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Speckle tracking during dobutamine stress echocardiogram in treadmill test positive patients with normal coronary angiogram

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Abstract
Strain Rate Imaging During Dobutamine Stress Echo is A Novel Concept to Study Coronary Artery Disease.
Objective: The Aim of the study was to compare the results of the Regional Wall Motion Abnormality assessed in DSE+STE with the ST-T changes in TMT. The study also uses the 17-segment model of the myocardium and compares DSE with DSE+STE to see if the later provides better accuracy over the former in assessing regional wall motion abnormality (RWMA) in the segments.
Methods: The current study has been undertaken in 25 patients with a positive Treadmill Test (TMT) test and a normal coronary angiogram (CAG) to look for any signs of myocardial ischemia detected on 3D-STE with and without Dobutamine Stress Testing.
Results: The mean trend observed was a decrease in GLS from pre-DSE (18.916) to post-DSE (14.152). In the study we found that GLS was affected by age, younger patients in the study had higher GLS as compared to the older patients20 of the 25 patients studied had reduced GLS as well as segmental strain. In 5 patients the GLS increased at peak HR than the base lineThe study demonstrates the presence of significant Myocardial Ischemia in number of patients with a positive TMT and a normal coronary angiogram with evidence of myocardial ischemia on DSE when analysed with speckle tracking.
Conclusions: The patients with a decrease in strain and SR on DSE with speckle tracking, potentially have ischemic myocardium despite a normal CAG.

Keywords: CAG, DSE, potentially, patients

Introduction

Exercise electrocardiographic testing is among the most fundamental and widely used tests for the evaluation of patients with cardiovascular disease (CVD). It is easy to administer, perform and interpret. It is flexible and adaptable, reliable, inexpensive, and readily available in hospital and practise settings. It is the first test ordered in a patient with suspected coronary artery disease (CAD).

Timely and prompt detection of coronary artery disease is of paramount importance for patient management in daily clinical practice. Dobutamine stress echocardiography (DSE) is a non-invasive method with established diagnostic accuracy. Still, it remains subjective mainly because of its dependence on operator experience in image acquisition and interpretation [1, 2]. It also allows only limited evaluation of radial displacement and deformation, without the possibility of assessing myocardial shortening and twisting [3, 4].

Echocardiographic strain and strain-rate imaging (deformation imaging) [3, 7]. is a new non-invasive method for assessing myocardial function. Due to its ability to differentiate between active and passive movement of myocardial segments, to quantify intraventricular dys-synchrony and to evaluate components of myocardial function, such as longitudinal myocardial shortening, that are not visually assessable, it allows comprehensive assessment of myocardial function and the spectrum of potential clinical applications is very wide. The high sensitivity of both tissue Doppler imaging (TDI) derived and two-dimensional (2D) speckle tracking derived myocardial deformation (strain and strain rate) data for the early detection of myocardial dysfunction recommend these new non-invasive diagnostic methods for extensive clinical use.

Three-dimensional speckle tracking imaging (3D-STE) technique is a new ultrasonographic method recently developed for non-invasive monitoring of regional and global myocardial function in clinical practice. Compared with the quantitative tissue velocity imaging and two-dimensional speckle tracking imaging, it has great advantages because it is independent of angle and does not ignore the characteristics of three-dimensional cardiac wall motion [8, 11]. 3D-STE has already been used for assessing different myocardial and systemic diseases, where it can predict probable sub-clinical cardiac disorder earlier in the course of the disease process when conventional 2D echocardiography appears to be normal [12, 16]. Speckle tracking derivatives are less susceptible to translational motion and tethering, which lead to erroneous qualitative evaluation of stress echo images.

The current study has been undertaken in 25 patients with a positive Treadmill Test (TMT) test and a normal coronary angiogram (CAG) to look for any signs of myocardial ischemia detected on 3D-STE with and without Dobutamine Stress Testing.

The Aim of the study was to compare the results of the Regional Wall Motion Abnormality assessed in DSE+STE with the ST-T changes in TMT. The study also uses the 17-segment model of the myocardium and compares DSE with

DSE+STE to see if the later provides better accuracy over the former in assessing regional wall motion abnormality (RWMA) in the segments. TMT was performed using the Bruce Protocol.

Materials and Methods

The study was conducted in a tertiary care hospital in a coastal city of Southern India between the months of October 2017 and June 2018. It was cross sectional study sampled by a convenience sampling technique.

