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Does the Presence of Diabetes Mellitus Make a Difference in Pharmacological Stress Echocardiography Outcome Results?

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Abstract

BACKGROUND: Coronary artery disease (CAD) is the leading cause of mortality and morbidity in patients with diabetes (DM).

AIM: The aim of our study was to analyse the ability of pharmacological SE to risk stratify patients with DM using qualitative and quantitative assessment of LV function.

METHODS: We prospectively assessed 105 consecutive patients (58.7 ± 9.5 y, 39 male) with known or suspected CAD who underwent dipyridamole or dobutamine SE.

RESULTS: Change of systolic LV function at maximal SE was less pronounced in patients with DM, while parameters of the diastolic function and its change with stress were almost insignificant. WMSI in comparison to GLS% didn't make a difference in SE outcome regarding DM presence. WMSI was almost unchanged at maximal stress in diabetic patients. Conversely, GLS% showed significant worsening at maximal stress in diabetic patients. However, only WMSI at maximal stress along with DM presence appeared as independent predictors of the presence of new and worsening CAD during SE. Longitudinal strain assessed using speckle tracking during pharmacological stress echocardiography was superior to conventional echocardiography expressed by wall motion analysis in making a difference regarding DM presence.

CONCLUSION: We confirmed the usefulness of stress echocardiography using qualitative and/or quantitative parameters in the detection of CAD in patients with DM.

Introduction

Coronary artery disease (CAD) is the leading cause of mortality and morbidity in patients with diabetes. Approximately one-half of deaths are attributed to CAD in diabetic patients [1], whose risk of myocardial infarction or cardiac death is two-to four-fold as great compared with nondiabetic patients [2] [3]. Moreover, cardiac events are as frequent in diabetic patients without evidence of CAD as in nondiabetic patients with known CAD [4]. The increased risk associated with diabetes calls for effective prevention [5], [6], [7], [8] and risk stratification strategies to optimise therapeutic interventions [9]. Exercise testing is of limited value in the diabetic population because exercise capacity is often impaired by peripheral vascular [10] or neuropathic disease [11]. Furthermore, test specificity is less than ideal [12] because of the high prevalence of hypertension [13] and microvascular disease[14]. Stress echocardiography (SE) represents an established diagnostic [15] and prognostic modality [16], [17], [18], [19] in diabetic patients. However, it is still undefined whether it retains the same prognostic value in diabetic and nondiabetic patients.

The aim of our study was to analyse the ability of pharmacological (dobutamine or

dipyridamole) stress echocardiography (SE) to risk stratify patients with DM using qualitative and/or quantitative assessment of LV function.

Methods

We prospectively assessed 105 consecutive patients, with a mean age of 58.7 ± 9.5 years, who underwent dipyridamole or dobutamine stress echocardiography between January 2016 and May 2018 in a University Clinic of cardiology in Skopje. Before the study, patients' demographic characteristics were obtained, and patients were questioned about the presence of atherosclerotic risk factors, previous CAD and angioplasty. Subjects were classified as having diabetes when treated for insulin-dependent or non-insulin-dependent diabetes or having elevated fasting glucose levels according to issued up-to-date standards from professional organisations.

The indications for the exam was a referral from a physician according to the complaints of the participating patient or was a result of inconclusive results of treadmill stress testing. Written informed consent to undergo stress testing and to participate in the study was obtained from each patient.

Echocardiographic examination was performed using GE, Vivid 7 with a recording of the views and later analysing on the machine itself or acoustic-tracking software (Echo Pac, GE). All measurements were performed according to guidelines suggested by professional echocardiographic societies [20], [21].

An accelerated high-dose dipyridamole protocol was used for all patients. Dipyridamole was infused intravenously at a dose of 0.84 mg/kg body weight over 6 min. Aminophylline (up to 240 mg) was routinely administered to patients 5 min after the end of the test or immediately if there were obvious clinical and/or ECG signs of ischemia. Dobutamine was administered intravenously beginning at a dose of 10 μg/kg body weight and minute and increased in steps every 3 minutes to 20, 30, and 40 μg/kg.

Two-dimensional echocardiography, blood pressure measurements and 12-lead electrocardiography (ECG) were used for continuous monitoring during the test and the recovery phase. Echocardiographic images were semi-quantitatively assessed using 17 segments, and wall motion score index (WMSI) was derived by dividing the sum of individual segment scores by the number of interpretable segments. Ischemia was defined as stress-induced new and/or worsening of pre-existing wall motion abnormality, or biphasic response (i.e. low-dose improvement followed by high-dose deterioration) [22], [23].

