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ARTYKUŁ ORYGINALNY / *ORIGINAL ARTICLE*

Lower limb pneumatic compression during dobutamine stress echocardiography in patients with normal resting wall motion: will it increase diagnostic accuracy?

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Abstract

Background: Pneumatic compression of the lower part of the body increases systemic vascular resistance and left ventricular afterload.

Aim: We compared the diagnostic accuracy of dobutamine stress echocardiography (DSE) with pneumatic compression of the lower extremities, vs. standard DSE, for detection of angiographically significant coronary artery disease (CAD) in patients with normal baseline resting wall motion.

Methods: We enrolled 70 consecutive patients with no resting wall motion abnormalities (WMA), who underwent DSE. DSE was repeated with pneumatic compression of the lower extremities three days after the initial standard DSE. A positive test was defined as the induction of WMA in at least two contiguous non-overlap segments at any stage of dobutamine infusion. Significant coronary stenosis was defined as ≥ 50% obstruction of ≥ 1 sizable artery by coronary angiography.

Results: The mean age of the study cohort was 54.7 ± 9.9 years; 55.7% were females. Thirty-eight (54.3%) patients had significant CAD. The mean test duration was 15.8 ± 5.1 min for standard DSE and 11.7 ± 4.1 min for DSE with pneumatic compression. Analysis of standard DSE revealed sensitivity, specificity, and positive and negative predictive values of 81.6%, 90.6%, 91.2%, and 80.6%, respectively; overall accuracy was 85.7%. Analysis of DSE with pneumatic compression revealed sensitivity, specificity, and positive and negative predictive values of 89.5%, 87.5%, 89.5%, and 87.5%, respectively; overall accuracy was 88.6%.

Conclusions: In symptomatic patients with suspected CAD referred for evaluation by DSE, who have no resting wall motion abnormalities, pneumatic compression of the lower extremities during DSE improved the sensitivity but slightly reduced the specificity for detection of angiographically significant CAD, compared with standard DSE. Moreover, it reduced the test duration.

Key words: dobutamine stress echocardiography, pneumatic compression, coronary artery disease, accuracy

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INTRODUCTION

Dobutamine stress echocardiography (DSE) is acknowledged for the diagnostic evaluation of patients with suspected coronary artery disease (CAD) [1]. However, a wide range of sensitivities (54% to 96%) and specificities (62% to 93%) was published in literature due to variation of baseline characteristics, angiographic selection bias, and several echocardiographic and angiographic technical factors [2, 3]. The presence of resting wall motion abnormalities (WMA) has a particular influence on the accuracy of DSE: in a meta-analysis of 62 studies, sensitivity tended to be lower ($p = 0.14$) and specificity was higher ($p < 0.01$) in studies that excluded patients with resting WMA, compared with studies that enrolled such patient subsets [3].

High-dose dobutamine infusion reduces systemic vascular resistance (afterload), left ventricular (LV) volumes, and subsequently LV wall tension; this tends to decrease the sensitivity of DSE [4]. Pneumatic compression of the lower

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part of the body increases systemic vascular resistance and LV end-diastolic pressure in normal subjects and in patients with CAD [5]. Evidence suggests that pneumatic compression of the lower extremities during DSE improves sensitivity for detection of significant CAD, with a slight decrease of specificity, in a cohort of patients scheduled for coronary angiography [6]. However, in that cohort no information was reported on baseline resting WMA. The value of pneumatic compression of the lower extremities during DSE in patients with normal resting wall motion remains unclear. Hence, we sought to compare the diagnostic accuracy of DSE with pneumatic compression of the lower extremities, vs. standard DSE, for detection of angiographically significant CAD in patients with normal baseline resting wall motion.

METHODS

Patient selection

Prospectively, we enrolled 70 consecutive patients referred to our stress echocardiography labs during the period from July 2013 to March 2014, for diagnostic evaluation of CAD. Patients were considered eligible for inclusion if they had ischaemic-type chest pain or other symptoms suggestive of myocardial ischaemia (atypical or non-ischaemic chest pain, or angina equivalent), and were considered for non-invasive stress testing. Diabetes mellitus was defined as a fasting plasma glucose ≥ 126 mg/dL and/or 2 h post-load glucose ≥ 200 mg/dL or specific anti-diabetic drug therapy. We excluded patients with previously diagnosed CAD, those with resting WMA, those with a significant valvular or congenital heart disease, those with congestive heart failure, LV hypertrophy, or bundle branch block, those with symptoms or signs of peripheral arterial disease or other lower extremities diseases (for example, diabetic foot) that preclude the application of pneumatic compression, those with a protruding fresh LV thrombus, those with a contraindication to dobutamine (for example: history of complex ventricular arrhythmia, uncontrolled hypertension defined as blood pressure > 180/110 mm Hg), and patients with limited life expectancy due to a coexistent disease (for example: malignancy). Before inclusion, informed written consent was obtained from each patient, and the study protocol was reviewed and approved by our local Institutional Human Research Committee as it conforms to the ethical guidelines of the 1975 Declaration of Helsinki, as revised in 2013.

