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Head-to-Head Comparison of Dobutamine Stress Echocardiography and Cardiac Computed Tomography for the Detection of Significant Coronary Artery Disease

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Key Words
Coronary calcium · Coronary artery disease · Cardiac computer tomography · Dobutamine stress echocardiography

Abstract
Objectives: Dobutamine stress echocardiography (DSE) and contrast-enhanced electron beam tomography (EBCT) both have the potential to noninvasively detect coronary artery disease (CAD). We compared the accuracy of both methods to detect significant CAD in a direct comparison. ***Methods:*** 79 patients (32 women, 47 men, mean age 62 years) who were admitted for coronary angiography due to suspected CAD were studied. By EBCT coronary calcification (CAC) as well as angiography (CTA) was assessed. Presence of significant CAD was assumed if the calcium score exceeded 400 or the contrast-enhanced images displayed significant lumen reduction. DSE was performed using a standard protocol (5–40 μg/kg/min dobutamine plus 0.25–1.0 mg atropine if necessary). DSE and EBCT were independently evaluated concerning the presence of signficant CAD. Results were compared to invasive, quantitative coronary angiography. ***Results:*** 6 patients (8%) in DSE and 2 patients (3%) in EBCT were unevaluable for various reasons and therefore excluded from further analysis. In the remaining 71 patients, 33 patients (46%) showed significant CAD. DSE demonstrated a sensitivity of 70% (23/33) and a specificity of 84% (32/38). EBCT showed a sensitivity of 91% (30/33) and a specificity of 74% (28/38). By combining DSE and EBCT sensitivity increased to 97% with a specificity of 63%. ***Conclusions:*** In a blinded comparison, DSE demonstrated lower sensitivity but higher specificity than EBCT for the detection of significant CAD. Sensitivity was improved by combining both modalities.

Introduction

Recent improvements in the technology of computed tomography (CT) have enabled imaging of the heart and coronary arteries. Electron beam CT (EBCT) was the first CT modality to provide sufficient temporal resolution for cardiac imaging [1–11]. Subsequently, multidetector CT (MDCT) with sub-second gantry rotation time and the ability to obtain up to 64 slices simultaneously has been introduced and has also enabled visualization of the heart with high spatial and temporal resolution [12–14]. Imaging of the coronary arteries by EBCT and MDCT met with considerable interest: coronary calcifications (CAC) can be assessed by nonenhanced CT scans [1–10], while imaging of the coronary artery lumen and

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Table 1. Validity of test results (n = 79), 'intention to treat' given as per patient accuracies

	DSE	EBCT	p value
Evaluable	92% (73/79)	97% (77/79)	
Sensitivity	70% (23/33)	91% (31/34)	0.03
Specificity	88% (35/40)	72% (31/43)	0.11
Accuracy	79% (58/73)	81% (62/77)	0.87
PPV	82% (23/28)	72% (31/43)	0.33
NPV	78% (35/45)	91% (31/34)	0.14
LR+	5.83 (95% CI 4.84, 7.02)	3.25 (95% CI 2.60, 3.99)	
LR–	0.34 (95% CI 0.28, 0.41)	0.12 (95% CI 0.10, 0.15)	

PPV = Positive predictive value; NPV = negative predictive value; CI = confidence interval.

detection of stenoses are possible after intravenous injection of a contrast agent [1, 5, 9, 12–14]. Mainly, validity has been compared with invasive coronary angiography. Fewer studies evaluated the relative significance of functional testing (most of them investigated asymptomatic patients and most suffered from some referral bias since patients were referred to the cath lab because of positive stress tests): on the one hand by electrocardiographic (ECG) stress testing [6, 7, 10, 11, 14], on the other by combining the stress test with an imaging modality, i.e. myocardial scintigraphy [thallium or technetium single-photon emission tomography (SPECT)] [3, 6]. In this regard, the focus has not yet been on stress echocardiography, although the nonexercise option of dobutamine stress echocardiography (DSE) is well established for assessing the functional parameter of ischemia [15–18] as potential complementary information on morphology. There is only one very recent retrospective study that compared CAC by EBCT versus exercise echocardiography and found a limited correlation between both (r = 0.17, increasing to a small extent in a subgroup with chest pain: r = 0.26) [19] underlining the different diagnostic targets and the potential complementary role of both methods. Our aim was to compare the validity of DSE versus EBCT versus both together in a prospective study design to detect significant coronary artery disease (CAD; angiographic presence of at least one hemodynamically relevant coronary artery stenosis) by direct comparison.