Global longitudinal strain (GLS%) for the LV was automatically provided as the average value of the regional peak systolic longitudinal strain of the three apical views by the software [24], [25], [26]. The images for analysis were obtained out of stress-echo protocol. All images were recorded with a high frame rate (> 50 frames/s). The LV was divided into 17 segments, and each segment was analysed individually. Only myocardial segments considered to be of adequate quality by both the automatic system and the operator were included in the analysis. All examinations were assessed by the same cardiologist.

Sixty-one patients underwent coronary angiography within a few days of the stress echocardiography tests. Angiographic assessments involved presence and quantification of stenosis severity as well as the calculation of Syntax score.

The study protocol was approved by the Medical Ethics Committee of Medical School, University "St. Cyril & Methodius), Skopje.

Categorical parameters were summarised as percentages and continuous parameters as mean ± SD. Comparisons between the two groups with and without DM was performed using the Mann-Whitney nonparametric test for continuous parameters and Pearson's chi-square test for categorical parameters. Comparisons between the two groups before and after stress were performed using Wilcoxon Signed Rank test. Assessment of correlation of various echocardiographic parameters was done using Pearson's correlation analysis. Multiple logistic regression analysis was performed in stepwise order to determine independent predictors among clinical and echocardiographic covariates of the positive stress echocardiographic result. All data analysis was performed using SPSS version 25.0 (IBM SPSS, Inc., Chicago, Illinois) and p-value ≤ 0.05 was considered significant.

Results

Out of 105 patients who underwent SE, DM was present in 36 (34.3%); 22/61,2% were taking oral antidiabetic drugs, and 14/38.9% were using insulin to control diabetes. In comparison to patients without DM, those with DM were older (p = 0.0001), with higher BMI (p = 0.034), less frequently were current smokers (p = 0.033), but more frequently had a history of hypertension (p = 0.013) and insignificantly higher percentage of the history of CAD

Table 1: Basal and functional characteristics, symptoms and ECG changes of patients divided according to the DM presence

Parameter	With DM N = 36	Without DM N = 69	p
Age (y)	63.1 ± 6.7	56.4 ± 9.9	0.0001
Gender (m/f %)	36.1/63.9	37.7/62.3	0.874
BMI (kg/m^2)	30.4 ± 4.6	28.3 ± 5.1	0.034
Current smoking (n/%)	9/25.0	32/46.4	0.033
History of hypertension (n/%)	32/88.9	46/66.7	0.013
History of dislipidemia (n/%)	25/69.4	48/69.6	0.580
History of CAD (n/%)	15/41.7	19/27.5	0.142
Beta-blocker therapy (n/%)	23/21.9	37/35.2	0.313
Calcium channel blocker therapy (n/%)	7/19.4	17/24.6	0.547
Symptoms (n%)	7/19,4	14/20.3	0,918
ECG changes (n/%)	10/27.8	13/18.8	0,293
Rhythm disorder (n/%)	4/11.1	6/8.7	0,689
Δ BPs (mmHg)	-1.2 ± 20.1	1.1 ± 17.4	0.525
ΔBPd (mmHg)	1.5 ± 10.3	2.2 ± 9.8	0.713
HR rest (Imp/min)	79.5 ± 15.2	72.0 ± 11.2	0.005
HR max (Imp/min)	105.9 ± 21.3	97.9 ± 18.1	0.048
ΔHR (Imp/min)	-26.4 ± 18.37	-25.8 ± 14.8	0.876

DM = diabetes mellitus; BMI = body mass index, CAD = coronary artery disease; ECG = electrocardiogram; BP = blood pressure; s = systolic;d=diastolic; HR = heart rate; Δ= change from rest to maximal dose of stressor; *p<0.05 for comparison between groups.

Dobutamine or dipyridamole pharmacological protocol was applied in equal half's of patients with DM, while those without DM receive more frequently dipyridamole protocol (p = 0.049). Although systolic blood pressure increase with SE in patients with DM while a decrease in patients without DM, there was no significant difference in change. With SE diastolic pressure decrease in both groups of patients without difference between them. Heart rate was significantly higher in patients with DM at rest as well as at maximal dose of the stressor (peak stress), but there was lack of significant difference in its change (delta) (Table 1).

Comparison of systolic LV functional data during SE showed an insignificant increase of LV ejection fraction (LVEF) and significant increase of indexed systolic volume (SV/BSA), indexed cardiac output (CI) and early diastolic mitral annular tissue Doppler velocity (s'TDI) in both groups of patients (Table 2). Although the change (delta value) from rest to peak stress was less pronounced in patients with DM, the difference between groups was not significant for all values (Table 2). As for parameters of diastolic function, comparison of data showed insignificant increase of left atrial volume index (LAVI), significant increase of early diastolic mitral annular tissue Doppler velocity (e'TDI) and insignificant increase of value of LV filling pressure expressed as E/e'ratio in patients with DM without significant difference between respective delta values (Table 2). Value of transmitral flow parameters showed a significant decrease in patients with DM and only for deceleration time (DT) and isovolumetric relaxation time for patients without DM, whereas delta value was border significant only for DT mostly for diabetic patients.