Resting echocardiographic assessment

Assessment of regional and global LV systolic function was performed in all patients by trans-thoracic echocardiography using a GE Vivid S5 cardiac ultrasound machine (GE HealthCare, USA) equipped with harmonic imaging capabilities. A 2.5-MHz phased array probe was used to obtain standard two-dimensional, M-mode, and Doppler images. Patients were examined in the left lateral recumbent position using standard parasternal and apical views. Images were digitised in cine-loop format and saved for subsequent playback and offline analysis. Views were analysed offline by a single observer (Z.A.) employing the software of the echocardiography machine. LV regional wall motion was assessed according to the standard 16-segment model of LV as recommended by the American Society of Echocardiography [7]. Regional wall motion was visually assessed for each segment individually, considering both endocardial excursion and systolic thickening, and each segment was graded according to the semiquantitative scoring system described by the American Society of Echocardiography [7].

DSE protocol

Dobutamine (Dobutrex®, Lilly, Eli and Company, Indianapolis, USA) was administered by intravenous infusion starting at a dose of 10 μg/kg/min for 3 min, and raised incrementally by 10 μg/kg/min every 3 min up to a maximum of 40 μg/kg/min, or until a study endpoint was reached. In patients not achieving 85% of their age-predicted maximal heart rate at the end of the final stage, atropine was administered intravenously in 0.25–0.5 mg increments at 1-min intervals up to a maximum dose of 2.0 mg, while dobutamine infusion was continued. Regional wall motion was recorded and saved for offline analysis at each stage of dobutamine infusion, as well as during recovery. DSE was repeated with pneumatic compression of the lower extremities three days after the initial standard DSE. Visual assessment of endocardial excursion and systolic thickening was performed offline, individually for each segment, by the same single observer (Z.A.) as before. The single observer was blinded to whether DSE was performed with or without pneumatic compression. A positive test was defined as the induction of WMA in at least two contiguous non-overlap segments at any stage of dobutamine infusion.

Pneumatic compression

Pneumatic compression of the lower extremities was performed using pneumatic trousers applied to the lower extremities without a bladder for compression of the lower abdomen (Fig. 1). A specially designed compressor was used to inflate the pneumatic trousers before the onset of dobutamine infusion to a pressure of 100 mm Hg on both sides. Inflation pressure was maintained throughout the dobutamine infusion. The pneumatic trousers were deflated after termination of dobutamine infusion.

Monitoring

All patients had continuous heart rate, electrocardiogram (ECG), and pulse oximetry monitoring. Heart rate and blood pressure readings were recorded at baseline, at the end of each stage of dobutamine infusion, and during the recovery phase. A 12-lead ECG was recorded at baseline and during recovery. Patients were questioned at the end of the test regarding any symptoms or adverse drug reactions.

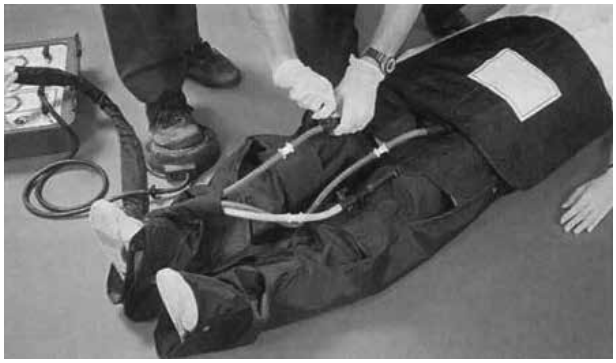

Figure 1. Pneumatic compression trousers fitted to the patient and connected to the compressor for inflation

Test termination endpoints

Endpoints for terminating the test included attainment of the maximum dose of dobutamine and/or atropine, achievement of target heart rate (greater than 85% of age-predicted maximal heart rate), echocardiographic detection of WMA, symptoms judged to be unacceptable by the attending cardiologist, serious arrhythmia detected by ECG, ST segment elevation > 0.1 mV at 80 ms from the J point, systolic blood pressure > 200 mm Hg, diastolic blood pressure > 110 mm Hg, or a decrease in systolic blood pressure > 30 mm Hg from the baseline value.

