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Mechanisms of regional wall motion abnormalities in contrast-enhanced Dobutamine Stress Echocardiography

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Summary *Background* In the diagnosis of coronary artery disease (CAD) with Dobutamine Stress Echocardiography (DSE), regional wall motion abnormalities (RWMA) are assumed to indicate a perfusion deficit. *Methods and results* For a more particular examination of RWMAs, we compared simultaneous echo-contrast (Optisone®)-enhanced DSE (0–40 µg/kg Dobutamine, 16-segment-model) and MiBi-SPECT in a prospective double-blinded study design in 69 non-selected consecutive patients (44 male, 25 female, age 64 ± 12 years). Additionally, all patients were examined by coronary-angiography. The prevalence of significant CAD (stenosis > 50% lumen diameter) was 52%. DSE had a sensitivity of 78% and a specificity of 66% for the detection of significant CAD with a positive and negative predictive value of 72 and 73%, respectively. Among 28 patients with significant CAD and positive DSE study (true positive), 78% displayed a corresponding perfusion deficit in MiBi-SPECT. Among 11 patients with a positive DSE study but no current significant coronary stenosis (false positive), 82% showed stress-induced RWMAs in the inferior/posterior region, 73% dis-

played left ventricular hypertrophy, 54% resting-ECG abnormalities and 45% resting-RWMA (3 previous MI, 2 previous CABG surgery). Among 8 patients with negative DSE study but significant coronary stenosis (false negative), 75% had a stenosis of the LCX, 63% displayed resting-RWMA, 63% displayed left bundle branch block or ST-segment depression, 50% displayed only peripheral coronary stenosis, and DSE visualization was suboptimal in 38%. *Conclusion* This prospective study in non-selected patients shows that the majority of RWMAs in DSE are matched to a perfusion deficit detectable by nuclear imaging. Nevertheless, pre-existing cardiac abnormalities may also lead to stress-induced RWMA not associated with a perfusion deficit or mask a perfusion deficit upon DSE. Particularly in patients with LV hypertrophy, resting-RWMA, bundle branch block or ST segment depression, the predictive value of DSE may, therefore, be limited.

Key words Dobutamine – stress-echocardiography – MiBi-SPECT – wall motion abnormalities – perfusion

Introduction

Dobutamine Stress Echocardiography (DSE) is an established technique for the non-invasive detection of coronary artery disease (CAD) with a higher accuracy than exercise electrocardiography (ECG), particularly in patients with limited exercise capacity [1, 2]. Dobutamine increases myocardial contractility, heart rate and left ventricular wall tension. Subsequently, regional perfusion deficits lead to decreased myocardial contractility [4] and consecutive wall motion abnormality (RWMA).

Nevertheless, DSE has often been challenged because of the indirect visualization of a perfusion deficit through RWMA, which may introduce bias through unspecific results. Also, the predictive values of DSE differ widely according to patient-selection, methodology, study protocol, examined coronary vessel or gender [4–7]. Sensitivity, for example, was reported to range from 66% in single-vessel disease [1] to 97% in multi-vessel disease [8].

In contrast to DSE, nuclear imaging by MiBi-SPECT offers a direct visualization of myocardial perfusion [1, 2, 9]. To investigate the mechanisms leading to RWMA in DSE more accurately and to delineate clinical situations which may lead to unspecific results, it was our objective to assess myocardial perfusion directly by nuclear imaging in a clinical sample of patients with suspected or known coronary artery disease undergoing DSE.

We hypothesized that a RWMA reflects regional hypoperfusion in the majority of the patients, but may also represent an unspecific finding in the presence of prior structural or functional (e.g., conduction abnormalities) damage. To address this hypothesis, we performed a simultaneous stress test in a clinical sample of 69 consecutive and unselected patients, who were also examined invasively for coronary artery disease.

Patients and methods

■ Patient selection

We examined 80 consecutive non-selected patients with suspected or progressive coronary artery disease. In 69 cases (44 men and 25 women aged 64 ± 12 years), all examinations (DSE, MiBi-SPECT, Coronary angiography) could be performed and were of sufficient diagnostic quality.

■ Dobutamine stress test

Dobutamine Stress Echocardiography and injection of Technetium-99m Sestamibi were performed simultaneously. Dobutamine was infused (i.v.) with a mechanical pump, starting at a dose of $10 \mu\text{g/kg/min}$ and increasing the rate at 3-min intervals to 20, 30 and $40 \mu\text{g/kg/min}$. Peak stress was maintained for at least 6 min before the injection of the radionuclide. During infusion, a 12-lead ECG was monitored continuously and recorded every 3 min. Blood pressure was measured at 3-min-intervals. Test end-points were: a) achievement of maximal predicted heart rate; b) severe angina or ST-segment depression; c) occurrence of severe side-effects.