As for WMSI, besides it was insignificantly higher in diabetic patients at rest, it has been shown that the index was almost unchanged during stress in both groups of patients, whereas in diabetic patients GLS% showed worsening (more positive or decreased negative value) at maximal stress which was significantly different to those without DM who showed slight improvement (less positive or increased negative value) of GLS% (Table 3).

Table 2: Comparison of systolic and diastolic parameters during SE in patients divided according to the DM presence

Parameter	With DM N = 36		Without DM N = 69		p**
	At rest	Max stress	At rest	Max stress	
LVEF (%)	60.1 ± 8.7	60.4 ± 10.1	62.0 ± 8.2	63.7 ± 8.5	0.378
p*	0.922		0.076		
SV/BSA (ml/m^2)	41.8 ± 12.0	90.6 ± 21.6	43.5 ± 10.7	95.2 ± 25.0	0.486
p*	0.0001		0.0001		
CI (L/min/m^2)	3.4 ± 1.3	9.2 ± 2.7	3.0 ± 0.8	8.8 ± 2.9	0.896
p*	0.0001		0.0001		
s'TVI (cm/s)	7.7 ± 1.4	9.1 ± 2.3	7.4 ± 1.0	8.6 ± 2.0	0.461
p*	0.0001		0.0001		
LAVI (ml/m^2)	19.5 ± 5.3	19.6 ± 5.6	18.3 ± 6.0	19.2 ± 7.0	0.756
p*	0.753		0.156		
E/A	0.9 ± 0.2	0.8 ± 0.2	1.0 ± 0.2	1.0 ± 0.3	0.318
p*	0.033		0.504		
DT (ms)	195.0 ± 53.1	130.9 ± 44.3	206.0 ± 47.1	167.6 ± 52.4	0.051
p*	0.0001		0.0001		
IVRT (ms)	83.3 ± 16.3	63.1 ± 11.2	85.4 ± 15.1	65.4 ± 8.6	0.787
p*	0.0001		0.0001		
e' TDI average	9.3 ± 2.2	10.1 ± 2.4	9.6 ± 1.9	10.7 ± 2.4	0.919
p*	0.009		0.0001		
E/e' average	9.5±2.8	9.6±2.7	8.9±2.4	8.9±2.6	0.973
p*	0.912		0.754		

LVEF = left ventricular ejection fraction; SVI = systolic volume indexed to BSA; CI = cardiac output indexed to BSA; s'TDI = peak systolic mitral annular velocity by TDI; LAVI = maximum left atrial volume indexed to BSA; E velocity = early mitral inflow velocity; A velocity = late mitral inflow velocity; DT = deceleration time; IVRT = isovolumetric relaxation time; e' TDI = early diastolic mitral annular tissue Doppler velocity; *p < 0.05 for comparison between groups; **p = comparison of delta values between two groups.

However, the significant difference of GLS% delta values between diabetic and non-diabetic patients was not confirmed (Table 3). About the number of segments with longitudinal LV strain < 12% the outcome of stress was the same as for GLS%. Thus there was no a significant difference in stress outcome in diabetic patients *vs* non-diabetic (Table 3). Also, the percentage of positive results according to the worsening of WMSI and/or GLS% during SE were insignificantly more frequent in diabetic patients (Table 3).

Table 3: Comparison of wall motion score index and global longitudinal LV strain values during SE in patients divided according to the DM presence

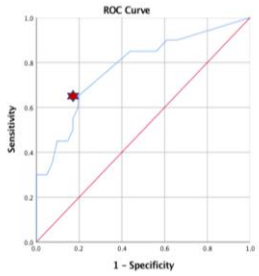
Parameter	With DM N = 36	Without DM N = 69	p
WMSI at rest	1.12 ± 0.14	1.05 ± 0.09	0.337
WMSI at peak stress	1.10 ± 0.15	1.07 ± 0.13	0.579
ΔWMSI	0.01 ± 0.17	-0.01 ± 0.12	0.126
GLS (%) at rest	-15.0 ± 3.7	-16.6 ± 5.0	0.905
GLS (%) at peak stress	-14.8 ± 3.5	-17.0 ± 4.4	0.008
Δ GLS (%)	-0.13 ± 2.85	0.36 ± 4.70	0.559
No. LS seg < -12% at rest	4.9 ± 3.0	3.4 ± 2.5	0.847
No. LS seg < -12% at peak stress	4.9 ± 3.8	4.0 ± 3.1	0.126
ΔNo. LS seg < -12%	0.00 ± 2.84	-0.60 ± 2.85	0.479
Positive results according to WMSI (n/%)	9/25	14/20.3	0.580
Positive results according to GLS% (n/%)	14/44.4	26/37.7	0.520

WMSI = wall motion score index; Δ = change from rest to maximal dose of stressor; GLS = global longitudinal strain; LG=longitudinal strain.

