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Evaluation of patients with myocardial infarction undergoing percutaneous coronary intervention (PCI) using low dose dobutamine stress echocardiography

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ABSTRACT

Coronary artery disease (CAD) is a spectrum of heart diseases which has the highest mortality in the world. Systolic left ventricular (LV) function is an important predictor of outcome, and its precise assessment remains of great importance for the choice of treatment in populations with myocardial infarction (MI). This study was aimed to assess the function and viability of ischemic myocardium of LV before and after the percutaneous coronary intervention (PCI) by using 2dimentional (2D) STE with LDDSE and to know the usefulness of low dose dobutamine (LDD) test in detecting the viable ischemic LV area. STE with LDDSE was performed in 30 Iraqi patients (mean age 39-74 years, mean ejection fraction 45.8±7.96%) with previous MI (ischemia before more than 30 days ago) who were referred to Ibn Al-Bitar Specialized Center for Cardiac Surgery in Iraq-Baghdad for evaluation of LV myocardial function and viability and possible need for coronary angiography. There was significant change (improvement) in the GLS and EF after 3-6 months of doing PCI of the viable ischemic LV area in comparison to its value at rest (P-value < 0.001). Left anterior descending artery (LAD) is the most common affected artery in our study. The study concluded that GLS provides a sensitive measure of LV function and appears reduced despite preserved LVEF also GLS can detect the viability of ischemic myocardium of LV with using LDD test which then assessed by PCI.

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INTRODUCTION

Coronary artery disease (CAD) is a spectrum of heart disease which has the highest mortality in the world. Systolic LV function is an important predictor of outcome, and its precise assessment remains of great importance for the choice of treatment in populations with MI (Steg *et al.,* 2012).

Echocardiography remains the most commonly used comprehensive cardiac imaging modality and is often the first test of choice for assessing cardiac structure and function (Shokr *et al.,* 2016). Speckle tracking echocardiography (STE) is a new noninvasive ultrasound imaging technique that allows for an objective and quantitative evaluation of global and regional myocardial function independently from the angle of insonation and from cardiac translational movements. Recently, speckle-tracking analysis with automated function imaging (AFI) has been introduced as a new echocardiographic technique to assess global LV longitudinal strain. Importantly, speckle-tracking analysis derived strain has been associated with the extent of viable myocardial tissue in patients with

chronic ischemic heart disease. Angle dependency is not a problem with 2 D STE, but this technique is dependent on image quality and operates at a limited frame rate (Biering-Sørensen *et al.,* 2017). Global longitudinal strain (GLS) assessed by 2D STE, has emerged as a new method for assessing LV function. GLS is altered despite preserved LV function as assessed by EF in conditions predisposing to cardiovascular disease, including increasing age, hypertension, diabetes mellitus, stable angina, renal dysfunction, and obesity. GLS, as an early marker of cardiac dysfunction, may, therefore, identify people in the general population at particularly high risk of cardiovascular morbidity and mortality (Lang *et al.,* 2016).

Dobutamine is a synthetic catecholamine (resulting from the modification of the chemical structure of isoproterenol) that causes both inotropic and chronotropic effects through its affinity for β1, β2, and α receptors in the myocardium and vasculature. Because of differences in affinity, the cardiovascular effects of dobutamine are dose-dependent that has predominant inotropic (increase contractility) effects when used at lower doses (less than 10 μg/kg/min) via its effect on β1-adrenergic receptors in the heart followed by a progressive chronotropic response at increasing doses. Dobutamine also has effects on β2-adrenergic and α1-adrenergic receptors, leading to a balanced effect on the peripheral vasculature at lower doses (Gong *et al.,* 2013). STE performed with LDD showed many advantages and appeared to be an effective method for the detection of viable myocardium. So, this study was aimed to assess the function and viability of ischemic myocardium of LV before and after the percutaneous coronary intervention (PCI) by using 2dimentional (2D) STE with LDDSE and to know the usefulness of low dose dobutamine (LDD) test in detecting the viable ischemic LV area.

