≥50% lesions in the same artery were included in the study.

Myocardial perfusion analysis

The phase with the least number of artifacts was selected in the reconstructed images. The images were evaluated, excluding the left ventricular (LV) apex, by two experts who used the 17 Segment Model recommended by the American Heart Association [11]. Each of the 16 myocardial segments was assessed visually for the absence or presence of myocardial contrasting defects (perfusion defects). The contrasting defect was a darker myocardial segment with reduced X-ray density in relation to the rest of LV segments. Experts assessing myocardial perfusion defects were unaware of the coronary stenosis locations.

3D cardiac reconstruction with automatic color coding based on X-ray myocardial density was used for visual imaging: 0 (blue) for normal perfusion, 1 (green) for mild perfusion reduction, 2 (yellow) for moderate perfusion reduction, 3 (orange) for severe perfusion reduction, 4 (red) for no perfusion.

CAG and FFR

CAG was performed with an Allura Xper FD-10 device with a 6F catheter, placed at the mouth of the coronary artery using a radial approach. Non-ion iodine-containing contrast agents were used. Angiograms were analyzed visually and automatically in the Xcelera system.

To dilate epicardial arteries for the FFR measurement, 250 mcg of nitroglycerin was injected intracoronarily. The intracoronal pressure sensor was then brought to the guiding catheter's tip to measure pressure in the proximal coronary bed. When the pressure curves normalized, the intracoronary probe was moved distally of the coronary stenosis. Maximum hyperemia was achieved by injecting papaverine into the artery (20 mg for the left coronary artery, 12 mg for the right coronary artery). FFR was then measured, followed by a manual retraction of the probe to the artery mouth, in order to determine the hemodynamic significance of

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an atherosclerotic plaque at different coronary artery levels. FFR ≥0.80 corresponded to a hemodynamically insignificant lesion, and FFR <0.80 corresponded to a hemodynamically significant lesion.

Statistical analysis

The data obtained was processed using MedCalc 19.2.0. Sensitivity, specificity, positive and negative predictive values (PPV, NPV) were calculated, in order to predict the ability of PCT to confirm or rule out ischemia in the area supplied by the artery of interest compared to the FFR measurements.

Results

If coronary CTA failed to assess coronary arteries (severe calcification, artifacts), patients were excluded. The study included 19 patients with NSTE-ACS and borderline coronary stenosis shown by coronary CTA and 6 patients with AMI after CAG.

All patients (n=25) completed the full investigation protocol. The artificial pacing lasted for 6 minutes. Four patients needed atropine sulfate during the stress phase with TEP. None of the patients had any ischemic changes on ECG or anginal attacks.