Material and Methods

Prospectively and consecutively, 79 patients (32 women, 47 men; mean age 62 years) admitted for elective, invasive coronary angiography due to symptoms suspicious of CAD (primary diagnostic procedure, i.e. no previous myocardial infarction, coronary intervention, or surgery) were included in the study. Exclusion criteria were severe arterial hypertension, severe arrhythmia, atrial fibrillation, valve disease, and/or contraindications to the intravenous application of dobutamine or X-ray contrast. The clinical condition had to be stable and regional, and global left ventricular function in echocardiography had to be normal.

DSE was performed via high-end echocardiography (HP Sonos 5500©, Philips, The Netherlands) using a standard protocol (5–40 µg/kg/min dobutamine plus 0.25–1.0 mg atropine if necessary) [17, 18]. All echocardiographic images were digitized and displayed as continuous cine loops by using an ECG-triggered and ECG-synchronized quad-screen display for a review of pre-, low, and high dose, as well as post-dobutamine infusion steps. Regional wall motion was analyzed according the 16-segment model of the American Society of Echocardiography [20]. A positive finding indicating significant CAD was defined by induced wall motion abnormalities in ≥1 segment.

Examinations of EBCT (C-150 XL; Imatron, Calif., USA) were 2-fold. First, CAC was assessed in 40 axial noncontrast images (3-mm table advance, 3-mm slice thickness, 1-mm overlap, 100-ms acquisition time, 26-cm field of view, matrix 512 × 512, Kernel: sharp, ECG trigger 40% of RR interval). A CT threshold of 130 Hounsfield units was utilized for identification of a calcific lesion. Measurements were according to the method of Agatston and Janowitz [2] with a minimal plaque requirement of 0.51 mm^2. Subsequently, in case of an Agatston score <400, coronary artery images were obtained during intravenous injection of contrast agent (120–160 ml iopromide; flow 4 ml/s) to visualize the coronary lumen as previously described in greater detail [1]. After the evaluation of the cross-sectional source images, maximum intensity projections as well as curved multiplanar reconstructions were obtained to most adequately detect significant coronary stenosis according experienced, qualitative visualization. The presence of significant CAD was also assumed if the CAC score according Agatston exceeded 400 [4, 7].

DSE and EBCT were independently evaluated in respect of the presence of significant CAD. Results were compared to invasive, quantitative coronary angiography (QuantCOr.QCA V 2.0©, Pie Medical Imaging, Maastricht, The Netherlands) [20] which followed both noninvasive tests within 1–3 days. Observers were blinded to invasive angiographic findings. Significant CAD was defined as coronary diameter reduction of ≥70% in at least 2 projections (NHLBI class II). The angiography observer was also blinded to the noninvasive tests. However, for the status of cor-

Table 2. Validity of matched pairs (both tests evaluable in every patient, 'per protocol') and combined test results (n = 73) given as per patient accuracies

	DSE	EBCT	p value	DSE + EBCT
Evaluable	92% (73/79)	92% (73/79)		92% (73/79)
Sensitivity	70% (23/33)	91% (30/33)	0.09	97% (32/33)
Specificity	84% (32/38)	74% (28/38)	0.45	63% (24/38)
Accuracy	77% (55/71)	82% (58/71)	0.71	79% (56/71)
PPV	79% (23/29)	75% (30/40)	0.45	70% (32/46)
NPV	76% (32/42)	90% (28/31)	0.09	96% (24/25)
LR+	4.37 (95% CI 3.36, 5.70)	3.50 (95% CI 2.82, 4.34)		2.62 (95% CI 2.03, 3.36)
LR–	0.36 (95% CI 0.28, 0.45)	0.11 (95% CI 0.08, 0.13)		0.05 (95% CI 0.03, 0.06)

PPV = Positive predictive value; NPV = negative predictive value; CI = confidence interval.

relation EBCT and DSE findings had to occur in the correlative vessel distribution.