The Inclusion criteria to participate in the study were

1. Age ≥18 years.
2. Informed consent (verbal and written consent) prior to DSE.
3. Patients presenting as TMT positive who are willing for CAG. Patients with normal CAG and TMT positive.

The Exclusion criteria considered were

1. Acute coronary syndrome
2. Presence of coronary artery disease.
3. Presence of arrhythmia.
4. Pacemaker implantation,
5. Valvular heart diseases,
6. Congenital heart diseases.
7. Patients with a poor echo window.
8. Previous known case of coronary artery disease who have undergone any intervention in the form of PTCA +stenting or CABG.

All the subjects were examined in the left lateral position, and ECG recorded simultaneously. Images acquired on GE vivid 9 machine and M5S transducer used. Strain quantification was performed by using commercially available software (Echo PAC version 7.0.0, General Electric-Vingmed).

Each patient was assessed for image quality using a four-grade scale based on the adequacy of visualization of LV segments. Image quality was graded as follows -

Good - if 0-1 segments are poorly visualized;

Moderate - if 2-3 segments are poorly visualized;

Poor - if 4-5 segments are poorly visualized;

Insufficient - if > 5 segments are poorly visualized (or) if image quality is significantly compromised due to other factors.

The 2D image was acquired with M5S transducer by one experienced operator. Apical full volume acquisition was obtained in all subjects to visualise the entire LV in a volumetric image within one breath hold. For acquisitions of a full-volume data set, six smaller real-time volumes were acquired from consecutive cardiac cycles and combined to provide a larger pyramidal volume. Care was taken to optimise the temporal and spatial resolution of images by decreasing depth and sector width as much as possible while retaining the entire LV within the pyramidal volume. The frame rate was 65(+/-5) frames per second (FPS). Two-dimensional speckle-tracking analysis was performed by one experienced observer. Each 2D data set was displayed in a 3-plane view:

a. An apical 4- chamber view;
b. Parasternal long axis;
c. Two chamber view

Dobutamine Stress Echocardiography (DSE)

Pharmacologic stress was applied with a graded dobutamine infusion starting from 5 μg/kg/min up to 40 μg/kg/min, with added atropine, if necessary, to achieve the target heart rate of '220-Age'. Echocardiographic images were acquired at peak heart rate or at the onset of angina. The echo was performed as per standard protocols and a DC machine was kept at the bed side of the patient at all times.

Table 1: Gradation of Dobutamine Infusion with Time

0 minutes	5 mic/kg/min	Heart rate	BP
3 minutes	10 mic/kg/min	Heart rate	BP
6 minutes	20 mic/kg/min	Heart rate	BP
9 minutes	30 mic/kg/min	Heart rate	BP
12 minutes	40 mic/kg/min	Heart rate	BP
15 minutes	Inj atropine 0.6 mg	Heart rate	BP

At peak heart rate during the DSE images were acquired and STE was done on the images at baseline heart rate and at the peak heart rate. And both the images were compared.

CAG was done through the radial or femoral approach, selectively cannulating the right and left coronary artery.

TMT in patients was advised according to the discretion of the consultant. 248 patients were found to be TMT positive during the time period, of those patients only 25 patients fulfilled the criteria for inclusion in the study. Rest of the patients had significant CAG findings and appropriate treatment/intervention offered.

Data was tabulated and analysed by simple statistical method like percentage, proportion, mean etc. Microsoft Excel 2016 was used for data entry and analysis.

Results

The Global longitudinal Strain (GLS) was measures in all patients using STE at baseline heart rate and post Dobutamine Stress Testing. The mean trend observed was a decrease in GLS from pre-DSE (18.916) to post-DSE (14.152). Out of 25 patients, 15 were female (60%) and 14 were below the age of 55 years (56%).

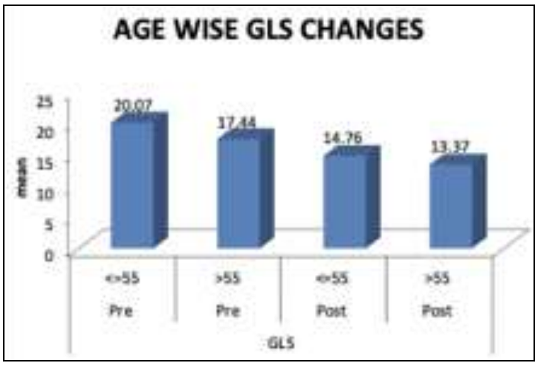

Fig 1: Age and GLS

In the study we found that GLS was affected by age, younger patients in the study had higher GLS as compared to the older patients.