Coronary angiography

All patients underwent selective left and right coronary angiography using the standard technique, and the angiographic data were individually analysed by an independent interventional cardiologist, blinded to both clinical and echocardiographic findings. The procedure was performed within one week after DSE evaluation. Reference vessel diameter and the percentage of diameter stenosis were measured using quantitative coronary analysis (Inturis Allura, Phillips Medical Systems, Netherlands). Significant coronary stenosis was defined as ≥ 50% luminal obstruction of at least one sizable epicardial coronary artery (≥ 2.5 mm in diameter), seen in two different projections. Multi-vessel disease was defined as significant stenosis of more than one sizable coronary artery, or significant stenosis of the left main coronary artery.

Statistical analysis

Continuous variables were presented as mean ± standard deviation if they were normally distributed. Data were tested for normal distribution using the Kolmogorov-Smirnov test. Categorical variables were described with absolute and relative (percentage) frequencies. Comparisons between the two test protocol parameters were performed using the paired t-test or Mann-Whitney test for continuous variables, and Pearson's χ^2 or Fisher Exact test for categorical variables, as appropriate. Taking the results of coronary angiography as the 'gold standard' for diagnosis, the sensitivity, specificity, positive and negative predictive values, and diagnostic accuracy were calculated according to the standard definitions, individually for standard DSE and DSE with pneumatic compression. Twenty cases were randomly selected for analysis of intra-observer variability of the single observer. Intra-observer variability was tested using Spearman correlation. All tests were two-sided, and a probability value of $p < 0.05$ was considered statistically significant. Analyses were performed with SPSS version 16.0 statistical package (SPSS Inc., Chicago, IL, USA).

Table 1. Baseline characteristics of the study cohort

Character	Study cohort (n = 70)
Age [years]	54.7 ± 9.9
Male gender	31 (44.3%)
Diabetes	38 (54.3%)
Hypertension	49 (70%)
Smoking	14 (20%)
Family history of CAD	25 (35.7%)
Dyslipidaemia	36 (51.4%)
Medications:	
Beta-blockers	58 (82.9%)
Statins	49 (70.0%)
Aspirin	57 (81.4%)
CCS class:	
Class II	39 (55.7%)
Class III	31 (44.3%)
Resting LVEF [%]	56.6 ± 1.2

Continuous variables are presented as mean ± standard deviation, whereas categorical variables are presented as number (percentage); CAD — coronary artery disease; CCS — Canadian Cardiovascular Society; LVEF — left ventricular ejection fraction

RESULTS

Baseline clinical characteristics

We enrolled 70 consecutive patients with suspected CAD and no resting WMA, referred for evaluation by DSE. The mean age of the study cohort was 54.7 ± 9.9 years; 55.7% were females, and 54.3% were diabetic. Table 1 shows the baseline clinical characteristics of the study cohort.

DSE test data

The mean test duration was 15.8 ± 5.1 min for standard DSE, and 11.7 ± 4.1 min for DSE with pneumatic compression ($p = 0.056$). DSE parameters were comparable between the two test protocols (Table 2). Standard DSE was positive in 34 (48.6%) patients, whereas DSE with pneumatic compression was positive in 38 (54.3%). Four patients with negative test result by standard DSE turned positive by DSE with pneumatic compression: three of these had single-vessel CAD, and one had normal coronaries. Out of 34 patients with positive results by both test protocols, 19 patients (18 with

Table 2. Dobutamine stress echocardiography (DSE) data for the two test protocols

