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Correlation between Transient Ischemic Left Ventricular Dilation and Severity of Coronary Artery Disease

Authors
Wala Abdelaziz Farid (MD)[1], Ahmed Abdelaziz Emara (MD) [2],
Mie Mohammed Abdalraouf (MD) [3], Mohamed Abd Al-Magid Mahmod, (MSc)[4]
[1,2,3]Department Of Cardiology, Menoufia University, Egypt
[4]Department Of Cardiology, Alexandria Police Hospital
Corresponding Author
Abd Al-Magid Mahmod
Address: Tantal - Gharbia, Egypt
Tel: 01003907167, Email: *gedo19812017@gmail.com*
Wala Abdelaziz Farid (MD)
Address: Tanta- Gharbia, Egypt
Tel: 01067840607, Email: *drwmosa@yahoo.com*

Abstract
Background: *Left ventricular (LV) transient ischemic dilatation (TID) during stress echocardiography is considered a marker of extensive coronary artery disease.*
Objectives: *To assess the relationship between (TID) ratio assessed by DSE and severity of CAD assessed by coronary angiography.*
Methods: *This study included 100 patients referred to stress echocardiography laboratory. All patients were subjected to detailed history, full cardiac examination, dobutamine stress echocardiography; The TID ratio was defined as the ratio of LV end-diastolic volume or end-systolic volume at post-stress to rest. MAPSE, was measured in (mm) by M. mode echocardiography from four different annuli in apical 4- and apical 2-chamber views . (Group I) (20) patients with normal findings, (group II) comprised (40) patients with abnormal ischemic stress echocardiography. These patients findings were further divided into two subgroups: Group (IIA): 40 patients with abnormal ischemic DSE without TID of the LV. Group (IIB): (40) patients with abnormal ischemic DSE with TID of the LV.*
Results: *A significant difference between group (IIA) and group (IIB) regarding ESV stress (P= 0.048) , EDV stress (P= 0.002). A highly significant difference between group (IIA) and group (IIB) regarding both the ESV ratio (P<0.001) and the EDV ratio (P<0.001). Also EDV ratio was statistically significant in group (IIB) regarding MAPSE at rest (P= 0.010) and stress (P=0.003). Also ESV ratio was statistically significant in group (IIB) regarding MAPSE at rest (P= 0.014) and stress (P=0.007).*
Conclusion: *Patients with TID have more sever and extensive ischemic defects and higher peak WMSI.*
Keywords: *Dobutamine stress echocardiography (DSE), Transient ischemic Dilation (TID), Mitral Annular Plane Systolic Excursion (MAPSE), Coronary artery disease (CAD).*

Introduction

Stress echocardiography is an established technique for the assessment of extent and severity of coronary artery disease.[1] The combination of echocardiography with a pharmacological stress allows detecting myocardial ischemia with an excellent accuracy.[2] A transient worsening of regional function during stress is the hallmark of inducible ischemia.[3] Stress echocardiography provides similar diagnostic and prognostic accuracy as radionuclide stress perfusion imaging or magnetic resonance, but at a substantially lower cost, without environmental impact, and with no biohazards for the patient and the physician.[4]

Dobutamine causes myocardial ischemia through a marked increase in myocardial oxygen demand, resulting from an increase in the heart rate, systolic blood pressure, and contractility .[5] When blood supply is limited, as in the presence of significant coronary stenosis, the increase in myocardial oxygen demand may exceed supply, resulting in sub endocardial ischemia necessary to induce regional dissynergy.[6] Typically, stress-induced myocardial ischemia is identified by regional wall motion abnormalities in the distribution of the affected vessels.[7] Reasonably, more extensive stress-induced wall motion abnormalities may predict a higher probability of underlying multi-vessel coronary artery disease.[8]

