ACTA CARDIOLOGICA
https://doi.org/10.1080/00015385.2021.1968154

ORIGINAL SCIENTIFIC PAPER

Dobutamine stress echocardiography in patients with moderate coronary artery disease detected by coronary computed tomography angiography could reduce the rate of unnecessary coronary angiography

Claudiu Ungureanu[a], Daniela Corina Mirica[b], Olivier Marcovitch[a], Auriane Ceulemans[a], Olivier Godefroid[a], Gregory Nicaise[a], Antoine de Meester[a] and Phillipe Van de Borne[b]

[a]Department of Cardiology, Jolimont Hospital, La Louviére, Belgium; [b]Department of Cardiology, University Hospital Erasme Brussels, Brussels, Belgium

ABSTRACT

Aims: To test the hypothesis that dobutamine stress echocardiography (DSE) reduces the rate of unnecessary invasive coronary angiography (CA) in patients with chronic stable coronary artery disease (CAD) and moderate to severe stenosis detected by coronary computed tomography angiography (CCTA).

Methods: This study included 49 consecutive, symptomatic CAD patients with coronary lesions greater than 50% detected by CCTA who underwent all DSE and a CA with pressure wire evaluation and FFR measurement. The DSE operators was aware of the CCTA results, but invasive physicians were blinded to DSE results. The primary endpoint was the negative predictive value of a CCTA followed by a DSE test for detecting significant coronary artery disease (CAD). This was defined by the presence of significant coronary lesions (>90% stenosis) or moderate coronary lesions (50–90%) with abnormal FFR value of less than 0.80 evaluated by invasive angiogram (CA). Secondary endpoints included major adverse cardiovascular events (MACEs).

Results: In patients with abnormal CCTA followed by CA, 33 patients (67.34%) had non-significant CAD lesions. In patients with both abnormal CCTA and DSE only 6 patients (12.24%) presented non-significant CAD. The negative predictive value of a CCTA followed by a DSE was significantly increased to 92.5%, when compared with CCTA alone. Thus DSE on top of abnormal CCTA could reduce unnecessary CA by 5.5 fold. During follow-up (mean 38.75 ± 12.25 months) 1 (2.1%) patient had a cardiac sudden death, 3 (6.12%) patients had an unplanned myocardial revascularization and 1 (2.1%) patient had a stroke, none of which occurred in patients with normal DSE. No patients experienced a myocardial infarction or needed un unplanned surgical revascularization.

Conclusions: The addition of DSE in case of abnormal CCTA increases significantly the negative predictive value for detecting significant CAD in need for revascularisation and thus reduces markedly the number of unnecessary CA. This diagnostic strategy has a higher diagnostic accuracy and negative predictive value to the opposite approach where an abnormal CCTA mandates a CA without additional functional testing.

ARTICLE HISTORY
Received 16 May 2021
Revised 22 June 2021
Accepted 8 August 2021

KEYWORDS
Dobutamine stress echocardiography; coronary artery disease; coronary computed tomography angiography; coronary angiogram; fractional flow reserve

Introduction

CCTA is increasingly being used to assess patients with chronic stable chest pain because it has high diagnostic performance for detection and exclusion of obstructive CAD [1].

The use of CCTA in addition to standard care resulted in better clinical outcomes than standard care alone [2]. In the SCOT-HEART trial adding CCTA to standard care for patients with stable chest pain result in a lower risk of cardiovascular death and non-fatal myocardial infarction [3].

The CCTA is a useful tool to assess the prognosis of the patients and improve the prediction established only on classical clinical risk factors or functional non-invasive testing in contemporary patients [4,5].

It has been demonstrated that CCTA has a low accuracy in detecting ischaemic stenosis, especially in the setting of moderate coronary lesions, where CCTA has a low specificity (39%) as compared to the fractional flow reserve (FFR) which is the reference for the evaluation of ischaemic lesions [6].

Stress echocardiography is a well-established, real-time imaging modality with several advantages

CONTACT Ungureanu Claudiu claudiu.ungureanu@jolimont.be Department of Cardiology, Jolimont Hospital, Rue Ferrer, 159, La Louvière, Belgium.

including lack of radiation exposure, versatility, and affordability. Dobutamine stress echocardiography is dedicated to the detection of ischaemic abnormal ventricular wall motion, but this modality has a specificity of 75% and overall diagnostic accuracy of 72% as compared to FFR during CA [6]. The introduction of ultrasound contrast agents (microbubbles) has optimised the detection of wall motion abnormalities and has enabled simultaneous assessment of left ventricular perfusion and viability, improving the sensitivity of the technique [7].