PATIENTS AND METHODS

Thirty patients (mean age 39-74 years; 28 were men; mean ejection fraction (EF) 45.8±7.96%) with old MI (ischemia before more than 30 days ago) and regional wall motion abnormality with or without LF dysfunction who were referred to Ibn Al-Bitar Specialized Center for Cardiac Surgery in Iraq-Baghdad were included in a prospective cohort study between October 2016 to June 2018 and consent form were taken from each subject.

Echocardiography: Baseline Two-dimensional (2D) echocardiographic examination was performed before dobutamine infusion in all patients by using a GE (Vivid E9) ultrasound machine equipped with the 2.5 MHz S5-1 transducer including standard 2D apical four- and two-chamber view (4C, 2C). LV ejection fraction (EF) was computed using the Simpson biplane method from 2C and 4C apical views.

$$LVEF = ((LVEDV - LVESV)/LVEDV) * 100\% \quad (2)$$

Speckle tracking echocardiography (STE) based Strain analysis

Beta-blockers, calcium antagonists and nitrates were discontinued in patients at least 48 hours before STE was performed. All the patients were examined in the left lateral decubitus position. Three standard apical (5-chamber, 4-chamber, and 2-chamber) views were acquired. Gray-scale images were obtained at a frame rate of 60–70 frames/s using harmonic (1/3 MHz) B-mode imaging. For each view, 3 consecutive cardiac cycles were acquired. The LV was analyzed using standard 17-segment model according to the standards of the American Heart Association (AHA) (Hutyra *et al.,* 2013; Armstrong and Ryan, 2109).

The LV in each apical image is divided into 6 segments: the septal, lateral, anterior, posterior, anteroseptal and inferior wall. Each myocardial wall was divided into a basal, mid-ventricular and apical segment. Automated function image (AFI) algorithm automatically traced 3 concentric lines on the endocardial border, mid-myocardial layer, and epicardial border, and followed the endocardium from this single frame throughout the cardiac cycle. If automated tracking would be inappropriate, we could manually adjust the region of interest (ROI). Then, the AFI algorithm tracks the percent of wall lengthening and shortening in a set of 3 longitudinal 2D-image planes. The peak systolic longitudinal strain for each segment is displayed based on a 17-segment model for each plane, and the results of all 3 planes were combined in a single bull's-eye summary. The closure of the aortic valve was marked, and the AFI software measured the time interval between the R-wave and aortic valve closure, which was used as a reference for the other view loops. The analysis of the deformation parameters was performed with the aid of a commercially available speckle tracking system in a GE machine. Subsequent calculation of peak systolic longitudinal strain (LV GLS) was software generated in a 17 segments model from the three apical views. Longitudinal strain (percentage) is defined as the physiological change in length of the region of interest from end-diastole to end-systole. During this period, strain in the longitudinal direction is a negative value as the length of the region of interest decreases. Longitudinal strain can be calculated using the following formula: longitudinal strain (%) [L(end-systole) L(end-diastole)]/L(end-diastole)100%; where L is the length of the region of interest (Picano, 2015).

Global longitudinal strain 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.

Speckle tracking echocardiography (STE) associated with Low Dose Dobutamine Stress Echocardiography (LDDSE)

After STE at baseline, Patient is prepared for standard stress testing, Intravenous access is obtained, and LDDSE was performed. Low dose dobutamine (LDD) ((No.1 Biochemical Pharmaceutical Co., Ltd. Shanghai, China) infusion was administered using an automated infusion pump (TE331, Terumo, Japan). Dobutamine was delivered intravenously using 3 minutes staged protocol starting from 5 μg /kg/min for three minutes, then 10 μg /kg/min for another three minutes, then 3 minutes' recovery without dobutamine. Images were acquired from apical five, four & two chamber views, with superimposition of speckle tracking data at the 2D images (Biering-Sørensen *et al.,* 2017). The recorded 2D image loops were digitally stored at rest, at 5 μg/kg/min and at 10 μg/kg/min low dose dobutamine (LDD) echocardiography for analysis.