Transient ischemic dilatation (TID), loosely defined as the stress- induced apparent increase in the size of the left ventricle visualized by myocardial perfusion scintigraphy, has been shown in numerous studies to correlate with critical multi vessele stenosis and an increased risk of adverse outcomes.[9] TID has been observed in a variety of settings, after exercise as well as after pharmacologic Stress, in planar projection imaging and Single-photon emission computed tomography (SPECT), and in combination with all commercially available single-photon myocardial flow tracers.[10] The mechanism for TID appears to be multifactorial, with sub endocardial ischemia temporary systolic dysfunction[11] and a true increase in the size of the left ventricle having been proposed as explanations for the phenomenon.[12,13]

MAPSE has been proposed as a well-established clinically useful echocardiographic parameter for the assessment of LV longitudinal function and correlates with global systolic function of the LV[14,15]. Previous clinical studies showed that, MAPSE, which reflects the mitral ring displacement at systole, can be used to assess cardiac global longitudinal function and is a sensitive parameter to define slight abnormalities in various patients with cardiovascular diseases at early stage where longitudinal function is affected before other components (which can even be increased in compensation).[16,17]

Aim of the Work

The aim of the current study is to assess the relationship between transient ischemic LV dilation (TID) ratio assessed by Dobutamine stress echocardiography and severity of coronary artery disease assessed by coronary angiography.

Patients and Methods

Population: The present study included 100 patients referred for dobutamine stress echocardiography lab during the period from July 2014 to December 2016 for assessment of chest pain or other symptoms suggestive of coronary artery disease. Our included criteria were Prediction of coronary artery disease in patients unsuitable for exercise stress testing, after coronary angiography to assess functional significance of an equivocal lesion, risk stratification of patients with known coronary artery disease, or to assess adequacy of revascularization in those with previous PCI or CABG. we excluded patients with Poor echogenic window, myocardial infarction or unstable angina in the preceding 4 weeks, known relevant left main stem stenosis, significant dysrhythmia (e.g. significant ventricular arrhythmias, paroxysmal supraventricular tachycardia, uncontrolled atrial fibrillation), uncontrolled systemic hypertension.

NYHA Functional class III & IV heart failure, congenital heart disease, valvular heart disease more than mild, acute peri-/myocarditis, endocarditis and hypertrophic obstructive cardiomyopathy. Before inclusion, informed consent was obtained from each patient and the study protocol was reviewed and approved by our local institutional human research committee.

Methods

All patients in this study were subjected to detailed history, full cardiac examination, complete two-dimensional echocardiography examination, dobutamine stress echocardio-graphy; regional wall motion was visually assessed considering both endocardial motion and systolic wall thickening. A score is assigned to each segment at baseline, with each stage of stress, during recovery, LV volumes were evaluated according to modified simpson s rule, for this purpose apical 4- and 2- chamber views were obtained in all patients and LV end-diastolic volume (EDV) and LV end-systolic volume (ESV) were analyzed offline at rest and post-stress by two skilled and independent operators who were unaware of other study data. The TID ratio was defined as the ratio of LV end-diastolic volume (EDV) or end-systolic volume at post-stress to rest. MAPSE ,Displacement of the mitral annulus was measured in millimeters (mm) by M.mode echocardiography from four different points (septal, lateral, inferior and anterior mitral annuli) in apical 4- and apical 2-chamber views .Analysis was performed for the average of MAPSE measured at the four annular sites during rest and at peak stress. Then patients underwent coronary angiography. Significant coronary stenosis was defined by luminal diameter narrowing of greater than or equal to 70% in either a main epicardial artery or a major branch.