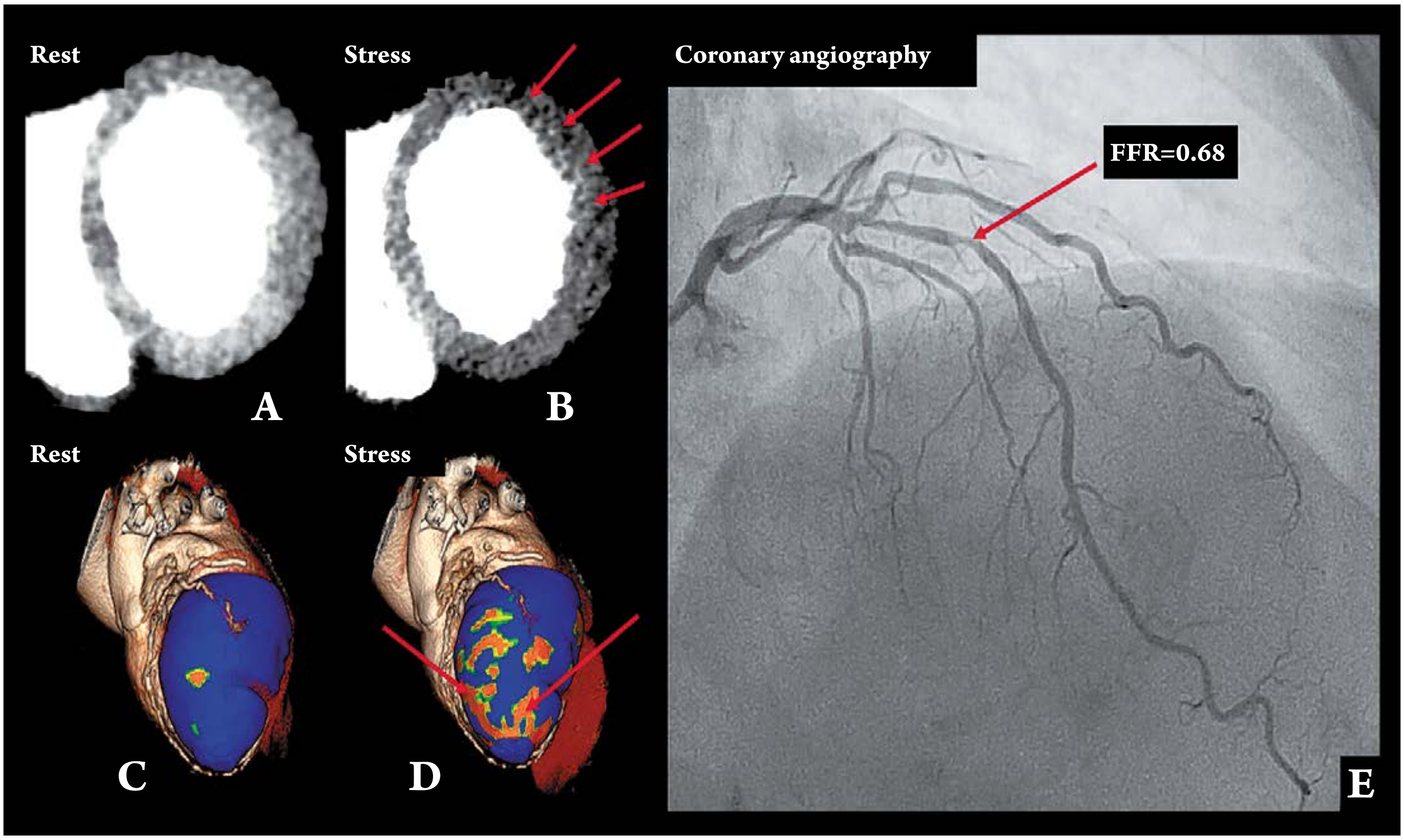
During myocardial perfusion assessment, transient perfusion defects were detected in 8 (32%) patients. Figure 1 shows the findings of PCT and CAG with FFR measurement in a 56-year-old patient with suspected ACS as a clinical case study. PCT detected a transient perfusion defect in the anterior and anterolateral mid-segments. CAG found 70% proximal stenosis in the left anterior descending artery; FFR was 0.68.

The consistency of expert opinion was 92%. Image quality was poor for 3 patients (12%) due to increased signal-to-noise ratio or heart contraction artifacts.

In patients with perfusion defects, stenosis in the corresponding artery was 70–75% in 5 cases and 60–69% in 3 cases.

Borderline stenosis was detected in a non-infarct-related artery in 6 patients during an emergency transcutaneous coronary intervention for AMI. FFR was measured after PCT in 19 patients with suspected ACS and 50–75% stenosis shown by coronary CTA.

Figure 1. Myocardial PCT and coronary angiography with FFR measurement



Uniform contrasting of the left ventricular (LV) myocardium is observed in the perfusion computed tomography (PCT) images at rest (A). The reduced contrast area (perfusion defect, arrows) in the anterior-lateral LV is observed in the stress PCT images (B). In the 3D cardiac CT images with color mapping obtained at rest (B) and during stress (D), the perfusion defect area is colored orange (H, arrows). The coronary angiogram (D) shows proximal 70% stenosis of the left anterior descending artery (arrow). Fractional flow reserve (FFR) was 0.68, which corresponded to hemodynamically significant stenosis.