There was statistically significant correlation between presence of DM and decrease of E/A ratio (r = -0.278; p = 0.004), shortening of DT (r = -0.332; p = 0.001) and worsening of GLS% (r = 0.245; p = 0.012) at maximal stress, while such correlation didn't appeared regarding stress WMSI. After SE coronary angiography was done in 61 patients. Diabetic patient in comparison to those without had with borderline significance more new and/or worsening CAD (44.8% *vs*. 21.9%; p = 0.057; respectively), especially multivessel disease (34.5% *vs*. 12.5%; p = 0.044; respectively) as well as significantly greater Syntax score (8.0 *vs*. 2.5; p = 0.010, respectively) and insignificantly more frequently presence of coronary artery plaque. There was statistically significant correlation between presence of DM and angiographycaly proven new and/or worsening CAD (r = 0.244; p = 0.058), multivessel disease (r = 0.267; p = 0.037), Syntax score (r = 0.327; p = 0.010) and diseased Cx coronary artery (r = 0.306; p = 0.016). In addition presence of new and/or worsening CAD was significantly correlated with WMSI at maximal stress (r = 0.386; p = 0.002) and its change during SE (r = -0.645; p = 0.0001) along with GLS% at maximal stress (r = 0.262, p = 0.042) as well as without any correlation to functional parameters either of systolic or diastolic LV function.

To determine the independent predictors of new and/or worsening CAD among patients who were pharmacologically stressed, we performed multiple stepwise logistic regression analysis with demographic, clinical and echocardiographic covariates that showed significant relation to it. The results that were adjusted for age and gender, demonstrated that WMSI at maximal stress (OR = 375.8; 95% CI 6.2-22649.7; p = 0.005) and presence of DM (OR = 3.8; 95%CI 1.078-13.396; p = 0.038) appeared as independent predictors of presence of new and/or worsening CAD during SE. Positive predictive value of the model was 69.2%, while the negative was 77%.

Figure 1 demonstrates the receiver operator characteristics curve (ROC) for predictive probability from the model which showed an AUC value of 0.777. Also, WMSI at maximal stress and the presence of DM during pharmacological SE as a model were associated with an acceptable sensitivity of 64% and higher specificity (1-20) of 80%.



Area Under the Curve

Test Result Variable(s): Predicted probability

Area	Std. Error[a]	Asymptotic Sig.[b]	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
.777	.066	.000	.648	.907

The test result variable(s): Predicted probability has at least one tie between the positive actual state group and the negative actual state group. Statistics may be biased.

a. Under the nonparametric assumption

b. Null hypothesis: true area = 0.5

Figure 1: ROC curve for the presence and/or worsening of angiographic CAD using WMSI and DM presence during pharmacological SE

Discussion

Given that the change of systolic LV functional data or rather its improvement from rest to peak stress was less pronounced in patients with DM, as well parameters of diastolic function and its change with stress were almost insignificant (slightly increase of E/e' in DM), we could not find the significant functional marker in order to make a difference in patients with and without DM. Such results mainly differ from our expectations taking into account that patients with DM were significantly older, had more frequently a history of hypertension, significantly more new and/or worsening CAD, especially multivessel disease and greater Syntax score. Although numerous studies highlighted the role of diastolic stress as predictor of CAD presence and its prognosis [27], [28], [29], [30], [31] as well in diabetic patients [32], [33], [34], we could not provide such evidence mainly due to small number of patients with DM in our study, lack of performed coronary angiography in all patients, possible good controlled risk factors as well as due to well-known technical factors regarding TDI velocity that can only be measured in one dimension and is significantly limited by angle dependence which produce difficulties in assessment of multiple wall segments (especially apical segments), along with influence of heart motion and contraction of adjacent segments on TDI data during SE, especially during dobutamine application [35]. Also, we could speculate that the results of our study were in line with those of Fang et al., [36] who detected the normal response to stress in diabetic patients without a significant difference with a control group that might be due to the early stage of diabetic cardiomyopathy.