Dobutamine stress echocardiography protocol: Dobutamine was administered intravenously by an infusion pump at a starting dosage of 5µg/kg per min. At 3-minute intervals, the dosage is increased to 10, 20, 30, and 40 µg/kg per min until a predetermined endpoint is reached. If neither target heart rate nor any of the other endpoints is reached, the infusion rate may be increased to 50µg/kg per min, or atropine is administered intravenously. A dose of 0.25 to 0.5 mg of atropine is repeated at 1-minute intervals to a maximal dose of 2 mg or until an endpoint is reached; dobutamine infusion is continued during atropine administration. Atropine has been used in numerous studies and can be administered safely in conjunction with the dobutamine test. ECG is monitored continuously and BP is recorded every third minute. Two-dimensional echocardiography is performed and baseline images are obtained at each level with gradual increasing dose of dobutamine and stored on compact disc. Digitalized images (parasternal long-axis and short-axis and apical two-chamber and four-chamber views) are obtained before stress, during administration of dobutamine at low dose and at peak dose and recovery.

Indications for termination were Target heart rate (85% of age-predicted maximal heart rate) is reached, development of new regional wall motion abnormalities > 2 segments, chest pain, ventricular tachycardia or sustained supraventri-cular tachycardia. severe hypertension (systolic blood pressure >220 mm Hg or diastolic blood pressure >110 mm Hg), substantial decrease in systolic blood pressure (a decrease of 20mm Hg from previous level of infusion may be used as a guideline lot terminating the test), Intolerable symptoms[18]

All echocardiograms were interpreted by consensus agreement of two experienced echocardiographers who were blinded to patient treatment and outcome. The LV was divided into 16 segments as recommended by Un- American Society of Echocardiography as follows: basal-, mid-ventricului and apical levels of the septum, lateral, anterior and inferior walls and basal- and mid-ventricular levels of the anteroseptal and posterior walls. Regional wall motion was visually assessed considering both endocardial motion and systolic wall thickening. A score is assigned to each segment at baseline, with each stage of stress, and during recovery. Each segment is scored as follows: 1 = normal; 2 = hypokinesis (reduced wall thickening and excursion); 3 = akinesis (no wall thickening or excursion); 4 = dyskinesis (paradoxical wall motion away from the center of the LV during systole; 5 = scar.

Definitions of response: Normal response to stress: It was defined as normal wall motion at rest (wall motion score index= 1 with increase in wall thickening and excursion during stress. Abnormal (ischemic) response to stress: It was defined as deterioration in LV wall segment thickening and excursion in two contiguous non overlap segments during stress (increase in wall-motion score > 1 grade).

A subgroup of (20) patients (Group I) with normal resting LV function and normal stress echocardiography findings was evaluated to develop normal limits for TID ratio, the abnormal study group (group II) comprised (40) patients with abnormal ischemic stress echocardiography. These patients findings were further divided into two subgroups: Group (IIA): consists of 40 patients with abnormal ischemic dobutamine stress echocardiography without transient ischemic dilatation of the LV. Group (IIB): consists of (40) patients with abnormal ischemic dobutamine stress echocardiography with transient ischemic dilatation of the LV.

Mitral Annular Plane Systolic Excursion: MAPSE ,Displacement of the mitral annulus was measured in millimeters (mm) by M.mode echocardiography from four different points (septal, lateral, inferior and anterior mitral annuli) in apical 4- and apical 2-chamber views .Analysis was performed for the average of MAPSE measured at the four annular sites during rest and at peak stress.

Coronary angiography

All cardiac catheterizations were performed with a standard Judkin’s technique. All angiograms are assessed by consensus agreement of two experienced readers who do not know the clinical history or stress echocardiography findings of the patients. Significant coronary stenosis was defined by a luminal diameter narrowing of greater than or equal to 70% in either a main epicardial artery or a major branch. The procedure was performed within one month after the stress echocardiography study. Patients with previous coronary artery bypass surgery were assessed regarding the patency of the grafts and the non-grafted sizable native vessels.

Statistical analysis [19]

Data were fed to the computer and analyzed using IBM SPSS software package version 20.0. (Armonk, NY: IBM Corp) Qualitative data were described using number and percent. The Kolmogorov-Smirnov test was used to verify the normality of distribution Quantitative data were described using range (minimum and maximum), mean, standard deviation and median. Significance of the obtained results was judged at the 5% level.