Previously detected borderline stenosis was confirmed in all patients. Borderline stenosis was located in the left anterior descending artery (n=13), right coronary artery (n=5), circumflex artery (n=4), obtuse marginal artery (n=2), and diagonal branch (n=1). Stenosis was 50–59% (n=40, 60–69% (n=8), and 70–75% (n=13).

FFR was measured in all 25 patients. FFR indicated hemodynamically significant stenosis in 15 (60%) patients. Mean FFR was 0.75 ± 0.14. FFR was significant in 2 patients with 50–59% stenosis, 4 patients with 60–69% stenosis, and 9 patients with 70–75% stenosis.

PCT identified FFR-significant stenosis with sensitivity, specificity, PPV, and NPV equal to 47, 90, 87, and 53%, respectively (Table 2).

FFR and PCT findings were consistent in 16 patients. PCT perfusion defects were true-positive in 7 of 15 patients and true-negative in 9 of 10 patients.

Sensitivity, specificity, PPV, NPV for PCT were 67, 81, 67, and 81%, respectively, for the FFR threshold of <0.75 (see Table 2).

Discussion

Several clinical studies have demonstrated the high diagnostic accuracy of the combination of coronary CTA and PCT of myocardium compared to CAG and various imaging techniques for stress-induced ischemia [12–16]. Vasodilator stress tests were used in all studies: adenosine, regadenoson, and dipyridamole. Most of the pharmaceuticals used as stress agents are not approved in the Russian Federation and cannot be administered. Experimental studies have been conducted to assess myocardial perfusion using CT with adenosine triphosphate [17], but the technique has not yet been commonly used. TEP is an accessible diagnostic method with a low risk of complications. It should be noted that we have used an improved TEP protocol, which made it possible to adapt the study to patients by reducing test duration while significantly increasing the diagnostic accuracy of the study [18].

Many studies evaluating the diagnostic accuracy of PCT for myocardial ischemia use stress SPECT as a reference technique [13, 19, 20]. For example, the multi-center study CORE 320 (n=381) [13] evaluated the combination of coronary CTA/PCT with the adenosine stress test compared to CAG/SPECT. The sensitivity of the analysis was 78%, specificity was 73%, PPV and NPV were 64 and 85%, respectively. When comparing PCT to SPECT in detecting perfusion defects, sensitivity, specificity, PPV, and NPV were 75, 54, 63, and 68%, respectively. However, stress SPECT is not the gold standard in assessing myocardial ischemia. It should be noted that in multiple-vessel coronary artery disease, due to diffuse reduction of LV contractility, hypoperfusion is possible, as shown by both SPECT [21] and CT [16]. The measurement of FFR is the gold standard in determining the functional significance of stenosis [7]. Clinical trials have shown that revascularization based on FFR measurements is associated with reduced incidence of clinically significant cardiovascular complications [8]. According to the literature, the sensitivity of stress SPECT compared to FFR is 56-86% [22, 23]. Therefore, our findings of stress PCT with TEP were compared with the values of FFR.

In this study, PCT with TEP showed relatively specificity (90%) and PPV (87%), but sensitivity and NPV were not high, 47 and 53%, respectively. The sensitivity was higher in studies evaluating the diagnostic accuracy of various imaging techniques of stress-induced myocardial ischemia compared to FFR. For example, in the meta-analysis performed in 2015 [24], the sensitivity of the techniques was: 61% for SPECT, 87% for MRI, 83% for positron emission tomography, and 78% for PCT. It should be noted that dynamic PCT was also included in the analysis in these studies [25, 26]. Its specific nature is that it allows a more accurate quantification of myocardial perfusion to be performed when compared to the static PCT used in our study. In our opinion, it is not entirely correct to combine the two perfusion defect assessment techniques for an overall assessment of CT sensitivity. According to a meta-analysis of the data from several studies of coronary CTA, PCT, and CT-FFR for the detection of hemodynamically significant stenosis compared to the invasive assessment of FFR,