Patients were continuously monitored by ECG and blood pressure (by cuff method) measurement during the LDD test. Dobutamine infusion was intended to be terminated if one of the following indications had occurred;

- Severe chest pain or intolerable side effects.
- 85% of age-related maximum predicted heart rate.
- ST-segment elevation >1 mm in leads without a Q wave
- Horizontal ST-segment depression > 2 mm in any lead.
- Significant ventricular or supraventricular arrhythmias.
- Uncontrolled systemic hypertension≥ 180/110 mmHg or Hypotension (8).

Myocardial response to Dobutamine

All stress echocardiographic diagnoses can be easily summarized in four equations centered on regional wall function and describing the fundamental response patterns: normal, ischemic, viable, and necrotic.

The corresponding stress echocardiography patterns are displayed as follow;

- The normal response, a segment is normokinetic at rest and normal or hyperkinetic during stress.
- In the ischemic response, the function of a segment worsens during stress from normokinesis to dyssynergy.
- In a viable response, a segment with resting dysfunction improves during stress.
- In the necrotic response, a segment with resting dysfunction remains fixed during stress.

Resting akinesia that becomes dyskinesia during stress reflects a purely passive, mechanical phenomenon of increased intraventricular pressure developed by normally contracting walls and should not be considered new active ischemia. It is conceptually similar to the increase in ST-segment elevation during exercise in patients with resting Q waves (Camm *et al.,* 2009).

Revascularization and Follow-Up

The indication for coronary angiography in the study subjects was determined by the clinical judgment of the referring providers including all the patients with abnormal DSE with viable myocardium. The detailed for coronary artery anatomy, including the location and the severity of stenosis were derived from our cardiac catheterization laboratory database in Ibn-Albitar Cardiac Center. All patients underwent coronary diagnostic angiography and subsequent revascularization after the dobutamine stress test. Significant coronary artery disease was defined as >70 % luminal diameter stenosis in at least one of the major coronary arteries (Shokr *et al.,* 2016). Follow-up 2D echocardiography was performed (3-6) months after revascularization. Segments with resting dysfunction that were adequately revascularized we deemed viable if the regional function had improved on a side-by-side comparison with pre-PCI results.

RESULTS

The General characteristics of the study groups

Table (1) showed baseline characteristics of 30 patients illustrating the mean age and gender also the number of patients presented with the risk factors including hypertension, diabetes mellitus, hypercholesterolemia, and smoking.

Table (2) showed the comparison between GLS before PCI of the patients in the study group according to LVEF by Simpson's method. We noticed that 5 (16.7%) patients with normal EF by Simpson's method but had abnormal GLS (-14.0±5.52).

Assessment of LV function and viability by using 2 D STE with LDD

GLS was measured before and after 5 μg/kg/min dobutamine as shown in table (3). We noticed that there was a significant decrease in GLS (increase contractility) before dobutamine from (-10.49±3.4) to (-12.87±3.44) after dobutamine.

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Table 1: Baseline characteristics of the study group

Variable		Value
Age (years)	Mean ± SD	53.97±9.31
	Range	39-74
Gender	Male	28 (93.3%)
	Female	2 (6.7%)
Hypertension	Present	22 (73.0%)
	Not present	8 (27.0%)
Diabetes	Present	12 (40.0%)
mellitus	Not present	18 (60.0%)
Hypercholesterolemia	Present	22 (73%)
	Not present	8 (27%)
Smoker	Present	18 (60%)
	Not present	12 (40%)

Table 2: Comparison of GLS at rest in patients according to left ventricular function by ejection fraction by ANOVA

Parameter	Normal LV function N=5	Mild LV dysfunction N=15	Moderate LV dysfunction N=10	P value
GLS at rest	-14.0±5.52	-10.47±2.85	-8.9±1.97	0.023∗

All parametric data expressed in the mean and standard deviation (SD); ∗ P value less than or equal to 0.05 was considered as statistically significant; LV= left ventricle; GLS= global longitudinal strain

Table 3: All parametric data expressed in the mean and standard deviation (SD)