Statistical analysis of data was performed with the SAS version 8.2 software system. For the statistical evaluation the McNemar test for matched pairs and the χ^2 test for the comparison of two independent proportions were used. In the case of small expected frequencies the Fisher exact test was employed (tables 1, 2). Further, the probability of getting a positive result if the patient actually had the condition of interest against the probability if he had been healthy was compared. The ratio of these probabilities is the likelihood ratio (LR) [LR+ = sensitivity/(1 – specificity)for a positive diagnosis and correspondingly LR– = (1 – sensitivity)/specificity for a negative diagnosis]. It indicates the value of a test for increasing the certainty of a positive or negative diagnosis. A value of 1 for LR signifies that the test does not contribute anything to finding a diagnosis, i.e. the higher LR+ the better whereas the closer LR– to zero the better. Pretest odds were calculated by 'prevalence/(1 – prevalence)' and posttest odds by pretest odds times LR. Significance was assumed if $p < 0.05$.

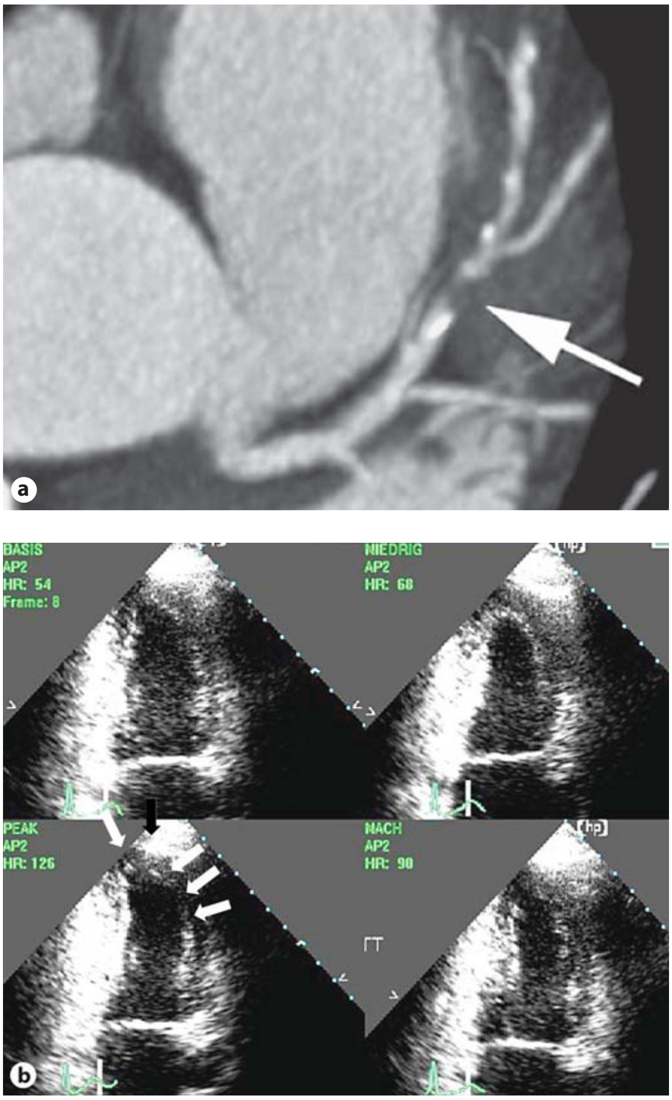
Results

Of the 79 patients included in this study 34 (43%) showed significant CAD [26 with 1-vessel, 5 with 2-vessel, and 3 with 3-vessel disease; stenosis location: 2 left main coronary artery, 16 left anterior descending (LAD), 15 left circumflex (CX), and 12 right coronary artery]. In both investigated noninvasive tests there were no complications. In EBCT the averaged Agatston score was 321 (0–2,442), in 19 patients the score was >400. Sensitivities, specificities, accuracy, predictive values, as well as LR are shown in table 1. Eight patients were technically not evaluable. In DSE this applied to 6 patients (8%) who had atrial flutter during the test (spontaneously converting into sinus rhythm) in 1, did not achieve the submaximal heart rate in 2, developed limited echogenicity in 2, and limited compliance in 1 patient. In EBCT 2 patients (3%) experienced respiratory artifacts. For the analysis of matched pairs and combined test results these cases had to be excluded. Hence, 71 patients remained, of whom 33 patients (46%) showed significant CAD (table 2). Sensitivity and negative predictive value (NPV) were superior in EBCT (sensitivity reaching significance in 'intention-to-treat' data, table 1), whereas for specificity and PPV this was vice versa (nonsignificant) (tables 1, 2).