■ Stress echocardiography

DSE was performed with a standard echocardiography system (HP, Sonos 5500) with a 2.5 MHz-Transducer at a low mechanical index (MI) of 0.3. Cine-loops from four standard views were digitized and saved for off-line analysis on a commercially available stress-echo-program (Tomtech). For the improvement of wall segment visualization and image quality, we used intravenous Optisone®, a second-generation echocardiographic contrast consisting of perfluorocarbon-filled albumin-encapsulated microbubbles.

Both analogue and digital images were interpreted by two independent investigators who had no knowledge of the patient's angiographic data. In case of disagreement among the investigators, an additional blinded referee performed the adjudication (in 7 out of 69 cases). The left ventricle was divided into 16 segments according to the recommended model of the American Society of Echocardiography. For each segment, systolic wall motion was visually graded with the following scoring system: 1 = normal, 2 = hypokinesia, 3 = akinesia, and 4 = dyskinesia. An increase in motion score by one grade or more at peak stress was considered to be a positive test result.

■ MiBi-SPECT imaging

After 6 min at peak Dobutamine stress, an intravenous dose of 370 MBq of MiBi was administered. Stress images were acquired 1 h after termination of the test. For resting studies, 370 MBq of MiBi were injected 24 h after the stress study. For each study, six oblique (short axis) slices, from the apex to the base, and three sagittal (vertical long axis) slices,

from the septum to the lateral wall, were recorded. Interpretation of the scan was performed by visual analysis. Stress and rest tomographic views were reviewed and graded by two expert observers who were not aware of the patient's angiographic and echocardiographic data. A reversible perfusion defect was defined as a defect on stress images that partially or completely resolved at rest. To compare MiBi-SPECT and echocardiographic images, the left ventricle was divided into four major segments: anterior/anteroseptal, posterior/posteroseptal, lateral, and inferior.

Coronary angiography

All patients underwent coronary angiography and left ventricular cineangiography. A reduction in luminal diameter of a proximal coronary segment of greater than 50% was defined as significant CAD. Coronary arteries were assigned to myocardial segments as described previously [1, 7]. The degree of coronary stenoses was defined by the blinded catheterization operator by visual assessment.

Statistics

Differences between studied groups with respect to categorized data were compared statistically by chi-square test and differences with respect to hemodynamic data by students T-test. The performance of DSE to predict significant CAD was assessed as sensitivity, specificity, positive predictive value, and negative predictive value after adjudication of each DSE study result as true positive, true negative, false positive or false negative with coronary angiography as standard of truth. P-values below 0.05 were defined as statistically significant.

Results

Patient population

We examined 69 consecutive patients (44 male, 25 female) with known or suspected coronary artery disease. Patient characteristics are depicted in Table 1.

Among all 69 patients, 36 (52%) had significant coronary artery disease and the remaining 33 (48%) exhibited either smooth coronary arteries (14 patients) or non-significant wall irregularities. One-vessel disease was present in 19 patients, two-vessel disease in 9 and the remaining 8 had three-vessel disease.

Table 1 Characteristics of the study population

	Significant CAD	Non-significant CAD	p
Total	36 (52%)	33 (48%)	p = n.s.
Gender (% Male)	27 (75%)	18 (55%)	p = n.s.
Age	65.2 ± 11	62.2 ± 10	p = n.s.
Previous MI	16 (44%)	9 (27%)	p = n.s.
Hypertension	31 (86%)	26 (79%)	p = n.s.
Angina pectoris	26 (72%)	30 (91%)	p = n.s.
LVH (Echo)	20 (56%)	27 (81%)	p = n.s.
Resting-WMA	19 (53%)	12 (36%)	p = n.s.
BP/rest	140 ± 23/72 ± 18 mmHg	138 ± 22/70 ± 13 mmHg	p = n.s.
BP/peak stress	149 ± 34/72 ± 19 mmHg	147 ± 38/66 ± 17 mmHg	p = n.s.

Mean ± SEM; CAD, coronary artery disease; MI, myocardial infarction; LVH, left ventricular hypertrophy; WMA, wall motion abnormality (echocardiography); BP, blood pressure

Among the 36 patients with CAD, 26 (72%) had a history of angina pectoris for more than 2 weeks and 31 (86%) had a history of known hypertension. Only 8 exhibited a normal resting electrocardiogram (ECG), whereas 5 had signs of left ventricular hypertrophy (LVH), 4 left bundle branch block (LBBB), 2 right bundle branch block (RBBB) and 17 various degrees of ST-T abnormalities. Of the 33 patients without CAD, 18 had a normal resting electrocardiogram, 7 LVH, 3 LBBB and 5 ST-T abnormalities.