Our study showed that visual wall motion analysis expressed as WMSI in comparison to longitudinal strain assessed using speckle tracking (GLS%) didn't make a difference in SE outcome regarding DM presence. WMSI was almost unchanged at maximal stress in diabetic patients, and paradoxically showed even slight increment in patients without DM. However, GLS% showed significant worsening at maximal stress in diabetic patients which was significantly different to those without DM who showed slight improvement. Presence of DM was significantly correlated with worsening of GLS% at maximal stress, while such correlation didn't appear regarding stress WMSI. Given that WMSI and GLS% at maximal stress were significantly correlated to new and/or worsening CAD, we were expected that two of them would appear as its predictors, but regression analysis revealed that only WMSI at maximal stress and DM appeared as independent predictors of presence of new and/or worsening CAD during SE providing sensitivity of the model of 64% and specificity of 80%.

Since Voight et al., [37] demonstrated that strain rate analysis during SE provides objective evidence of ischemia, the interest of using quantitative

assessment of LV systolic function by 2D speckle tracking during SE gained interest because it removes the subjective nature of visual assessment by wall motion analysis (WMA) in detecting CAD. Hence, a number of studies have shown that imaging GLS% was as good as [38], [39] or even superior [37], [40] [41] to conventional echocardiography, subsequently lot of them concluding that GLS% provides incremental diagnostic accuracy in combination with expert WMA [42] in detecting CAD. Our results were partly in line with such conclusions; however only WMSI appeared as independent predictor of CAD which was consistent with the results of dobutamine SE study of Celutkiene et al., [43] who stressed that none of the single quantitative parameters investigated was able to identify significant CAD with a comparable diagnostic accuracy *vs* visual assessment using WMA. Also, Nagi et al., [44] fail clearly to demonstrate the diagnostic benefit of strain analysis over expert WMA alone during contrast-enhanced SE.

Given that in diabetic patients risk stratification is a major objective considering their increased risk for CAD and its' major cardiovascular events, several well-known studies published their results that revealed prognostic ability of SE in diabetic patients on the basis of conventional WMA [45], [16], [18], [44], [33], [34]. Thus, the degree of worsening WMSI during SE, especially its' multivessel distribution correlated with the extent of CAD which was consistent with our study, but more importunately with increasing cardiac events, including death in subsequent years. In this respect, it should be born in mind that data from studies [33], [34] emphasised that regardless a negative test result of SE based solely on wall motion criteria in diabetic patients it is associated with the less benign outcome which is why assessment of GLS% using speckle tracking would be an advantage. To our knowledge, data concerning LV myocardial deformation during SE in patients with DM are available only for longitudinal deformations and are still limited to very few studies. Although we could not confirm GLS% as independent predictor of CAD either in diabetic or nondiabetic patients, the value of GLS% at maximal stress appeared as significant distinctive parameter for DM presence as well as for more extensive CAD which is consistent with the study of Wierzbowska-Drabik et al., [45] who found more impaired GLS% in patients with DM and CAD at rest as well as at maximal SE in comparison to their counterparts with CAD but without DM, hence they concluded that coexisting CAD and DM had synergistic detrimental effect on myocardial strain. Furthermore, Philouze et al., [46] confirmed in their study that dobutamine SE unmasks functional alterations expressed by myocardial mechanics in patients with DM that could be barely detectable at rest mainly in asymptomatic patients with uncomplicated DM.

The main limitation of our study was a relatively small number of patients, especially with DM. Patients with DM were older, with higher BMI, more frequent history of hypertension and previous CAD, which might influence the obtained longitudinal strain data. There was no assessment of the influence of metabolic control and therapeutic interventions in diabetic patients. Coronary angiography was not available in all patients, but this is in line with clinical guidelines, which do not recommend invasive testing in asymptomatic patients. Aiming to good spatial resolution and image quality for satisfactory speckle-tracking during SE, we included in the study and analysed only individuals with good acoustic windows.

The additional long-term analysis of the prognostic significance of reduced GLS% at rest and stress in patients with DM may potentially increase the clinical utility of our observations.

In conclusion, although wall motion score index (WMSI) was insignificantly higher and GLS% was worse in diabetic patients at rest, it has been shown that the WMSI was almost unchanged during stress in both groups of patients, whereas in diabetic patients GLS% showed significant worsening at maximal stress which. However, besides assessment of GLS% appeared superior to qualitative analysis expressed by WMSI in making difference regarding DM presence, regression analysis revealed that only WMSI at maximal stress and DM appeared as independent predictors of presence of new and/or worsening CAD during SE which lead to conclusion of usefulness of using qualitative and/or quantitative parameters in detection of CAD in patients with DM during stress echocardiography.