For DSE the LR+ was 5.83, whereas it was 3.25 for EBCT (table 1). This means that for a positive diagnosis DSE is somewhat better and seems to be more useful than EBCT. LR+ is almost twice higher. The posttest odds for DSE was 4.79 (pretest odds 0.82) and for EBCT 2.57 (pretest odds 0.79) indicating the usefulness of both tests for positive diagnosis and for the greater likelihood for DSE to make a positive diagnosis correctly compared to EBCT. LR– for DSE was 0.34 and for EBCT 0.12, indicating that for a negative diagnosis EBCT performs better. The diagnostic information of the combined tests (table 2) is not superior in comparison to each single test. Sensitivity is higher, but in contrast, for specificity, one test confirms the finding even better. A typical example of a patient of the study is represented in figure 1.

Discussion

To the best of our knowledge this is the first prospective study on the relative significance of stress echocardiography versus CAC in addition to noninvasive coronary angiography by a CT modality in a head-to-head comparison. The major finding is the comparable validity of both noninvasive tests, DSE being more specific and EBCT more sensitive. Notably, referral bias can be excluded as stress test results did not indicate coronary angiog-



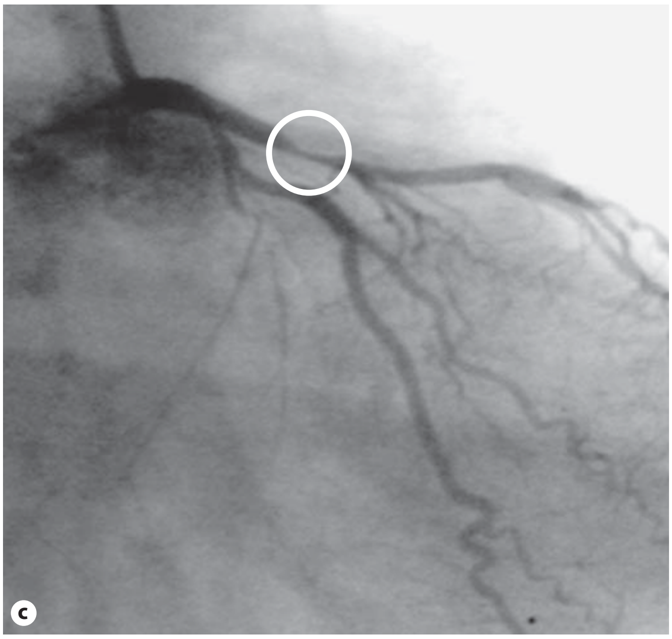


Fig. 1. 67-year-old female patient suffering from angina pectoris; nondiagnostic exercise ECG due to insufficient heart rate increase. **a** Maximum intensity projection by EBCT coronary angiography demonstrating high-grade stenosis in the proximal LAD (arrow). Note also multiple calcified plaques within this vessel segment. **b** DSE documented by 2-chamber view (ECG-triggered and ECG-synchronized end-systolic images by quad-screen display; titration steps: preinfusion = left upper corner, low-dose infusion = right upper corner, high-dose infusion = left lower corner, postinfusion = right lower corner). Induced hypo- to akinesia of anterolateral, apical and inferoapical segments at high-dose infusion (arrows). In addition, note increased end-systolic volume in comparison to low-dose and postinfusion. **c** Invasive X-ray coronary angiography showing high-grade stenosis of LAD (circle).