Parameter	Standard DSE (n = 70)	DSE with pneumatic compression (n = 70)	P
Resting heart rate [bpm]	79 ± 5	79 ± 5	0.87
Resting systolic BP [mm Hg]	122 ± 12	124 ± 11	0.39
Resting diastolic BP [mm Hg]	77 ± 7	78 ± 7	0.34
Peak heart rate [bpm]	162 ± 14	157 ± 22	0.15
Peak systolic BP [mm Hg]	156 ± 20	161 ± 19	0.14
Peak diastolic BP [mm Hg]	80 ± 13	84 ± 14	0.09
Hypertensive BP response	44 (62.9%)	51 (72.9%)	0.28
Chronotropic incompetence	3 (4.3%)	7 (10.0%)	0.32
Stress-induced WMA	34 (48.6%)	38 (54.3%)	0.54
Stress-induced WMA suggestive of SVD	23/34 (67.6%)	27/38 (71.1%)	NA
Stress-induced WMA suggestive of MVD	11/34 (32.4%)	11/38 (28.9%)	NA
Territory affected in SVD:			
LAD	17/23 (73.9%)	18/27 (66.7%)	NA
RCA	3/23 (13.0%)	5/27 (18.5%)	NA
LCx	2/23 (8.7%)	2/27 (8.7%)	NA
Diagonal vs. OM	1/23 (4.3%)	2/27 (7.4%)	NA

Continuous variables are presented as mean ± standard deviation, whereas categorical variables are presented as number (percentage); BP — blood pressure; LAD — left anterior descending; LCx — left circumflex; MVD — multi-vessel disease; NA — not available; OM — obtuse marginal; RCA — right coronary artery; SVD — single-vessel disease; WMA — wall motion abnormality

single-vessel CAD and one with multi-vessel CAD) had augmented WMA by DSE with pneumatic compression: 16 patients with single-vessel CAD developed a positive response earlier (two stages earlier in 14 patients and one stage earlier in two patients), two patients with single-vessel CAD turned to multi-vessel CAD, and one patient with multi-vessel CAD developed a positive response one stage earlier.

At peak DSE, the LV end-systolic volume was 28.8 ± 4.5 mL for standard DSE, vs. 37.2 ± 6.8 mL for DSE with pneumatic compression, p = 0.048. Similarly, at peak DSE, the LV end-diastolic volume was 91.3 ± 19.5 mL for standard DSE, vs. 102.1 ± 20.8 mL for DSE with pneumatic compression, p = 0.24.

Coronary angiographic data

Thirty-eight patients (54.3%) had significant CAD by coronary angiography, of whom 24 (63.2%) had single-vessel CAD and 14 (36.8%) had multi-vessel CAD. Out of 24 patients with single-vessel CAD, significant stenosis affected the left anterior descending artery in 17, the right coronary artery in four, and the left circumflex in three.

Accuracy of DSE to detect significant CAD

For standard DSE, there were 31 true positive, 29 true negative, three false positive, and seven false negative results, compared with coronary angiography. Analysis of standard DSE revealed sensitivity, specificity, and positive and negative predictive values of 81.6%, 90.6%, 91.2%, and 80.6%, respectively; overall accuracy was 85.7%. For DSE with pneumatic compression, there were 34 true positive, 28 true negative, four false positive, and four false negative results, compared with coronary angiography. Analysis of DSE with pneumatic compression revealed sensitivity, specificity, and positive and negative predictive values of 89.5%, 87.5%, 89.5%, and 87.5%, respectively; overall accuracy was 88.6% (p values for comparison with corresponding parameters of standard DSE were 0.049, 0.14, 0.18, 0.058, and 0.37, respectively). Analysis of intra-observer variability of the single observer (Z.A.) revealed a high agreement between repeated assessments of regional wall motion for standard DSE (r = 0.93) and for DSE with pneumatic compression (r = 0.92).

Safety of DSE protocol

No complications were observed during standard DSE or DSE with pneumatic compression. No major side effects were reported with either protocol. There was no need for earlier termination of the procedure due to patient's inconvenience. Moreover, no patient reported any clinical events during the period from DSE evaluation to coronary angiography.

DISCUSSION

Major findings

The current study demonstrated that in symptomatic patients with suspected CAD referred for evaluation by DSE, who have no resting WMA, pneumatic compression of the lower extremities during DSE improved the sensitivity but slightly reduced the specificity for the detection of angiographically

significant CAD compared with standard DSE; accuracy was comparable between the two test protocols. Moreover, it reduced the test duration.

Accuracy parameters of DSE for diagnosis of CAD

Accuracy parameters of DSE are influenced by many patient- and test-related factors; among these are baseline patient characteristics, angiographic referral bias, and technical factors [3]. The inclusion of patients with resting WMA or those with prior myocardial infarction increases the sensitivity but decreases the specificity of DSE, primarily because they more often have more extensive CAD [3]. Likewise, angiographic referral bias increases the sensitivity at the expense of decreased specificity of DSE. Similarly, the definition of positive results based on the presence of pre-existing WMA at rest, rather than dobutamine-induced new WMA, increases the sensitivity but hinders the specificity [3]. Routine early administration of atropine during DSE, rather than conventional administration at peak stress only in patients who do not achieve their target heart rate, slightly improved the sensitivity and decreased the specificity in diabetic patients with suspected CAD [8].