The mean blood pressures at rest or peak exercise did not differ between patients with significant CAD and non-significant CAD (Table 1). In both groups, there was a significant rise in heart rate during the stress test, but there was no difference between patients with or without significant CAD.

Stress echocardiography

Stress-induced WMA was detected in 28 of 36 patients with significant coronary artery stenosis, and in 11 of the 33 patients without significant coronary artery stenosis (Fig. 1). The sensitivity of DSE for the detection of significant CAD was 78% and specificity was 66%. Positive predictive value and negative predictive value were 72 and 73%, respectively (Fig. 1 a).

When significant CAD was defined as lumen diameter stenosis >70%, sensitivity of DSE increased to 91%, whereas specificity decreased to 61% with a PPV of 64% and a NPV of 88%.

Of the 28 patients with positive DSE and significant CAD (true positive), 22 (78%) showed a simultaneous perfusion deficit in MiBi-SPECT in the cor-

Fig. 1 (a) Agreement between Dobutamine Stress Echocardiography (DSE) and coronary angiography (Coro) on the overall diagnosis of myocardial ischemia; PPV, positive predictive value, NPV, negative predictive value. (b) Agreement (white) and disagreement (black) of stress-induced wall motion abnormality in DSE and perfusion deficit in nuclear imaging

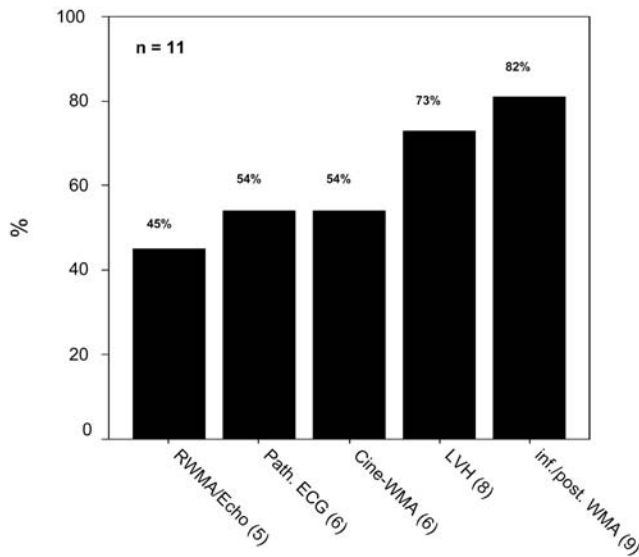
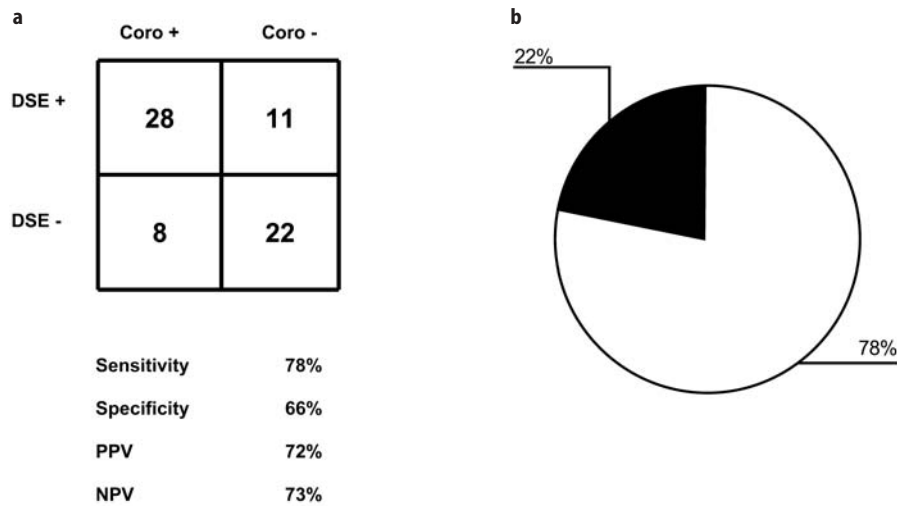


Fig. 2 Potential reasons for false positive analysis of Dobutamine Stress Echocardiography in ascending order; WMA, wall motion abnormality, ECG, electrocardiogram, LVH, left ventricular hypertrophy

responding area of the left ventricle (Fig. 1b). Eight perfusion deficits (36%) were located anterior/septal, 2 lateral (9%), and 12 (55%) in the inferior/posterior area.