Table 2. Diagnostic accuracy of PCT compared to FFR measurements

FFR	PCT			
	Sensitivity, %	**Specificity, %**	**PPV, %**	**NPV, %**
0.8	47	90	87	53
0.75	67	81	67	81

PCT, perfusion computed tomography;
FFR, fractional flow reserve; PPV, positive predictive value; NPV, negative predictive value.

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the PCT sensitivity in detecting ischemia was 83% [27]. This meta-analysis also included studies with both static and dynamic PCT. Another characteristic of the studies is that different FFR thresholds were used: 0.8 and 0.75. According to the Guidelines on Myocardial Revascularization of the European Society of Cardiology (2018), stenosis is hemodynamically significant at FFR <0.80 [7]. We used this threshold in our study. However, FFR <0.75 is often used to detect lesions which cause more severe ischemia with a high predictive value [9]. In our study, sensitivity, specificity, PPV, NPV for PCT were 67, 81, 67, and 81%, respectively, for an FFR threshold of <0.75 (see Table Thus, it can be assumed that gray-zone FFR (0.75–0.8) was associated with lower ischemia volume and its underestimation in the myocardial perfusion analysis.

The fundamental feature of the studies of PCT diagnostic accuracy compared to FFR [28–30] is the inclusion of patients with coronary stenosis of >50% without restricting the upper value of the degree of narrowing. Our work studied patients with so-called borderline (50-75%) stenosis. Our choice of the study design was based on the fact that clarifying the hemodynamic significance of stenosis is of the greatest clinical interest in such patients, especially in those cases where the clinical picture and data of laboratory tests and clinical investigations raise doubts about the presence of CHD.

Moreover, we initially evaluated PCT independently of the coronary imaging techniques. In all studies analyzing the diagnostic capabilities of PCT, the method was studied in combination with the assessment of stenosis. The criterion for the hemodynamic significance of stenosis was its value of ≥50% according to coronary CTA or corresponding perfusion defect shown by PCT. Therefore, if a perfusion defect is doubtful, the decision on the presence or absence of ischemia can be made based on the location and nature of coronary stenosis. In most studies, the combined analysis of coronary CTA and PCT using this approach has a higher sensitivity than the assessment of ischemia by PCT alone [31].

TEP is an accessible and safe type of stress test, but it has limitations: sometimes it is impossible to deliver a probe in the esophagus due to increased vomiting reflex, and in some cases pacing is impossible. This technique also has contraindications, for example, esophageal diseases: tumor, diverticulosis, strictures, achalasia. PCT should be performed with caution in patients with chronic kidney disease, as the stress/rest combination study requires two-time administration of a contrast agent. According to our findings, the sensitivity of PCT with TEP is not high, which can also limit this method. However, sensitivity and specificity can be assessed with confidence with more observations.

Our study is a pilot. Obviously, more patients with stenotic coronary lesions of different degrees, different forms of CHD should be included to continue studying the method. Before introducing the method into clinical practice, a combined analysis of PCT and coronary CTA must be performed as well as an assessment of the predictive value of this approach. It is interesting to compare this technique with other imaging methods of myocardial ischemia with a high diagnostic accuracy: stress SPECT, stress echocardiography, stress MRI.

Conclusion

Perfusion computed tomography is a well-established technique that improves the diagnostic accuracy of CTA in detecting ≥50% coronary stenosis. Our study demonstrates that the use of transesophageal pacing as a stress test for perfusion computed tomography allows identifying transient defects in myocardial perfusion in patients with coronary heart disease. This approach is particularly relevant in detecting borderline (50-75%) coronary stenosis.

No conflict of interest is reported.

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