Using CCTA was associated with increased referral to coronary angiography compared to other non-invasive modalities, especially when an intermediate lesion was detected [8]. One important task of non-invasive anatomic or functional tests is to avoid unnecessary coronary angiograms.

This study tested the hypothesis that DSE enhances the negative predictive value for detecting significant CAD in need for revascularisation when associated with abnormal CCTA findings in stable CAD patients, and thereby reduces the burden of unnecessary coronary angiographies.

Methods

Design

This study took place in two centres between September 2015 and April 2016, was prospective and non-randomized. The protocol was approved by the local ethic committee and all patients provided written informed consent.

Trial population

We included 49 consecutive stable CAD patients with moderate to severe stenosis (>50%) at CCTA.

The exclusion criteria were: previous coronary revascularization, symptoms of unstable coronary syndrome, contraindication to perform DSE (critical aortic stenosis, hypertrophic cardiomyopathy, uncontrolled hypertension, uncontrolled atrial fibrillation, known severe ventricular arrhythmias and electrolyte abnormalities (mainly hypokalemia), contraindications to perform CA (allergy to iodine agents, renal insufficiency) and poor accuracy of CCTA regarding the high degree of coronary calcifications.

All patients underwent the same day DSE and CA with FFR measurement.

The operators of DSE were aware of the CCTA results, but invasive physicians were blinded to the results of DSE.

All patients were clinically followed during 4 years. All major adverse cardiac events (MACE) including all-cause mortality, myocardial infarction (MI), recurrent symptoms requiring urgent repeat target vessel revascularization with PCI or coronary artery bypass graft (CABG), stroke and major bleeding, target vessel failure (TVF), stent thrombosis, in-stent restenosis were recorded.

Diagnostic testing

Protocols for CCTA scans were performed on a 128-slice CT (Somatom Definition CT, Siemens). Imaging of a test bolus of contrast was performed at 2 mm superior to the take-off of the left main coronary artery for precise timing of contrast injection. During the CCTA acquisition, 80–140 ml of iodinated contrast (Isovue 370, Bracco Diagnostics, Princeton, New Jersey; Omnipaque, GE Healthcare, Princeton, New Jersey; Visipaque, GE Healthcare, Princeton, New Jersey) was injected, followed by a 50-ml saline flush. Contrast timing was performed to optimise uniform contrast enhancement of the coronary arteries. The scan parameters were as follows: 64% 0.625/0.750-mm collimation, tube voltage 100 or 120 mV, effective 400–650 mA. Dose reduction strategies—including electrocardiogram-gated tube current modulation, reduced tube voltage, and prospective axial triggering—were used whenever feasible. The mean effective dose for CCTA was 341 mGy.cm.

Protocols for DSE

The examinations were performed on a Phillips IE33 system. The patient had an adequate venous access, and he (or she) was attached to a cardiac monitor in order to observe heart rate, rhythm and blood pressure.

According to this protocol, a rest electrocardiogram (ECG) and two-dimensional echocardiogram were acquired, intravenous access is secured, and dobutamine is then administered intravenously by an infusion pump, starting at 10 mg/kg per min for 3 min, increasing by 10 mg/kg per min every 3 min up to a maximum of 40 mg/kg per min. In patients not achieving 85% of their theoretic maximal heart rate (220 beats/min minus age for men, beats/min 200 minus age for women) and without symptoms or signs of myocardial ischaemia, atropine is administered on top of the maximal dose of dobutamine, starting with 0.25 mg intravenously and repeated up to a maximum

of 1.0 mg within 4 min, with continuation of dobutamine infusion.

Echocardiography was performed with harmonic imaging, and images acquired consisted of the parasternal long and short axis views (PLAX and PSAX) and apical views, two-, three- and four -chamber views (A2C, A3C, A4C). All acquired images could be displayed on a quad screen to allow side-by-side comparison at each stage: rest, low-dose dobutamine, peak dose dobutamine and recovery.

Sonographic images were taken at regular intervals (3 min) for each stage.