The 2013 European Society of Cardiology guidelines on the management of stable CAD recommend the performance of an imaging stress test as the initial test for diagnosis of stable CAD in patients with the 'higher range' of intermediate pre-test probability of obstructive CAD (66–85%), or in those with a LV ejection fraction < 50% without typical angina (class I, level of evidence B) [9]. DSE is preferred in patients who already have resting WMA, and in those unable to exercise. The prevalence of diabetes was rather high in our study cohort (54.3%). This high prevalence of diabetes could have influenced the pre-test probability of obstructive CAD since diabetics may cause atypical chest pain, non-ischaemic pain, or even silent ischaemia. Whether this has influenced the results of our study remains speculative. Although not widely employed, myocardial contrast echocardiography can be used to increase the diagnostic accuracy of DSE; it enhances image quality and allows the detection of myocardial perfusion [10]. Contrast agent should be used during DSE when two or more contiguous segments are not visualised at rest [10]. Tissue Doppler imaging and strain rate imaging may also enhance the diagnostic accuracy of DSE by improving the ability to detect ischaemia beyond that provided by the assessment of WMA [11]. Recently, automated functional imaging has offered faster and less operator-dependent assessment of regional and global longitudinal systolic strain during DSE, which correlated well with standard speckle tracking echocardiography parameters [12].

Pneumatic compression of lower extremities during DSE

A single previous study suggested that pneumatic compression of the lower extremities during DSE improves the sensitivity for detection of CAD, with slight reduction of the specificity [6]. Yet, the issue is still controversial since that study had a small sample size (40 patients) and it enrolled patients already scheduled for coronary angiography; moreover, no information was reported on baseline resting WMA [6]. In the current study we opted to exclude patients with resting WMA, in order to improve the visual detection of new WMA in response to dobutamine stress, both during standard DSE and during DSE with pneumatic compression. Enrolment of patients with normal resting wall motion avoids confusion in recognising dobutamine-induced WMA. Similar to our findings, Sohn et al. [6] reported increased sensitivity of DSE by adding pneumatic compression (from 75% to 94%), with slight reduction of specificity (from 88% to 83%) for diagnosis of CAD. This was explained by the increased LV end-systolic volume and end-systolic wall stress (a surrogate of the afterload) during DSE with pneumatic compression, compared with standard DSE [6, 13]. A sustained increase of the afterload by pneumatic compression during DSE may underlie the increased sensitivity — and decreased specificity — for detection of CAD in both studies. In this sense, diastolic blood pressure at peak dobutamine stress was higher during DSE with pneumatic compression vs. standard DSE ($p = 0.09$). This probably reflects augmented afterload during DSE with pneumatic compression. Additionally, augmented afterload during pneumatic compression shortened the mean test duration by 26% in the current study; a similar observation was made in the study by Sohn et al. [6]. We adopted the value of 100 mm Hg as a standardised increment of peripheral vascular resistance, and hence afterload, in order to obtain an adequate increase of peripheral vascular resistance on one hand, and to avoid limb ischaemia from higher values on the other hand. Using this value for all patients makes our protocol comparable with the previous study by Sohn et al. [6]. Isometric handgrip exercise during DSE is another method of increasing peripheral vascular resistance and has been reported to be associated with similar benefits to pneumatic limb compression [14–17]. The advantage of handgrip exercise over pneumatic limb compression is that it is easier to perform because it does not require any special equipment (such as pneumatic trousers); however, it is inferior to pneumatic limb compression in terms of standardisation, in terms of the magnitude of increase in peripheral vascular resistance, and for not being suitable for the long duration of the test.

Clinical implications

The added value of pneumatic compression of the lower extremities during DSE resides in its ability to enhance the diagnostic accuracy of the test in patients with a low pre-test probability of CAD. One such example is patients with normal resting wall motion. Another potential implication of DSE with pneumatic compression is patients whose DSE test result was inconclusive/equivocal. In such cases it would serve to confirm

doubtful WMA detected at peak stress with standard DSE. Moreover, the addition of pneumatic compression shortened the mean test duration by 26% in the current study. Shorter duration of dobutamine infusion entails a lower dose of dobutamine received by the patient — or even a lower infusion rate if the test was terminated one stage earlier — and this reduces the risk of arrhythmia and the potential for adverse effects, rendering the test safer, and shortening the time needed for restoration of baseline heart rate.