Referencies

1. Kannel WB, McGee DL. Diabetes and cardiovascular risk factors: the Framingham study. Circulation. 1979; 59(1):8-13. https://doi.org/10.1161/01.CIR.59.1.8

2. Consensus development conference on the diagnosis of coronary heart disease in people with diabetes: 10-11 February 1998, Miami, Florida. American Diabetes Association. Diabetes Care. 1998; 21(9):1551-9. https://doi.org/10.2337/diacare.21.9.1551 PMid:9727908

3. The BARI Investigators. Influence of diabetes on 5-year mortality and morbidity in a randomized trial comparing CABG and PTCA in patients with multivessel disease. Circulation. 1997; 96(6):1761-9. https://doi.org/10.1161/01.CIR.96.6.1761

4. Haffner SM, Lehto S, Rönnemaa T, Pyörälä K, Laakso M. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic dubjects with and without prior myocardial infarction. N Engl J Med. 1998; 339(4):229-34. https://doi.org/10.1056/NEJM199807233390404 PMid:9673301

5. The sixth report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure national institutes of health national heart, lung, and blood institute national high blood pressure education program. http://www.sld.cu/galerias/pdf/servicios/hta/6to._reporte_del_jnc_u

sa.pdf

6. Collins R et al. MRC/BHF Heart protection study of cholesterol lowering with simvastatin in 5963 people with diabetes: a randomised placebo-controled trial. Lancet. 2003; 361:1005-16

7. Collaborative overview of randomised trials of antiplatelet therapy--I: Prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. Antiplatelet trialists' Collaboration. BMJ. 1994; 308(6921):81-106. https://doi.org/10.1136/bmj.308.6921.81 PMid:8298418 PMCid:PMC2539220

8. Supplement 1. American Diabetes Association: clinical practice recommendations 2000. Diabetes Care. 2000; 23(Suppl 1):S1-116. PMid:10859117

9. Detre KM, Guo P, Holubkov R, et al. Coronary revascularization in diabetic patients: a comparison of the randomized and observational components of the Bypass Angioplasty Revascularization Investigation (BARI). Circulation. 1999; 99(5):633-40. https://doi.org/10.1161/01.CIR.99.5.633 PMid:9950660

10. Cameron M et al. Diabetes and periferal vascular disease. J Vasc Surg. 1999; 30(2);373-84. https://doi.org/10.1016/S0741-5214(99)70154-0

11. May O, Arildsen H, Damsgaard EM, Mickley H. Cardiovascular autonomic neuropathy in insulin-dependent diabetes mellitus: prevalence and estimated risk of coronary heart disease in the general population. J Intern Med. 2000; 248(6):483-91. https://doi.org/10.1046/j.1365-2796.2000.00756.x PMid:11155141

12. Koistinen MJ. Prevalence of asymptomatic myocardial ischaemia in diabetic subjects. BMJ. 1990; 301(6743):92-5. https://doi.org/10.1136/bmj.301.6743.92 PMid:2390590 PMCid:PMC1663397

13. Tarnow L, Rossing P, Gall MA, Nielsen FS, Parving HH. Prevalence of arterial hypertension in diabetic patients before and after the JNC-V. Diabetes Care. 1994; 17(11):1247-51. https://doi.org/10.2337/diacare.17.11.1247 PMid:7821162

14. Nahser PJ, Brown RE, Oskarsson H, Winniford MD, Rossen JD. Maximal coronary flow reserve and metabolic coronary vasodilation in patients with diabetes mellitus. Circulation. 1995; 91(3):635-40. https://doi.org/10.1161/01.CIR.91.3.635 PMid:7828287

15. Elhendy A, van Domburg RT, Poldermans D, et al. Safety and feasibility of dobutamine-atropine stress echocardiography for the diagnosis of coronary artery disease in diabetic patients unable to perform an exercise stress test. Diabetes Care. 1998; 21(11):1797-802. https://doi.org/10.2337/diacare.21.11.1797 PMid:9802723

16. Bigi R, Desideri A, Cortigiani L, Bax JJ, Celegon L, Fiorentini C. Stress echocardiography for risk stratification of diabetic patients with known or suspected coronary artery disease. Diabetes Care. 2001; 24(9):1596-601. https://doi.org/10.2337/diacare.24.9.1596 PMid:11522705

17. Elhendy A, Arruda AM, Mahoney DW, Pellikka PA. Prognostic stratification of diabetic patients by exercise echocardiography. J Am Coll Cardiol. 2001; 37(6):1551-7. https://doi.org/10.1016/S0735-1097(01)01199-8

18. Marwick TH, Case C, Sawada S, Vasey C, Short L, Lauer M. Use of stress echocardiography to predict mortality in patients with diabetes and known or suspected coronary artery disease. Diabetes Care. 2002; 25(6):1042-8. https://doi.org/10.2337/diacare.25.6.1042 PMid:12032112

19. Sozzi FB, Elhendy A, Roelandt JRTC, et al. Prognostic value of dobutamine stress echocardiography in patients with diabetes. Diabetes Care. 2003; 26(4):1074-8. https://doi.org/10.2337/diacare.26.4.1074 PMid:12663576

20. Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: An update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging. 2015; 16:233-71. https://doi.org/10.1093/ehjci/jev014 PMid:25712077

21. Nagueh SF, Smiseth OA, Appleton CP, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography: An update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr. 2016; 29:277-314. https://doi.org/10.1016/j.echo.2016.01.011 PMid:27037982

22. Pellikka PA, Nagueh SF, Elhendy AA, Kuehl CA, Sawada SG, American Society of Echocardiography. American Society of Echocardiography Recommendations for performance, interpretation, and application of stress echocardiography. J Am Soc Echocardiogr. 2007; 20(9):1021-41. https://doi.org/10.1016/j.echo.2007.07.003 PMid:17765820

23. Sicari R, Nihoyannopoulos P, Evangelista A, et al. Stress echocardiography expert consensus statement: European Association of Echocardiography (EAE) (a registered branch of the ESC). Eur J Echocardiogr. 2008; 9(4):415-37. https://doi.org/10.1093/ejechocard/jen175 PMid:18579481

24. Mor-Avi V, Lang RM, Badano LP, et al. Current and evolving echocardiographic techniques for the quantitative evaluation of cardiac mechanics: ASE/EAE Consensus statement on methodology and indications. J Am Soc Echocardiogr. 2011; 24(3):277-313. https://doi.org/10.1016/j.echo.2011.01.015 PMid:21338865

25. Yingchoncharoen T, Agarwal S, Popović ZB, Marwick TH. Normal ranges of left ventricular strain: A meta-analysis. J Am Soc Echocardiogr. 2013; 26(2):185-91. https://doi.org/10.1016/j.echo.2012.10.008 PMid:23218891

26. Sugimoto T, Dulgheru R, Bernard A, et al. Echocardiographic reference ranges for normal left ventricular 2D strain: results from the EACVI NORRE study. Eur Hear J - Cardiovasc Imaging. 2017; 18(8):833-40. https://doi.org/10.1093/ehjci/jex140 PMid:28637227

27. Burgess MI, Jenkins C, Sharman JE, Marwick TH. Diastolic stress echocardiography: hemodynamic validation and clinical significance of estimation of ventricular filling pressure with exercise. J Am Coll Cardiol. 2006; 47(9):1891-900. https://doi.org/10.1016/j.jacc.2006.02.042 PMid:16682317

28. Hyodo E, Hirata K, Hirose M, et al. Clinical use of doppler echocardiography and doppler tissue imaging in the estimation of myocardial ischemia during dobutamine stress echocardiography. J Am Soc Echocardiogr. 2008; 21(4):331-6. https://doi.org/10.1016/j.echo.2007.09.005 PMid:18029141

29. Joyce E, Delgado V, Bax JJ, Marsan NA. Advanced techniques in dobutamine stress echocardiography: focus on myocardial deformation analysis. Heart. 2015; 101:72-81. https://doi.org/10.1136/heartjnl-2013-303850 PMid:24760702

30. Agarwal R, Gosain P, Kirkpatrick JN, et al. Tissue doppler imaging for diagnosis of coronary artery disease: a systematic review and meta-analysis. Cardiovasc Ultrasound. 2012; 10(1):47. https://doi.org/10.1186/1476-7120-10-47 PMid:23199010 PMCid:PMC3542063

31. Hoffmann S, Jensen JS, Iversen AZ, et al. Tissue Doppler echocardiography improves the diagnosis of coronary artery stenosis in stable angina pectoris. Eur Hear J - Cardiovasc Imaging. 2012; 13(9):724-9. https://doi.org/10.1093/ehjci/jes001 PMid:22323549

32. Ha J-W,Lee H-C,Kang E-S, et al.Abnormal left ventricular longitudinal functional reserve in patients with diabetes mellitus:implication for detecting subclinical myocardial dysfunction using exercise tissue Doppler echocardiography. Heart. 2006; 93(12):1571-6. https://doi.org/10.1136/hrt.2006.101667 PMid:17449503 PMCid:PMC2095774

33. Cortigiani L, Bigi R, Sicari R, Landi P, Bovenzi F, Picano E. Prognostic value of pharmacological stress echocardiography in diabetic and nondiabetic patients with known or suspected coronary artery disease. J Am Coll Cardiol. 2006; 47(3):605-10. https://doi.org/10.1016/j.jacc.2005.09.035 PMid:16458144

34. Budoff MJ, Raggi P, Beller GA, et al. Noninvasive cardiovascular risk assessment of the asymptomatic diabetic patient: The imaging council of the American College of Cardiology. JACC Cardiovasc Imaging. 2016; 9(2):176-92. https://doi.org/10.1016/j.jcmg.2015.11.011 PMid:26846937