In patients with suboptimal echocardiographic images defined as more than three segments with poor endocardial border definition a contrast agent was used (SonoVue Bracco, Milan, Italy). This contrast agent is based on stabilised sulphur hexafluoride microbubbles surrounded by a phospholipid shell with a mean size of 2.5 μm.5 After mixing with saline, the suspension is obtained with SonoVue microbubbles in a concentration of 1–5 × 108 per ml. This suspension was injected intravenously in a straight access through a three-way stopcock as a bolus (0.5 ml with additional 0.25 ml injections when necessary) at each stage.

Throughout dobutamine infusion, the ECG (three leads) was continuously monitored and recorded (12 leads) at 1-min intervals. Prior to the examination all patients stopped beta-blocker medication at least 48 h.

Reasons for interruption of the test were severe or extensive new wall motion abnormalities; horizontal or downsloping ST segment depression: 0.2 mV at an interval of 80 ms after the J point compared with baseline; ST segment elevation of 0.1 mV or more in patients without a previous MI; severe angina; a symptomatic reduction in systolic blood pressure by more than 40 mm Hg from baseline; hypertension (blood pressure higher than 240/120 mm Hg); significant tachyarrhythmias; and any serious side effect regarded as due to dobutamine.

The addition of atropine was contraindicated in patients with narrow angle glaucoma, myasthenia gravis, obstructive uropathy or obstructive gastrointestinal disorders.

Echocardiogram analyses were performed separately, by two experienced observers who were not blinded to results of CCTA, and disclosed a favourable good overall inter-observer agreement (kappa: 0.94) [9].

Qualitative analysis of segmental myocardial contraction was based on visual assessment of myocardial thickening and was graded according to a scoring system as follows: 1-normal, 2-hypokinesis (reduced systolic wall thickening); 3-akinesis (absent systolic wall thickening) and 4-dyskinesis (outward systolic wall motion).

Regional wall motion abnormalities (WMA) were analysed and encoded using the 17 segments model of left ventricular wall motion analysis. The wall motion score index (WMSI) was calculated at rest, low dose and peak stress.

A test was considered positive for WM analysis if new segmental WM abnormalities were present in one or more segments.

Protocols for coronary angiography and FFR

After administration of 200 mcg of intracoronary nitroglycerine, angiography was performed in at least 5 orthogonal projections. In presence of lesions greater than 50% an invasive measurement by fractional flow reserve (FFR) (PressureWire, St JudeMedical) was performed for all the patients without any complications and using one single pressure wire per patient. The wire was introduced through a 6- or 7-F guiding catheter, calibrated, advanced into the coronary artery, and positioned distal to the stenosis. Adenosine was administered to induce maximum hyperaemia, either intravenously (140 g/kg/min) or intracoronary (20 mcg in the left coronary artery).

The protocol for performing FFR was realised in respect with our clinical practice and current recommendations.

Significant coronary disease was defined as critical stenosis of more than 90% or a positive FFR value of less than 0.80. The pressure wire was placed after the most distal intermediate lesion and two different measurements were done for all patients.

Two different operators validated the hemodynamic curves of FFR recordings and the test was repeated 10 min after the first recording. No difference between the first of the second measurements was noticed.

In this series of patients, no left main lesions were evaluated by FFR. We did not perform a pull back of the pressure wire and all measurements were done only in the distal segments of the coronary artery maintaining a stable classical position.

End points

The primary endpoint was protocol-defined unnecessary coronary angiography (moderate coronary lesions with normal FFR value of more than 0.80 or mild

coronary atherosclerosis with lesion less than 50% stenosis evaluated by invasive angiogram).

Secondary end points included a composite of major adverse cardiovascular events MACEs: cardiovascular death, myocardial infarction, stroke and unplanned coronary revascularization.

Statistical analysis: Data are expressed as mean +/− SD. Comparisons were made using unpaired Student's tests and Chi tests. A p level < 0.05 was considered significant.

Results

We included 49 stable CAD consecutive patients with at least moderate lesions (more of 50%) at CCTA. The clinical characteristics are summarised in Table 1.

Data presented as mean SD or number (%). BMI: body mass index; CHD: coronary heart disease; PCI: percutaneous coronary interventions; CABG: coronary artery bypass graft surgery; ACC: American College of Cardiology Classification.

The extent of coronary artery calcification based on CCTA was as following: CAC score $<$ 10 Hounsfield units (HU) in 6%, 10%$<$CAC score $<$400 HU in 69% and CAC score$>$ 400 HU in 25% of patients

There was a significant difference in CAC score according to the treatment strategy, with statistically significant higher scores in the revascularisation group ($p = 0.00029$).