Results

A subgroup of (20) patients (Group I) with normal resting LV function and normal stress echocardiography findings was evaluated to develop normal limits for TID ratio, The abnormal study group (group II) comprised (40) patients with abnormal ischemic stress echocardiography. These patients findings were further divided into two subgroups: Group (IIA): consists of 40 patients with abnormal ischemic dobutamine stress echocardiography without transient ischemic dilatation of the LV. Group (IIB): consists of (40) patients with abnormal ischemic dobutamine stress echocardiography with transient ischemic dilatation of the LV.

There was a statistically significant difference between the three groups regarding age (P= 0.027). There was no significant difference between the three studied groups regarding sex (P= 0.229) (Table 1).

There was a highly significant difference between group (I) and group (IIB) regarding both the EDVr ($p < 0.001$) and the ESVr ($p < 0.001$).and a highly significant difference between group (I) and group (IIA) regarding both EDVr (p <0.001) and ESVr (p<0.001). There was a highly significant difference between group (2A) and group (2B) regarding both the EDVr (p < 0.001) and the ESVr (p < 0.001).(Table2)

There was a highly statistically significant difference between group (I) and group (IIA) as regarding the MAPSE at rest (p < 0.001) and stress (p < 0.001) , also there was a highly statistically significant difference between group (I) and group (IIB) as regarding the MAPSE at rest (p < 0.001) and stress (p < 0.001) but there was no significant difference between group (IIA) and group (IIB) as regarding the MAPSE at rest (p =0.460) and stress (p = 0.070).(Table 3)

There was positive correlation between number of coronary vessels affected and ESV ratio in group (IIB) (p value= 0.016) and also a positive correlation between numbers of coronary vessels affected and EDV ratio in group (IIB) (p value = 0.006). It also shows a positive correlation between MAPSE at rest and number of coronary vessels affected in group (IIB) (p value= 0.005) and also a positive correlation between numbers of coronary vessels affected and MAPSE at stress in group (IIB) (p value = 0.008). (Table 4)

There was positive correlation between EDV ratio and MAPSE at rest in group IIB (p = 0.10) and between EDV ratio and MAPSE at stress in the same group (p= 0.014) and also a positive correlation between ESV ratio and MAPSE at rest in group (IIB) (p= 0.003) and between ESV ratio and MAPSE at stress in group (IIB) (p= 0.007). (Table 5). There was also positive correlation between MAPSE at rest and ejection fraction in group IIB (p= 0.008) and also between MAPSE at stress and ejection fraction (p= 0.010) (Table 6)

The dobutamine stress echocardiography protocol was well-tolerated by all patients with no majorside effects during or after the test. Moreover, no patient reported any clinical events during the period from the stress echocardiography study to the time of coronary angiography.

Table (1): Comparison between the three studied groups according to different parameters

	Group I (n = 20)	Group II		Test of Sig.	p	Post hoc test (LSD or Dunn's multiple comparisons test)		
		Group A (n = 40)	Group B (n = 40)			I vs. II A	I vs. IIB	IIA vs. IIB
Age (years)	49.7 ± 9.8	55.2 ± 5.5	53.3 ± 7.6	F= 3.738*	0.027*	0.007*	0.080	0.240
Gender								
Male	8(40%)	20(50%)	25(62.5%)	χ^2= 2.951	0.229	-	-	-
Female	12(60%)	20(50%)	15(37.5%)					
EDV ratio	0.7 ± 0.2	0.9 ± 0.2	1.2 ± 0.2	F=55.765	<0.001*	<0.001*	<0.001*	<0.001*
<1.2	20(100%)	40(100%)	21(52.5%)	χ^2= 35.185*	<0.001*	-	<0.001*	<0.001*
≥1.2	0(0%)	0(0%)	19(47.5%)					
ESV ratio	0.7(0.4 – 1.2)	1(0.7 – 1.1)	1.3(0.7 – 3.3)	H=63.814	<0.001*	0.007*	<0.001*	<0.001*
<1.2	20(100%)	40(100%)	13(32.5%)	χ^2= 55.479*	<0.001*	-	<0.001*	<0.001*
≥1.2	0(0%)	0(0%)	27(67.5%)					
Rest (mm)	12.04 ± 2.29	8.37 ± 2.28	8.0 ± 2.27	F=23.149*	<0.001*	<0.001*	<0.001*	0.460
Stress (mm)	15.59 ± 3.09	10.42 ± 2.69	9.35 ± 2.23	F=40.091*	<0.001*	<0.001*	<0.001*	0.070