PMCid:PMC5371352

35. Picano E. Diabetic cardiomyopathy. the importance of being earliest. J Am Coll Cardiol. 2003; 42(3):454-7. https://doi.org/10.1016/S0735-1097(03)00647-8

36. You Fang Z, Najos-Valencia O, Leano R, Marwick TH, Brisbane F. Echo assessment of diabetes and mitral regurgitation patients with early diabetic heart disease demonstrate a normal myocardial response to dobutamine. J Am Coll Cardiol. 2003; 42:446-53. https://doi.org/10.1016/S0735-1097(03)00654-5

37. Voigt JU, Exner B, Schmiedehausen K, et al. Strain-rate imaging during dobutamine stress echocardiography provides objective evidence of inducible ischemia. Circulation. 2003; 107(16):2120-26. https://doi.org/10.1161/01.CIR.0000065249.69988.AA PMid:12682001

38. Ng ACT, Sitges M, Pham PN, et al. Incremental value of 2-dimensional speckle tracking strain imaging to wall motion analysis for detection of coronary artery disease in patients undergoing dobutamine stress echocardiography. Am Heart J. 2009; 158(5):836-44. https://doi.org/10.1016/j.ahj.2009.09.010 PMid:19853706

39. Uusitalo V, Luotolahti M, Pietilä M, et al. Two-dimensional speckle-tracking during dobutamine stress echocardiography in the detection of myocardial ischemia in patients with suspected coronary artery disease. J Am Soc Echocardiogr. 2016; 29(5):470-9. https://doi.org/10.1016/j.echo.2015.12.013 PMid:26852941

40. Bjork Ingul C, Stoylen A, Slordahl SA, Wiseth R, Burgess M, Marwick TH. Automated analysis of myocardial deformation at dobutamine stress echocardiography. J Am Coll Cardiol. 2007; 49(15):1651-9. https://doi.org/10.1016/j.jacc.2007.01.059 PMid:17433958

41. Rumbinaitė E, Žaliaduonytė-Pekšienė D, Vieželis M, et al. Dobutamine-stress echocardiography speckle-tracking imaging in the assessment of hemodynamic significance of coronary artery stenosis in patients with moderate and high probability of coronary artery disease. Medicina (B Aires). 2016; 52(6):331-9. https://doi.org/10.1016/j.medici.2016.11.005 PMid:27932192

42. Aggeli C, Lagoudakou S, Felekos I, et al. Two-dimensional speckle tracking for the assessment of coronary artery disease during dobutamine stress echo: clinical tool or merely research method. Cardiovasc Ultrasound. 2015; 13:43. https://doi.org/10.1186/s12947-015-0038-z PMid:26498476 PMCid:PMC4619392

43. Celutkiene J, Zakarkaite D, Skorniakov V, et al. Quantitative approach using multiple single parameters versus visual assessment in dobutamine stress echocardiography. Cardiovascular ultrasound. 2012; 10:31. https://doi.org/10.1186/1476-7120-10-31 PMid:22846395 PMCid:PMC3495225

44. Nagy AI, Sahlen A, Manouras A, et al. Combination of contrast-enhanced wall motion analysis and myocardial deformation imaging during dobutamine stress echocardiography. Eur Hear J - Cardiovasc Imaging. 2015; 16(1):88-95. https://doi.org/10.1093/ehjci/jeu171 PMid:25187604

45. Elhendy A, Arruda AM, Mahoney DW, et al. Prognostic stratification of diabetic patients by exercise echocardiography. J Am Coll Cardiol. 2001; 35:1551-7. https://doi.org/10.1016/S0735-1097(01)01199-8

46. Chaowalit N, Arruda AL, McCully RB, Bailey KR, Pellikka PA. Dobutamine stress echocardiography in patients with diabetes mellitus. J Am Coll Cardiol. 2006; 47(5):1029-36. https://doi.org/10.1016/j.jacc.2005.10.048 PMid:16516089

47. Wierzbowska-Drabik K, Trzos E, Kurpesa M, et al. Diabetes as an independent predictor of left ventricular longitudinal strain reduction at rest and during dobutamine stress test in patients with significant coronary artery disease. Eur Hear J - Cardiovasc Imaging. 2017; 0:1-11.

48. Philouze C, Obert P, Nottin S, Benamor A, Barthez O, Aboukhoudir F. Dobutamine stress echocardiography unmasks early left ventricular dysfunction in asymptomatic patients with uncomplicated type 2 diabetes: A comprehensive two-dimensional speckle-tracking imaging study. J Am Soc Echocardiogr. 2018; 31(5):587-97. https://doi.org/10.1016/j.echo.2017.12.006 PMid:29526563