Table 1. Baseline characteristics of study population.

Baseline characteristics	
Number of patients	49
Age (years)	61.7 ± 22.3
BMI	28.1 ± 11.1
Males gender	33 (67.3 %)
Diabetes	13 (26.5%)
Hypertension	34 (69.3%)
Dyslipidemia	40 (81.6%)
Family history of premature CHD	18 (36.7%)
Chronic kidney disease	1 (2.1%)
Congestive heart failure	3 (6.12%)
Peripheral vascular disease	7 (14.28%)
Cerebrovascular disease	1 (2.1%)
Tobacco abuse	28 (57.14%)
Prior PCI	0%
Prior CABG	0%
Angina type	
Atypical	15 (30.6%)
Typical	34 (69.4%)
Medications	
Aspirine	49 (100%)
Beta Blockers	29 (59.18%)
Nitrates	0%
Statins	45 (91.83%)
ACC type B/C	10 (20.40%)
Moderate/severe calcification	8 (16.32%)
Pre-test likelihood %	21.56%
Mean Follow-up (month)	38.75 ± 12.25

The study population had a substantial burden of cardiovascular risk factors: 13 (26.5%) patients had diabetes, 34 (69.3%) patients had hypertension, 28 (57.14%) patients were past or current tobacco users, 40 (81.6%) patients had dyslipidemia, and 18 (36.7%) patients had a family history of premature CHD.

All patients were symptomatic with 34 (69.4%) reporting typical chest pain and 15 (30.6%) reporting atypical chest pain.

The mean pre-test likelihood of obstructive coronary disease (PTPs) according to the score published recently in the European guidelines [10] was 21.56%.

DSE was successfully performed in all 49 patients. Good quality images were obtained in most patients 41 (83.6%), contrast agent was used in 8 patients (16.4%) with suboptimal echocardiographic images defined as more than 3 segments with poor endocardial border definition. Of the patients 38 (77%) attained at least 85% of their maximal heart rate, 11 (33%) attained maximal heart rate of 100%. Atropine was used in 26 patients (53%) in order to attain at least 85% of age predicted maximal heart rate. In 22 (44.89%) patients DSE was interrupted due to contractility changes suggestive of myocardial ischaemia. ECG changes were observed as ST depression in 10 patients, arrhythmias such as isolated ectopic ventricular beats were recorded in 3 patients, chest pain was reported in 12 patients. No severe side effects or complications were reported. The chest pain was reversible by stopping the dobutamine infusion and after beta-blockers and nitrates administration.

During follow-up (mean 38.75 ± 12.25 month) 1 patient (2.1%) had a cardiac sudden death, 3 patients (6.12%) have been treated by unplanned PCI, 1 patient (2.1%) had a stroke related to a severe carotid artery disease. No patients experienced a myocardial infarction or needed un unplanned surgical revascularization.

22 (44.89%) patients had an abnormal DSE test suggestive of ischaemia. Among those patients, CA revealed that 14 (28.57%) patients had a significant coronary artery disease and 8 (16.32%) patients had non-significant artery coronary disease.

The predictive positive value of DSE for detecting significant coronary disease was 63.6% in this study.

Table 2. Results of the dobutamine stress echocardiography (DSE) and coronary angiography (CA).

	DSE − 27 patients (55.10%)	DSE + 22 patients (44.89%)
CA −	25 patients (51.02%)	8 patients (16.32%)
CA + Intervention	2 patients (4.08%)	14 patients (28.57%)

27 (55.10%) patients did not disclose ischaemia at DSE. Among those patients 25 (51.02%) had non-significant coronary artery disease and 2 (4.08%) patients needed a revascularization procedure. The negative predictive value for significant coronary artery disease was 92.5% (see Table 2).

CA− (No need for revascularization after invasive coronary angiography).

CA+ Intervention (Need for revascularization).

DSE - (negative dobutamine stress echocardiography).

DSE + (positive dobutamine stress echocardiography).

The sensitivity of an abnormal DSE test for significant coronary artery upon CA in patients with abnormal CCTA was 87.5% and the specificity was 75.7%.

28 (57.14%) patients had confirmed mild coronary disease by CA and they were treated medically. 5 (10.20%) patients had moderate coronary lesions with a negative FFR and 2 (4.08%) patients had moderate coronary lesions and a positive FFR.