Qualitative data were described using number and percent and was compared using Chi square test or while Normally quantitative data was expressed in mean ± SD and was compared using F test (ANOVA) abnormally distributed data was expressed in median (Min. - Max.) and was compared using Kruskal Wallis test

*:Statistically significant at p ≤ 0.05

Table (2): Correlation between different parameters in each group

	Group II A		Group II B	
	COFF.	p	COFF.	p
CAD vessel vs EDV ratio	0.129	0.429	0.425*	0.006
CAD vessel vs ESV ratio	0.279	0.081	0.380*	0.016
CAD vessel vs MAPSE Rest (mm)	-0.060	0.712	-0.433*	0.005
CAD vessel vs MAPSE Stress (mm)	-0.023	0.888	-0.416*	0.008
MAPSE Rest (mm) vs EDV ratio	-0.140	0.388	-0.346*	0.029*
MAPSE Rest (mm) vs ESV ratio	-0.386*	0.014*	0.087	0.595
MAPSE Stress vs EDV ratio	-0.107	0.511	-0.323*	0.042*
MAPSE Stress vs ESV ratio	-0.355*	0.025*	0.081	0.621
EF vs MAPSE Rest (mm)	0.252	0.117	0.414*	0.008*
EF vs MAPSE Stress (mm)	0.209	0.196	0.405*	0.010*

COFF: Pearson coefficient or Spearman coefficient
*: Statistically significant at $p \leq 0.05$

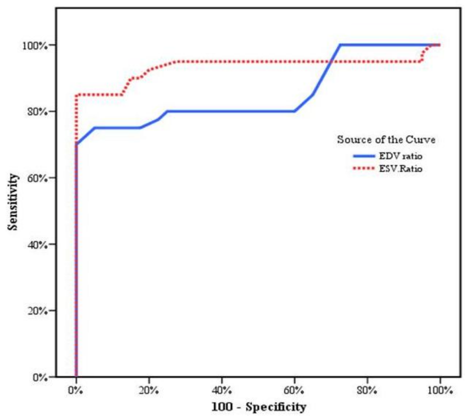

Figure (1): Receiver-operating-characteristic curve.(ROC curve)

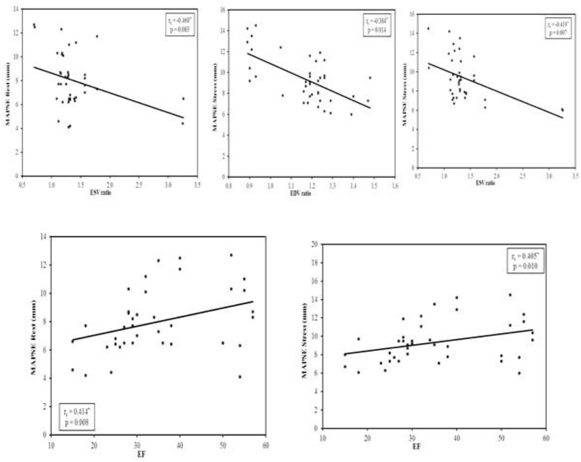

Figure (2): Correlation between no. of CAD vessels affected and EDV ratio in each group. Correlation between no. of CAD vessels affected and ESV ratio in each group. Correlation between no. of CAD vessels affected and MAPSE Rest (mm) in each group. Correlation between no. of CAD vessels affected and MAPSE Stress (mm) in each group