raphy. Considering also predictive values and LRs it turned out that DSE seems to be the superior diagnostic procedure if CAD is seriously suspected (typical and severe angina, high-risk profile) whereas EBCT [considering CAC and CT angiography (CTA)] might be preferred to rule out disease (atypical angina, low risk, and/or young age). Accordingly, in low to moderate disease prevalence, Rumberger et al. [22] documented EBCT as an initial testing approach to maximize cost effectiveness, whereas this did not hold true for more disease-prevalent groups. It is interesting that the hypothesis of a major additional value by combining both tests could not be verified although diagnostic targets (morphology vs. function) and diagnostic adequacies (sensitivities vs. specificities) differed and a multivariate analysis reported independent information for predicting obstructive CAD by stress testing and EBCT [10]. In contrast, preceding studies demonstrated the improvement of the low specificities of EBCT (but notably only evaluating CAC) by treadmill ECG and technetium stress [11] as well as the identification of false-positive [6] or false-negative results [14] of stress tests by excluding or confirming CAC in EBCT. In suspected CAD in which stress testing remains equivocal, additional CT scanning might imply incremental information [11]. The moderate improvement of NPV in EBCT (EBCT 90% vs. DSE + EBCT 96%) should not be overrated, since various preceding studies on EBCT and MDCT confirmed the very high NPV for CT scanning (in the range of 98–100%) [1, 5, 9]. Sensitivity is increased to 97% but only at the expense of a decrease in specificity to 63%. Thus, our data do not support a principally combined use of EBCT/MDCT and DSE in symptomatic patients to increase the 'gatekeeper' function for reducing the demand on invasive procedures (increasingly claimed by 16- and 64-slice MDCT demonstrating actual sensitivities of 80–95% and specificities of 95–98%) [23]. However, prospective studies are necessary unless a more definite statement on this clinical possibility can be made. Each is considered to be of sufficient appropriateness. DSE is well-defined by echocardiographic guidelines [15] and CT scanning modalities are confirmed by recent guidelines, too [4, 24]. Also nuclear myocardial perfusion imaging is well-defined [3, 6] and was recently compared to EBCT in a very similar head-to-head comparison as in our stress echocardiographic study [25]. In this study also symptomatic patients (high pretest probability) scheduled for cardiac catheterization were included prospectively. However, CTA (without an algorithm of initial CAC and consecutive CTA) detected obstructive CAD more accurately than nuclear testing not only by higher sensitivities as in our study, but also higher specificities. Those authors concluded – as we would do for echocardiography – that larger studies in a more diverse population are needed.

The presentation of the patients represents a limitation of our study. The prevalence of significant CAD (43%) was relatively low, and the extent of CAD in the individual patient was also quite low (76% of cases had 'only' single vessel disease), and CX lesions were detected relatively often (44%). These aspects might explain the finding of a relatively low sensitivity in DSE (70%). Especially the physical problem of sonographic lateral resolution weakness (CX perfusion territory) is well known [26], although native second harmonic imaging used in this study bypasses this problem to some extent [17]. Nevertheless, also for EBCT [1] and MDCT [13], lowest sensitivities and specificities to detect coronary lesions were shown for CX due to perpendicular orientation in the imaging plane as well as more rapid diastolic motion, the greatest accuracy applying to left main coronary artery and LAD. As far as the low prevalence of CAD is concerned, the LRs are independent in respect of pretest probability. The small number of patients recruited in this study is a matter of concern as no statistical modeling analysis could be performed; furthermore this study does not enable differentiation into subgroups. Since most EBCT studies comparing findings to exercise stress tests relied on CAC and not on (additional) CTA [3, 6, 10, 11] it would have been especially interesting to also consider these separate aspects in our data. This holds true although several previous studies demonstrated the presence of CAC by CT as extremely sensitive for obstructive CAD with a lesser specificity [4]. If the cutoff value of CAC score is increased to >100, sensitivity and specificity are at a rational balance of 85 and 75% [4, 27, 28]. Schmermund et al. [29] even constructed a CAC score index [log(e)(LAD score) + log(e)(LCX score) + 2(if diabetic) + 3(if male)] for separating patients with versus without obstructive CAD. Thus, our combined criterion of CAC and CTA may suffice for the rationale of our study although the limitation is a tendencially lower specificity. Nevertheless, one has to be aware that this protocol is not in widespread use any longer. The findings of our study have to be confirmed by more up-to-date protocols (only CTA) along with a preferable multicenter approach.

Although most data on CAC and CTA so far have been acquired by EBCT, technological developments of MDCT have shown definite progress [12, 30, 31]. Thus, our data should be reasonably challenged by consecutive series employing the latest technologies. This holds good for increased temporal and spatial resolution by a greater increase of X-ray sources [12] and detector slices [31] at the CT side, but also by a further increase of piezoelectric crystals of transducers with real-time three-dimensional image acquisition as well as automatic border detection [32] and quantitative measures of myocardial tissue function in echocardiography [18]. In addition, advances in multimodality imaging processing [33] may provide the ability to fuse ECG-triggered CT and DSE images within one image.

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