Parameter	Before 5 μg/kg/min dobutamine (at rest)	After 5 μg/kg/min dobutamine	P value
GLS	-10.49±3.4	-12.87±3.44	<0.001∗

All parametric data expressed in the mean and standard deviation (SD); ∗P value less than or equal to 0.05 was considered as statistically significant; GLS= global longitudinal strain (%)

Table 4: Comparison between patients in the study group after giving 5 μg/kg/min and after 10 μg/kg/min dobutamine

parameter	After 5 μg/kg/min dobutamine	After 10 μg/kg/min dobutamine	P value
GLS	-12.87±3.44	-11.56±3.29	<0.001∗

All parametric data expressed in the mean and standard deviation (SD); ∗ P value less than or equal to 0.05 was considered as statistically significant; GLS= global longitudinal strain (%)

Table 5: Comparison between patients in the study group assessed by 5 μg/kg/min dobutamine and after PCI

Parameter	After 5 μg/kg/min dobutamine	After PCI	P value
GLS	-12.87±3.44	-13.48±3.7	0.081

All parametric data expressed in the mean and standard deviation (SD); GLS= global longitudinal strain (%)

Table 6: Comparison between patients in the study group before and 3-6 months after PCI using different modes of echocardiography among the study group

Parameters	Before PCI	After PCI	P value
GLS	-10.49±3.4	-13.48±3.71	<0.001∗
EF%	45.8±7.96	54.7±7.2	<0.001∗

All parametric data expressed in the mean and standard deviation (SD); ∗ P value less than or equal to 0.05 was considered as statistically significant; GLS= global longitudinal strain; EF=ejection fraction

Table (4) revealed that there was a significant increase in GLS (decrease contractility) from (-12.87±3.44) after giving 5 μg/kg/min dobutamine to (-11.56±3.29) after giving 10 μg/kg/min dobutamine (P value < 0.001).

Regarding table (5) which showed that there were no significant differences in GLS after low dose dobutamine (-12.87±3.44) with the same parameters 3-6 months after PCI (-13.48±3.7) respectively.

Table (6) showed significant changes in GLS and EF before and 3-6 months after PCI (P-value <0.001).

Table 7: Percentage of patients in the study group treated with Percutaneous Coronary Intervention (PCI)

Stenosed artery	Frequency	Percent
LAD	20	66.7
RCA	5	16.7
LCx	2	6.6
LAD + LCx	3	10
Total	30	100

LAD= left anterior descending artery; LCx= left circumflex artery; RCA= right coronary artery

Table (7) revealed the percentage of patients in the study group treated with PCI. Among the patients with significant coronary stenosis, the 1-vessel disease was present in 27(90%) patients while the 2-vessel disease was present in 3(10%) patients. The percentage of patients with critically diseased LAD is (66.7%).

DISCUSSION

The mean age of the study population was 53.97±9.31 years, and most of them were men. Seventy-three percent of the patients had hypertension, and about 40% are diabetics. Seventy-three percent have their total cholesterol >250 mg /dl, and 60% was a smoker. These findings were expected in those ischemic heart disease patients as the mentioned risk factor is common in these selected patients (Li *et al.,* 2016). Revascularization has become an important therapeutic strategy for patients with old MI. However, the prognosis is dependent on the ratio of VM. Therefore, preprocedural identification of VM segments of the impaired myocardium is mandatory (Tomasz *et al.,* 2016).