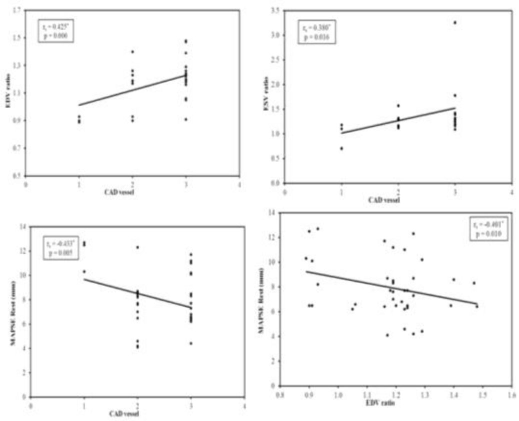

Figure (3): Correlation between MAPSE Rest (mm) and EDV ratio in each group. Correlation between MAPSE Rest (mm) and ESV ratio in each group. Correlation between MAPSE Stress (mm) and EDV ratio in each group. Correlation between MAPSE Stress (mm) and ESV ratio in each group. Correlation between EF and MAPSE Rest (mm) in Group IIB. Correlation between EF and MAPSE Stress (mm) in Group IIB

Discussion

Stress echocardiography (SE) is widely used in clinical settings and plays an important role in defining the diagnosis, risk stratification, and prognosis for patients with known or suspected severe coronary artery disease. During both exercise and pharmacologic stress, the normal response of the LV is a reduction in both diastolic and systolic volumes. This response is due to many factors including enhanced contractility and stroke volume, reduced preload either due to direct drug effect (for pharmacologic stress) or reduced filling time with increasing heart rate and altered afterload with dobutamine. With experimentally induced acute ischemia due to coronary ligation, an increase in LV volume can be observed at rest. However, with stress-induced ischemia, the enhanced contractility of non-ischemic segments and reduced diastolic filling time may counteract the regional dilation. When the extent of ischemia reaches a certain threshold, however, the resultant systolic dysfunction and the regional geometric distortion induced by regional ischemia result in cavity enlargement.[20]

Left ventricular (LV) transient ischemic dilatation (TID) during stress echocardiography is considered a marker of extensive coronary artery disease and a predictor of future cardiac events. TID has been noted on SE as a marker of extensive angiographic coronary artery disease (CAD) and worse prognosis. However, it is not clear which phase of TID, end diastolic or end systolic, should be used for quantification of TID. While TID during SE has been associated with extensive angiographic CAD, it is not clear how it relates to inducible myocardial ischemia on SE.[21]

MAPSE has been proposed as a well-established clinically useful echocardiographic parameter for the assessment of LV longitudinal function and correlates with global systolic function of the LV.Previous clinical studies showed that, MAPSE, which reflects the mitral ring displacement at systole, can be used to assess cardiac global longitudinal function and is a sensitive parameter to define slight abnormalities in various patients with cardiovascular diseases at early stage where longitudinal function is affected before other components (which can even be increased in compensation).[22]

Our results demonstrated that patients with TID have more sever and extensive ischemic defects and higher peak WMSI and presence of TID with abnormal ischemic stress echocardiography are a sensitive marker of multi vessel CAD. Thus, the presence of TID post-stress indicates high-risk of sever CAD. Also, patients with abnormal dobutamine stress echocardiography had higher mean WMSI, mean ESV rest and stress) mean EDV (rest and stress). And also the higher number of coronary vessels affected than those with normal stress echocardiography or abnormal ischemic stress echocardiography without TID. We found that the ESV appeared to be more important than the EDV but that both values are important. According to LV volumes measured in patients with normal resting LV function and normal stress echocardiography, the best threshold for TID ratio abnormality was TID ratio greater than 1.12