16 (32.65%) patients had significant coronary artery disease of which 14 (28.57%) patients were treated by PCI and 2 (4.08%) by CABG. Regarding the type of revascularization, PCI was needed in 2 patients with false negative DSE test and CABG was needed in 1 patient with positive DSE test.

No clinical complications were noticed in this series of patients during the hospitalisation and after the procedures were performed.

Discussions

This study tested the hypothesis that DSE on top of abnormal CCTA (coronary artery stenosis of more than 50%) in patients with chronic stable CAD could reduce the rate of unnecessary invasive CA. The main new finding of our study is that DSE is a very useful and performant gate keeper for unnecessary coronary angiographies in patients with an abnormal CCTA.

CCTA has a high accuracy diagnostic performance for detecting significant coronary artery disease with a high sensitivity of 95% and an excellent negative predictive value of 99% in previous published study [11].

The sensitivity of CCTA for detecting significant CAD is nearly identical to a combined anatomical and functional evaluation by CCTA and myocardial perfusion imaging (MPI). At the per-vessel level, coronary CTA outperformed MPI [12].

This is why the National Institute for Health and Care Excellence guidelines ranks to place coronary CCTA as the first-line test in low- to intermediate-risk patients [13].

One of the main limitations of CCTA is a low specificity and positive predictive value. CCTA specificity was 83% for detecting moderate coronary lesions [11] and only 39% when directly compared with an FFR reference standard in detecting significant coronary disease. The absence of coronary calcification by CCTA is a highly sensitive to predict very low probability of significant stenoses but the presence of calcification is only moderately specific to predict stenotic disease and this is also confirmed by our findings since patients with an elevated calcium score had only mild or non-ischaemic coronary lesions.

The positive predictive value of CCTA was only 64% for detecting $>$ or $=$50% or $>$ or $=$70% coronary stenosis upon CA [11]. These limitations of CCTA were the main cause of increase number of unnecessary invasive CA when compared with functional stress testing [14].

The hybrid approach with functional and anatomic evaluation was already tested with success in the past. Adding myocardial CT perfusion imaging was safe and improved the accuracy and the positive predictive value of coronary CTA alone in a previous study [15]. Fractional flow reserve derived from computed tomography showed also higher diagnostic performance than CCTA for vessel-specific ischaemia [16].

The addition of myocardial perfusion imaging (MPI) with either stress nuclear scanning or CMR significantly improved the per-patient specificity to 93%, with an absolute 17% or 10% improvement over solitary coronary CTA or MPI, respectively [12]. A limitation if this latter study [12] is however that authors used quantitative coronary angiogram as a reference for significant CAD, which discloses critical limitation for detecting hemodynamically relevant stenosis [12]. An important strength of our study is that coronary artery lesions were evaluated by means of pressure wire guided-FFR, currently considered as the most accurate methods for the assessment of revascularization need.

We report that DSE performed when the coronary anatomy is known by CCTA has a very high negative predictive value of 92.5%. Knowing the results of CCTA may have reduced the incidence of false positive DSE tests and allowed the echocardiographers to better scrutinise contractility changes in specific territories where significant CA lesions were suspected in our study.

The low penetration of the hybrid approach we addressed in nowadays clinical practice could be related to the difficulty of pre-test selection of patients with an abnormal CCTA which would benefit from a DSE to improve risk stratification. While in a patient with a negative coronary CCTA test result no further testing is generally needed, we did not assess if adding a CCTA in case of a positive or doubtful DSE would prevent a CA without a significant stenosis [17].

We strongly believe that the non-invasive hybrid approach combining the anatomic and functional features of coronary arteries assessed in our study would benefit from a standard operating procedure where starting with an highly performant imaging modality like CCTA, and followed if abnormal with an functional test such as a DSE, would result in lower need in local resources, reduce radiation burden for the patient, and result in overall larger availability of diagnostic resources together with restrained costs.

In our patients CCTA alone had a specificity 32.65% and DSE alone a sensibility 75% and specificity of 54.55%. This is less to previous studies [5,18] which considered the presence of coronary lesions of more than 50% degree but did not perform a complete evaluation by CA and FFR as we did in this study.

Regarding the clinical evolution of the patients, the non-invasive approach by CCTA and DSE appeared very safe. After a prolonged follow-up the major cardiac events occurred only in the patients with significant coronary disease treated by revascularization.