Among the 11 patients with positive DSE but no significant CAD (false positive), 5 showed rest wall motion abnormalities (45%), 6 showed rest-ECG abnormalities (54%), 6 (54%) abnormalities in left ventricular cineangiography (3 previous MI, 2 ACVB, 1 cardiomyopathy), 8 displayed left ventricular hypertrophy in echocardiography (73%), 9 stress-induced wall motion abnormalities in the posterior/inferior regions (81%) (Fig. 2), and all 11 patients showed vessel irregularities in coronary angiography (100%).

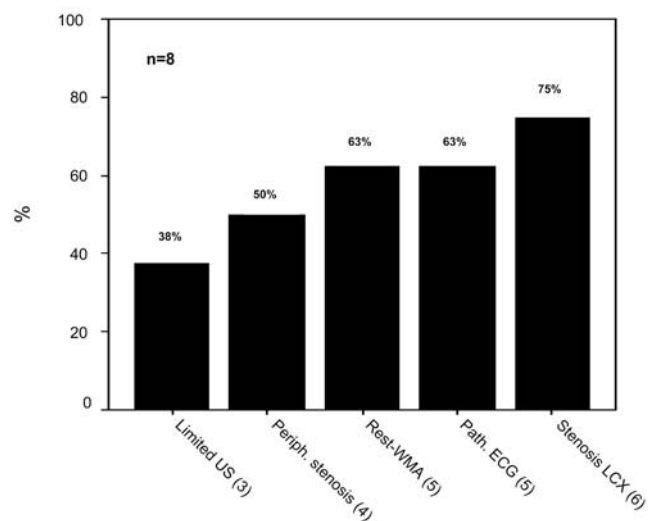


Fig. 3 Potential reasons of false negative analysis of Dobutamine Stress Echocardiography in ascending order; US, ultrasound, WMA, wall motion abnormality, ECG, electrocardiogram, LCX, left circumflex artery

Among the 8 patients with negative DSE but significant coronary artery disease (false negative), 5 had resting-WMA (62.5%), 5 rest-ECG abnormalities (62.5%), 6 showed a significant stenosis of the RCX (75%), and in 3 patients (38%) we found limited ultrasound conditions during the examination (Fig. 3).

■ MiBi-SPECT

Ischemia was detected in 28 patients with significant CAD and in 5 patients without CAD. Among the 5 false positive tests, 2 showed a rest perfusion deficit after a myocardial infarction (40%), and 4 (80%) left ventricular hypertrophy. Among the 8 false nega-

tive analyzed, 2 showed significant stenosis of the LAD, 2 of the LCX, and 4 of the RCA.

Discussion

Stress-induced transient wall motion abnormalities in echocardiography are used as a non-invasive clinical marker of myocardial ischemia. However, the underlying cause may not necessarily be due to a true perfusion deficit and, consequently, the predictive value of stress echocardiography varies in a heterogeneous population, which is usually examined in a stress-imaging laboratory [8, 9, 12].

Our aim was to examine the mechanisms leading to RWMA in DSE more accurately by direct comparison with nuclear imaging in order to reveal clinical situations that may limit the predictive value of DSE. To reach best possible image quality, all studies were performed with left ventricular contrast enhancement in order to improve border delineation [10, 11, 28]. Our observation was that the majority (78%) of stress-induced RWMAs is associated with a corresponding perfusion deficit. However, a minority of stress-induced RWMAs is unrelated to a perfusion deficit, but associated with prior structural damage or conduction abnormalities. It is important for the investigator to realize that these factors may reduce the predictive value of DSE.

Dobutamine increases myocardial oxygen consumption by sympathetic stimulation and arteriolar coronary dilation due to metabolic stimulation and increased ATP breakdown [23]. In case of reduced myocardial perfusion due to decreased coronary blood flow, a successive systolic dysfunction can be detected as a stress-induced regional wall motion abnormality. In our current study, we found a perfusion deficit in the corresponding segment in 22 of 28 correctly analyzed RWMAs upon nuclear imaging (Fig. 1). As we performed simultaneous nuclear imaging with a tracer injection at peak Dobutamine stress, it is evident that the RWMA is a result of a reduced local myocardial blood flow according to the ischemic cascade [3, 9].

Among the patients assigned to have CAD by stress echocardiography, but without corresponding perfusion deficit in nuclear imaging, 50% had a significant stenosis of the right coronary artery. Our study, therefore, confirms Oraby et al. who also found the lowest agreement between myocardial contrast echocardiography and SPECT in the area of the RCA [27].