GLS decreased with age in both base line and at peak heart rate. As seen in table no 4. in patients less than 55 years of age the mean GLS is 20.07 at base line which reduced to 14.76 at peak heart rate. In the patients of age more than 55 years, the GLS at baseline was 17.44 which dropped to 13.37 at peak heart rate. GLS decreased at peak heart rate in all the patients except five patients.

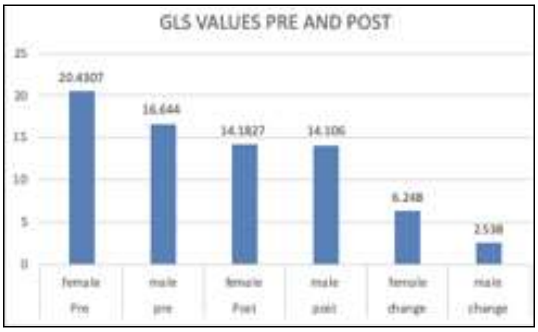

Fig 2: Gender and GLS

GLS was higher in the female group, which at base line is 20.4307 and at peak heart rate it is 14.1827. In males the base line GLS is 16.644 and at peak HR it is 14.106. The drop in GLS in female group is 6.248, which is higher as compared to the male group, which is 2.538, as seen in table number 8.

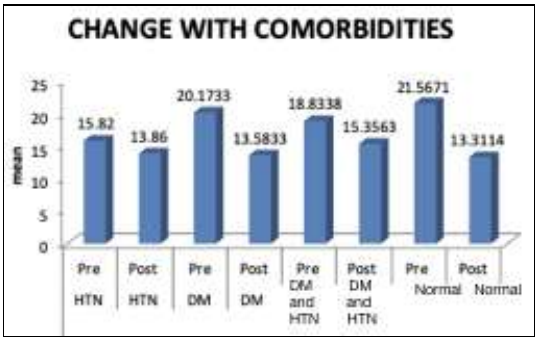

Fig 3: Co-morbidities and GLS. (Hypertension – HTN)

GLS at base line is good in normal patients without any comorbidities as compared to patients with comorbidities. No comorbidities >> Diabetes Mellitus (DM) >> DM + Hypertension >> Hypertension. Patients with Hypertension had the lowest of GLS. The maximum drop in GLS was seen with normal patients who had no comorbidities followed by patients with DM.

One of the patients in the study was having a recanalized left anterior descending artery (LAD), with stunned and viable myocardium. Despite having normal coronary angiogram, her baseline echo showed RWMA to LAD, which improved at peak heart rate, appreciable on DSE. In strain evaluation of the same patient antero-septal, anterior and apical segments were involved, and at peak heart rate, the same territory showed significant improvement. The GLS at baseline was 15.47 and at peak HR it improved to 18.05, suggesting a stunned myocardium. On further evaluation patient was found to have recanalized lad, with TIMI3 flow in the artery.

Out of the 25 patients in the study 5 patients had minor CAD.

Table 2: Details of Lesion Characteristics of 5 subjects with Minor CAD

Lesion characteristics	Number of study subjects	Baseline GLS	Peak heart rate GLS
Lad slow flow	1	14.11	12.41
Mid lad moderate bridging	1	13.11	7.76
Mild lad bridging	1	22.76	13.88
Ramus 50% lesion	1	18.52	11
Mid RCA 50%	1	16.23	16.47

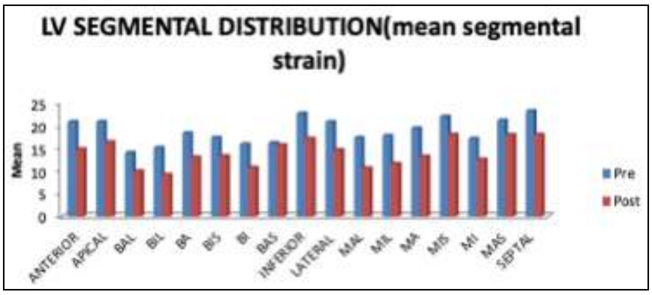

Fig 4: Left ventricular segmental strain values

In this study the anterolateral, inferolateral and the inferior segments are affected the most in both the pre dobutamine and the post dobutamine at peak heart rate. 20 of the 25 patients studied had reduced GLS as well as segmental strain. In 5 patients the GLS increased at peak HR than the base line. The maximal variation is found in basal segments, followed by the mid segments. The apical segments were found to have least variation.