Conclusions

The addition of a DSE when CCTA suggests a coronary stenosis of more than 50% reduces drastically unnecessary coronary angiograms. This approach markedly improves the diagnostic accuracy of CCTA alone.

Disclosure statement

No potential conflict of interest was reported by the author(s).

References

[1] Miller JM, Rochitte CE, Dewey M, et al. Diagnostic performance of coronary angiography by 64-row CT. N Engl J Med. 2008;359(22):2324–2336.

[2] Williams MC, Hunter A, Shah ASV, et al. Use of coronary computed tomographic angiography to guide management of patients with coronary disease. J Am Coll Cardiol. 2016;67(15):1759–1768.

[3] Newby PD, Adamson MC, Williams DE, et al. Coronary CT angiography and 5-year risk of myocardial infarction. N Engl J Med. 2018;379(10):924–933.

[4] Min JK, Dunning A, Lin FY, et al. Age- and sex-related differences in all-cause mortality risk based on coronary computed tomography angiography findings. J Am Coll Cardiol. 2011;58(8):849–860.

[5] Hoffmann U, Ferencik M, Udelson JE, et al. Prognostic value of noninvasive cardiovascular testing in patients with stable chest pain. Circulation. 2017;135(24):2320–2332.

[6] Danad I, Szymonifka J, Twisk JWR, et al. Diagnostic performance of cardiac imaging methods to diagnose ischaemia-causing coronary artery disease when directly compared with fractional flow reserve as a reference standard: a meta-analysis. Eur Heart J. 2017;38(13):991–998.

[7] Maffei E, Seitun S, Guaricci AI, et al. Chest pain: coronary CT in the ER. Br J Radiol. 2016;89(1061):20150954.

[8] Shreibati JB, Baker LC, Hlatky MA. Association of coronary CT angiography or stress testing with subsequent utilization and spending among medicare beneficiaries. JAMA. 2011;306(19):2128–2136.

[9] Hoffmann R, Lethen H, Marwick T, et al. Analysis of interinstitutional observer agreement in interpretation of dobutamine stress echocardiograms. J Am Coll Cardiol. 1996;27(2):330–336.

[10] Knuuti J. ESC guidelines for the diagnosis and management of chronic coronary syndromes. Eur Heart J. 2019;00:171.

[11] Budoff MJ, Dowe D, Jollis JG, et al. Diagnostic performance of 64-multidetector row coronary computed tomographic angiography for evaluation of coronary artery stenosis in individuals without known coronary artery disease: results from the prospective multicenter ACCURACY (Assessment by Coronary Computed Tomographic Angiography of Individuals Undergoing Invasive Coronary Angiography) trial. J Am Coll Cardiol. 2008;52:1724–1732.

[12] Branch KR, Hamilton-Craig C. The dye don't lie but may not tell the truth. Combining coronary computed tomography angiography with myocardial perfusion imaging. JACC Cadiovasc Imaging. 2018;11(4):600–602.

[13] National Institute for Health and Care Excellence (NICE). Chest pain of recent onset: assessment and diagnosis of recent onset chest pain or discomfort of suspected cardiac origin. Clinical guideline CG95. London (UK): NICE; 2016.

[14] Foy AJ, Dhruva SS, Peterson B, et al. Coronary computed tomography angiography vs functional stress testing for patients with suspected coronary artery disease: a systematic review and meta-analysis. JAMA Intern Med. 2017;177(11):1623–1631.

[15] Seitun S, De Lorenzi C, Cademartiri F, et al. CT myocardial perfusion imaging: a new frontier in cardiac imaging. Hindawi BioMed Res Int. 2018;2018:1–21.

[16] Driessen RS, Knaapen P, et al. Comparison of coronary computed tomography angiography, fractional flow reserve, and perfusion imaging for ischemia diagnosis. J Am Coll Cardiol. 2019;73(2):161–173.

[17] Flotats A, Knuuti J, Gutberlet M, et al. Hybrid cardiac imaging: SPECT/CT and PET/CT. A joint position statement by the European Association of Nuclear Medicine (EANM), the European Society of Cardiac Radiology (ESCR) and the European Council of Nuclear Cardiology (ECNC). Eur J Nucl Med Mol Imaging. 2011;38(1):201–212.

[18] Rollán MJ, San Román JA, Vilacosta I, et al. Dobutamine stress echocardiography in the diagnosis of coronary artery disease in women with chest pain: comparison with different noninvasive tests. Clin Cardiol. 2002;25(12):559–564.