In the current study, false positive results were obtained by DSE in 11 out of 69 patients. It is of note that 82% of these false positive results were lo-

cated in the inferior and posterior segments of the left ventricle (Fig. 2). Therefore, our findings are in agreement with previous studies by Bach et al. who showed a high number of false positive stress-induced abnormalities in the posterior/inferior regions, and Latcham et al. who reported that false positive DSE often involves the inferobasal and mid-posterolateral segments [17, 18]. The underlying mechanism might be related to the difficult visualization of these myocardial regions. Also, a decreased contractility, especially in basal segments of these regions, has been suggested to result from a fixation to the fibrous skeleton of the heart [17]. In addition to inferior RWMA, resting WMA have also been described as an important factor of false positive analysis in stress echocardiography [16, 17]. In our current study, 45% of the false positive results were associated with resting WMA. Indeed, resting hypo- or akinesia can cause dys- and hypokinesia during Dobutamine stress. This observation cannot be interpreted as a further reaction due to ischemia in this segment, but as a mechanistic phenomenon caused by a hypercontractility of the neighbored segments [17]. Thus, structural damage like a myocardial scar may impair the accuracy of DSE. Interestingly, Spencer et al. also reported a considerably reduced sensitivity of stress echocardiography in patients with pre-infarcted myocardium [19]. Also, functional abnormalities like bundle branch blocks may lead to a misinterpretation of stress-induced wall motion abnormalities. This is also consistent with our study where we found 54% of all false positive DSE studies in patients with resting-ECG abnormalities (Fig. 2).

The close examination of the false negative results in our study also showed resting wall motion abnormalities and pathological resting-ECGs in a considerable number of cases. However, the most remarkable finding was that 75% of these cases had a coronary artery stenosis in the area of the left circumflex artery (LCX), corresponding to the lateral wall in echocardiography (Fig. 3). The lateral wall can be visualized in DSE in the apical four-chamber view and the parasternal short axis. In both views, the ultrasound hits the myocardium tangentially, which aggravates adequate endocardial border delineation. Possibly, even contrast-enhancement study protocols as used in our study may not completely resolve this problem. The current finding is also consistent with other studies which showed a significantly lower sensitivity for detection of a stenosis in the LCX perfusion area in comparison to the LAD and RCA for both DSE and myocardial scintigraphy [8, 21, 22]. Nevertheless, it is also a limitation of the current definition of significant CAD that we used lumen diameter stenosis rather than a functional parameter of hemodynamic relevance such as fractional flow reserve.

With respect to the predictive values of contrast-enhanced DSE, our study is in accordance with a recent meta-analysis by Schinkel et al. who compared 17 studies of stress echocardiography and MiBi-SPECT with different stressors [9]. After data pooling, they found a sensitivity for DSE of 80% which is almost identical to our data. However, stress echocardiography had a specificity of 77% in this meta-analysis which is higher than the rate in our study. The underlying reason might be related to the unselected population with an overall prevalence of coronary artery disease of 52% in our study. Importantly, 45% of all our patients and even 53% of the patients diagnosed for relevant CAD already had rest-wall-motion-abnormalities in echocardiography, which will considerably reduce specificity as discussed above.

Pharmacological stress tests are useful non-invasive diagnostic methods in patients that cannot be examined by exercise stress tests for different kinds of reasons (e.g., neurological, orthopaedic, peripheral vessel disease). As wall motion abnormalities are mainly a result of myocardial ischemia caused by disproportion of oxygen-availability and demand in a stress-situation, Dobutamine might be more physiological than vasodilators like adenosine or dipyridamole, and additional metabolic effects were also

demonstrated [13]. Besides that, a number of comparative studies showed a higher sensitivity of Dobutamine compared to vasodilators for the diagnosis of CAD with a similar specificity [5, 14, 15]. However, not all pharmacological stress tests are performed with Dobutamine. Nevertheless, we believe that our findings can be generalized and that pre-existing structural damage or conduction abnormalities may also limit the predictive value of the other pharmacological and possibly non-pharmacological stressors.

In conclusion, stress-induced wall motion abnormalities in DSE are predominantly the result of a corresponding perfusion deficit. Nevertheless, we have also identified conditions in which the predictive values are reduced, and have presented their relative importance. Specifically, our studies have shown limited accuracy of DSE in the presence of prior structural or functional damage as well as LCX-stenosis. Although it will be important to see whether technical progress in stress-echocardiography may further improve the accuracy of the method, or new methods like myocardial contrast echocardiography can be established in clinical use [29], it is unlikely that these limitations will be completely diminished since they are linked to organic heart disease.

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