Discussion

The study demonstrates the presence of a significant number of patients with a positive TMT and a normal coronary angiogram with evidence of myocardial ischemia on DSE when analysed with speckle tracking. Such subjects are mostly young females with normal baseline 2D Echocardiogram.

Iwase M *et al.*, [17] performed a study comparing the efficacy of TMT and DSE in detecting CAD. They concluded that DSE was more sensitive, specific and accurate than TMT in detecting CAD at an earlier stage. In our study, we found out that though TMT was positive, baseline DSE was normal in all the patients. Only changes were appreciable on applying strain to the DSE.

A study by Voigt *et al.*, [18] compared DSE with strain rate imaging and concluded that the ratio of peak systolic strain to maximum segmental deformation was the best quantitative parameter to identify stress-induced ischemia. In the present study we were able to appreciate change only on applying Strain rate Imaging (SRI) to DSE both at baseline and at peak Heart rate. Thus, this study agrees with the above study in appreciating the superior results of DSE +SRI over DSE alone.

Another study done by Amundsen *et al.*, [19] concluded that STE provides accurate and angle-independent measurements of LV dimensions and strains. Egle Rumbinaite *et al.*, [20] in 2015, observed that during DSE, the longitudinal and circumferential strain increased from rest to low dose dobutamine only in patients without evidence of myocardial ischemia as determined through Adenosine MRI. Hence, they concluded that Longitudinal strain and strain rate (SR) are important in distinguishing healthy from ischemic myocardium.

Hence it may be extrapolated to our study to imply that the patients with a decrease in strain and SR on DSE with speckle tracking, potentially have ischemic myocardium despite a normal CAG.

It is known that longitudinal strain and SR are the most sensitive markers for ischemia [12, 15]. The rationale is explained by sub-endocardial myocardial fibres that are oriented mainly along the stems, and as a result, are affected in the earliest stages of ischemia.

In our study, we found homogeneity among the various segments of the myocardium in every single patient with either decrease or an increase in strain in all the segments. This is in contrast to a study by Karina Wierzbowska-Drabik *et al.*, [21] in which different segments of the myocardium were found to have different directions of change in strain with the change in patients with ischemic myocardium showing reduction in basal and mid ventricular segments with an increase in the apical segments.

The rationale behind patients with a normal CAG, positive TMT and evidence of ischemia on DSE with STE may be explained using a concept first described by Harvey Kemp in 1973, called Microvascular Angina or Coronary microvascular disease (CMVD). Most of the patients in the study had chest pain and were being evaluated for the same. Most patients also had strain positive regional areas rather global changes except for two patients. It may thus be proposed that these patients had microvascular ischemia which was not seen in DSE but was picked up on STE combined with DSE at peak heart rate.

Functional abnormalities involving Nitric Oxide, Acetylcholine and Endothelins along with structural alterations including smooth muscle hypertrophy in the coronary arterioles resulting from conditions like systemic hypertension or HOCM are implicated in the pathophysiology of CMVD [22, 25]

Patients with CMVD have higher endothelium-dependent and endothelium-independent impairment of microvascular function [26]. Coronary flow reserve (CFR), which is the ratio of coronary blood flow (CBF) at maximal dilatation to CBF at rest, is abnormal in patients with microvascular dysfunction. Hypertension, insulin resistance, and hyperlipidaemia are well-known risk factors [27]. While it is proven that fewer women have obstructive CAD than men, many reports have demonstrated a higher prevalence of CMVD in women [28]. In the Women's Ischemia Syndrome Evaluation (WISE) trial, angina was linked to increased mortality at 5 years [29]. In fact, in patients with angiographically documented non-obstructive disease, the risks are the same as patients with significant single-vessel disease. CMVD may be responsible for 'false positive' stress tests in which ischemia is detected but without significant or even 'normal' coronaries visualized by coronary angiography.

More recently CMVD has been linked to the development of heart failure with preserved ejection fraction (HFpEF) [30] and Takotsubo syndrome [31]. Patients with various chronic inflammatory diseases, such as rheumatoid arthritis and systemic lupus erythematosus, also have an increased risk of premature CAD. In such conditions, oxidative stress and inflammation may trigger endothelial dysfunction, and thus altered vasomotion of the microcirculation [32]

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