We demonstrated also that change in the mean ESVr (1.38 in ischemic patients with TID compared with 0.71 in non-ischemic patients) was much greater than the changes observed in the EDVr (1.17 in ischemic patients with TID compared with 0.72 in non-ischemic patients). Also, Female patients showed almost equal mean TID indices than male patients for both EDVr (1.13 ± 0.15 vs. 1.19 ± 0.16) and ESVr (1.34 ± 0.56 vs. 1.41 ± 0.44). Which was not statistically significant ($p = 0.192$ and 0.067 respectively). Patients with TID have reduced MAPSE (mitral annular plan systolic excursion) at rest or stress compared with patients with normal stress echocardiography or abnormal ischemic stress echocardiography without TID

For detection of sever and extensive CAD (defined by luminal diameter narrowing of greater than or equal to 70% in either a main epicardial artery or a major branch) , the ESVr demonstrated a sensitivity of 85%, a specificity of 100 % , a positive predictive value of 100% and negative predictive value of 87%, while the EDVr demonstrated a sensitivity of 75%, a specificity of 95 % , a positive predictive value of 93.7% and negative predictive value of 79.2% .

Data from stress echocardiography, new ischemic wall motion abnormalities, TID and MAPSE should be used together to identify high risk patients requiring catheterization and consideration of coronary revascularization.

Limitations of the study

Patients were heterogeneous and multiple variables were present so, insufficient degree of freedom giving the study less power statistically. The type of exercise stress (treadmill, upright bike, or supine bike) or pharmacologic agent (dobutamine or vasodilator agent) may influence LV volume differently because of their different effects on loading conditions. The primary cohort of 80 patients with an abnormal ischemic stress echocardiogram study were all referred for diagnostic stress echocardiography. This referral bias likely contributed to high incidence of multi vessel disease among the entire abnormal study cohort. WMA during dobutamine stress echocardiography is dependent on subjective qualitative interpretation of visual information, a process which has been shown to be extremely sensitive to the experience of the echo reader. So, there may be considerable differences in the interpretation of the test. TID requires good view and proper placing of the cursor without excessive angulations. Also interpretation of TID remains subjective, although the analysis was performed by a consensus of two experienced echo-cardiographers .Not all patients can benefit from this test due to patient poor echogenicity and lack of experienced personnel in all echocardiographic labs. In addition to the side effect of dobutamine as: chest pain, palpitation, headache, light headness, nausea, breathlessness, hypertension, hypotension and paradoxical bradycardia (mediated by Bezoldjarisch reflex). Assessment of many variables is time consuming, during assessment of LV dimensions at rest and post-stress, TID parameters and MAPSE then calculating differences and means. After cardiac surgery, septal MAPSE, together with RV function, might be more reduced compared with lateral MAPSE. Sometimes in patients with mitral valve disease, the mitral ring is extremely calcified. In these patients, the direct MAPSE measurement at the mitral ring is not possible and longitudinal functional assessment should be done slightly more above in the myocardium. Another limitation of this parameter is that small localized abnormalities (i.e. small areas of fibrosis) cannot be detected as it is only possible to assess longitudinal function of the complete wall.

Conclusions

We concluded that the presence of TID during stress echocardiography is a sensitive and specific marker of multi vessel CAD. Patients with TID have higher peak WMSI and reduced MAPSE (mitral annular plan systolic excursion) at rest or stress compared with patients with normal or abnormal ischemic stress echocardiography without TID.

Recommendations

Assessment of transient ischemic dilation of the LV in patients undergoing dobutamine stress echocardiography can be used as decision making test for management of patients with coronary artery disease. It may be recommended to use this parameter to identify patients with severe and extensive CAD who will benefit most from cardiac catheterization and potential for coronary revascularization. Large prospective studies need to be conducted to document this result or nullify it.

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