In this study, there were 16.7% of the study group had normal EF by using Simpson's biplane method, but they were included because of their focal LV wall motion abnormality. LVEF is a well-established marker of global LV function related to prognosis after MI (Larsen *et al.,* 2018). But it has some inherent conceptual problems which limit its value as a guide in clinical decision-making, due to its dependence not only on contractility but also on afterload, preload, heart rate, and synchronicity. However, the use of EF entails limitations, too. It is a global index which does not discriminate between the segmental and diffuse nature of the myocardial dysfunction; it remains insensitive to mild or limited regional myocardial dysfunctions (Camm *et al.,* 2009). The long axis parameter, LV GLS, is a comprehensive parameter of LV systolic function, which has proved valuable in detecting subtle myocardial dysfunction in patients with normal LVEF. This characteristic is conceivably related to the longitudinal orientation of the subendocardial muscle fibres and their sensitivity to ischemic damage, edema, and fibrosis (Ternacle *et al.,* 2013). The accuracy and reproducibility of GLS measurements, regardless of image quality, may be explained by the use of the whole stack of images for 2D speckle tracking analysis and by the fact that endocardium–blood interface is less crucial for longitudinal strain analysis. In addition, GLS computed from the 16 or 17 segments of the myocardium may provide a more global and accurate assessment of myocardial function than the Simpson biplane model, which only includes 12 segments (Joyce *et al.,* 2015).

From our results we noticed that there were significant increases in global and regional functions of ischemic myocardium as assessed by GLS after giving a baseline dose of dobutamine (5 μg/kg/min), then a significant relative decrease in LV functions (as assessed by above mentioned parameter) after giving a second dose of dobutamine (10μg/kg/min) (biphasic response: increased contractility in resting dysfunctional myocardium at low dose but deterioration of contractility at peak doses as demand/supply mismatch leads to ischemia and it is the most specific finding for viability), these results were considered as an indicator of viable ischemic myocardial segments because dobutamine is an adrenoreceptor agonist, and a low dose can improve systolic myocardial function by enhancing coronary blood flow and these results are in agreement with Joyce *et al.,* 2015 who found that the hallmark of viability assessment with DSE is the identification of contractile reserve, defined as resting myocardial dysfunction that recruits in response to inotropic stimulation with dobutamine (Bansal *et al.,* 2010). Also, Lang et al.; 2016 stated that myocardium that is dysfunctional at rest but improves in response to low-dose dobutamine (less than 20 μg/kg/min) is considered to be viable (Gong *et al.,* 2013). Similarly, Bansal *et al.,* 2010 concluded that the combination of STE methods with dobutamine echocardiography could predict viability (Allman *et al.,* 2002).

And by comparing the results of GLS after giving LDD with that after doing PCI, it was noticed that there were no significant differences in values, this means that dobutamine test is a valuable indicator test for viability. This is similar to the conclusion of Allman *et al.,* 2002 who demonstrates a strong association between myocardial viability on noninvasive testing and improved survival after revascularization in patients with chronic CAD and LV dysfunction (Allman *et al.,* 2002).

Then we followed up those groups by 2D and STE within 3-6 months after PCI, this time limit was

used to avoid as possible, the effect of the DES-ISR (drug-eluting stent-in stent restenosis) (the most probable to occur), (Restenosis was defined by quantitative coronary angiography as the recurrence of 50% diameter narrowing in a coronary segment that had previously been dilated), and giving the time for enabling the detection of those segments of viable myocardium that recovered slowly. This time limit was also used by Pleva *et al.,* 2018 who stated that the presence of DES-ISR could appear from 6–9 months after the PCI intervention (Pleva *et al.,* 2018).

Regarding the angiographic results of the patients in the subjects group, we noticed that all of them had ≥70% coronary stenosis and among them, there was significant LAD stenosis in most of the patients. So we found that LAD was the most common artery with critical lesions followed by RCA and LCX, this finding can be explained possibly by a hemodynamic milieu that could be involved in the genesis of atherosclerosis also we found that the proximal LAD segment susceptibility to atherosclerosis can be attributed to the milking effect of septal perforators. Also, systolic compression of the septal intramural branch segment can lead to disturbed flow in the adjacent LAD segment at the side of the septal origin. This result was similar to Wasilewski *et al.,* 2015 who found that the predominant location of coronary artery atherosclerosis in the left anterior descending (LAD) artery (Wasilewski *et al.,* 2018).

CONCLUSION

The study concluded that GLS provides a sensitive measure of LV function and appears reduced despite preserved LVEF also GLS can detect the viability of ischemic myocardium of LV with using LDD test which then assessed by PCI.

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