Limitations of the study

Our findings are based on a single-centre study with a relatively small sample size. Multi-centre studies employing the same protocol in a larger number of patients are needed. Moreover, the study cohort consisted of patients who had no resting WMA. Therefore, it is difficult to extrapolate our results to patients with prior myocardial infarction or baseline resting WMA. The technique of pneumatic compression of the lower extremities is limited by patient inconvenience, and in patients with peripheral arterial disease. The technique is further limited by the lack of routine availability of pneumatic compression trousers and the additional cost. Moreover, it would have been better to have two independent observers assessing the DSE studies and two independent observers assessing angiographic studies, since both echocardiographic and angiographic evaluations were based on visual (subjective) assessment.

CONCLUSIONS

In symptomatic patients with suspected CAD referred for evaluation by DSE, who have no resting WMA, pneumatic compression of the lower extremities during DSE improved the sensitivity but slightly reduced the specificity for the detection of angiographically significant CAD compared with standard DSE. Moreover, it reduced the test duration.

Conflict of interest: *none declared*

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Ucisk pneumatyczny kończyn dolnych w trakcie echokardiograficznej próby obciążeniowej z dobutaminą u chorych z prawidłową ruchomością ścian serca w spoczynku: czy zwiększa dokładność diagnostyczną?

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Streszczenie

Wstęp: Ucisk pneumatyczny dolnej części ciała zwiększa systemowy opór naczyniowy i obciążenie następcze lewej komory.

Cel: Autorzy ocenili dokładność diagnostyczną echokardiograficznej próby obciążeniowej z dobutaminą (DSE) z uciskiem pneumatycznym kończyn dolnych w porównaniu ze standardową DSE w wykrywaniu istotnej angiograficznie choroby wieńcowej (CAD) u chorych z prawidłową ruchomością ścian serca w spoczynku.

Metody: Do badania włączono 70 kolejnych pacjentów poddanych DSE, u których nie wykryto spoczynkowych zaburzeń ruchomości ścian serca (WMA). Trzy dni po wykonaniu standardowej DSE badanie powtórzono, stosując ucisk pneumatyczny kończyn dolnych. Dodatni wynik testu definiowano jako indukcję WMA w co najmniej dwóch sąsiednich nienakładających się segmentach na jakimkolwiek etapie wlewu dobutaminy. Istotne zwężenie tętnicy wieńcowej definiowano jako stwierdzone w koronarografii zwężenie sporej tętnicy wieńcowej o ≥ 50%.

Wyniki: Średni wiek w badanej grupie wynosił 54,7 ± 9,9 roku; 55,7% stanowiły kobiety. U 38 (54,3%) chorych stwierdzono istotną CAD. Średni czas trwania badania wynosił 15,8 ± 5,1 min w przypadku standardowej DSE i 11,7 ± 4,1 min w przypadku DSE z uciskiem pneumatycznym. Analiza wyników standardowej DSE wykazała, że czułość, swoistość, wartość prognostyczna dodatnia i wartość prognostyczna ujemna wynosiły odpowiednio 81,6%, 90,6%, 91,2% i 80,6%; ogólna dokładność wynosiła 85,7%. Analiza wyników DSE z uciskiem pneumatycznym wykazała, że czułość, swoistość, wartość prognostyczna dodatnia i wartość prognostyczna ujemna wynosiły odpowiednio 89,5%, 87,5%, 89,5% i 87,5%; ogólna dokładność wynosiła 88,6%.

Wnioski: U bezobjawowych chorych z podejrzeniem CAD skierowanych na DSE, u których nie wykryto WMA w spoczynku, ucisk pneumatyczny kończyn dolnych w trakcie DSE spowodował poprawę czułości badania, lecz nieznacznie zmniejszył jego swoistość w wykrywaniu istotnej angiograficznie CAD w porównaniu ze standardową DSE. Ponadto ucisk pneumatyczny powodował skrócenie czasu badania.

Słowa kluczowe: echokardiograficzna próba obciążeniowa z dobutaminą, ucisk pneumatyczny, choroba wieńcowa, dokładność

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