Objective Evidence of Inducible Ischemia in Patients with Ischaemic Heart Disease by Global Longitudinal Strain During Dobutamine Stress Echocardiography

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ABSTRACT

Background: Operator dependent two-dimensional (2D) echocardiography is a noninvasive test to assess myocardial hypokinesia. Inter observer variability is more as it is subjective. Objective evidence of 2D global longitudinal strain (2D GLS) and strain rate imaging are getting popularity. **Methods:** This cross sectional study was done on 20 patients who came for dobutamine stress echo (DSE) in the department of cardiology of BSMMU, Dhaka from 1st February 2019 to 31st July 2019. 2D GLS was done before and just after DSE. **Results:** DSE findings revealed 6 patients had viable LAD, 9 had viable LCX and 6 had viable RCA, 9 had nonviable LAD, 2 had nonviable LCX and 3 had nonviable RCA territories. Difference in Post-systolic strain rate (SRps) in myocardial segments supplied by LAD at baseline peak stress in patients who had normal and nonviable LAD (-21% to. -23%, p=0.98) and (-6%to – 7%, p= 2.87) which were not significant. At peak exercise there was a trend towards greater SRps in viable territory of LAD in compared with baseline and peak stress (-1% to -16%, P = 0.05) which was significant. SRps in myocardial segments supplied by LCX at baseline and peak stress in patients who have normal and nonviable LCX (-20% to. -21%, p=0.82) and (-5%to – 5%, p=1.18) which had similar result as LAD territory. At peak exercise there was a trend towards greater SRps in viable territory of LCX compared with baseline and peak stress (-12% to -15%, P = 0.06). There was no significant difference in SRps in myocardial segments supplied by RCA at baseline and peak stress in patients who had normal and nonviable RCA (-23% to. -24%, p=1.72) and (-4%to – 5%, p=2.10). At peak exercise there was a trend towards greater SRps in viable territory of RCA compared with baseline and peak stress (-10% to -15%, P = 0.04). **Conclusion:** Results of subjective interpretation of DES has compared with objective evidence 2D GLS on peak stress which has similarity. It was a small study. Future large study is needed to establish these findings.

Keywords: Ischemia, ischemic Heart Disease, Dobutamine Stress Echocardiography.

INTRODUCTION

Echocardiography is a non-invasive method for the assessment of myocardial performance including hypokinesia.[1,2] This technique is highly operator dependent as it is based on two-dimensional visual evaluation of myocardial wall thickening and endocardial border motion. So it is subjective and has considerable inter-observer variability depending on operator experience.[3,4] Small but clinically significant changes in myocardial function are sometimes missed which are below the threshold of visual resolution of the operator.[5] Tissue Doppler Imaging provides a more objective assessment of myocardial contractility but effects of cardiac translational motion and passive pathological tethering may affect the findings.[8] These limitations may be overcome by strain and strain rate echocardiography (SRI) which is the measurement of local myocardial deformation parameters to an applied force. It is determined from the spatial gradient of local myocardial tissue velocities between two points. Strain is calculated from the time integral of strain rate and reflects the magnitude of deformation.[9,10] As these ultrasound modalities are derived from the motion of segments relative to each other, any velocities contributed by tethering or translation are excluded because these would affect both sampled points equally. These parameters are

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potentially more accurate and more specific measure of local myocardial function and may offer an opportunity to improve the detection of regional abnormalities.[10,11] This study was designed to determine the role of strain and strain rate imaging in the detection of dynamic regional wall motion abnormalities in response to stress and to compare with the subjective visual impression results of dobutamine stress echocardiography (DSE).

MATERIALS AND METHODS

Subjects:
The study population was 20 patients undergoing elective PCI or CABG who came for dobutamine stress echocardiography.

Study place:
Department of Cardiology, Bangabandhu Sheikh Mujib Medical University, Dhaka.

Study period: From 1st February 2019 to 31st July 2019 (6 months)

Exclusion criteria:
1. The presence of collateral arteries (to prevent the masking of myocardial ischemia),
2. Moderate to severe valvular heart disease,
3. Atrial fibrillation,
4. Bundle branch block.
A written informed consent was obtained from all participants.

Study protocol:
DSE was done in 20 subjects and global longitudinal strain (GLS) was obtained before and after DSE in all patients, both by an expert investigator blinded to the patients' clinical and angiographic data. And then DSE findings and 2D GLS findings were compared.

Echocardiographic data acquisition was done with E9 ultrasound scanner (GE Vingmed, Horten, Norway) which was used to obtain conventional two-dimensional and colour tissue Doppler images from the standard apical three chamber, four-chamber and two-chamber views in the left lateral decubitus position. Depth and image sector width were set to obtain the highest possible frame rates of 120 f/s. For each view, data was obtained from three consecutive cardiac cycles. Wall motion was manually tracked to maintain the sample area in the mid-wall position of the segment being interrogated throughout the cardiac cycle. This was then integrated over time to derive the mean natural longitudinal strain profile using end-diastole, defined by the onset of the peak R-wave of the ECG trace that is Aortic valve closure point as the reference point. For each myocardial segment, strain rate was calculated from the spatial derivative of myocardial velocity over a defined sample area of 6 mm within the mid-myocardial layer by using new ROI. Data from three consecutive cardiac cycles were averaged to improve the signal-to-noise ratio and used to determine the mean strain rate profile. Myocardial tissue velocity curves from the basal septum were used to define end-systole because aortic valve closure induces a clearly identifiable rapid directional change in the basal septal velocity curve coinciding with the peak negative left ventricular dP/dt.[12] By convention, strain rate and strain are expressed as a negative parameter for shortening and a positive parameter for lengthening. Longitudinal directional changes from the apical window in normal myocardium are characterized by systolic shortening and diastolic lengthening and thus, an increase in the magnitude of systolic shortening would be reflected by more negative strain or strain rate values.

Working definitions:
Strain rate is rate of deformation.
Peak systolic strain rate (SRsys)—greatest shortening during ejection period.
Post-systolic strain rate (SRps)—defined as any shortening that occurs during isovolumetric relaxation.
Post-systolic strain rate index (SRps/sys) = SRps/SRsys
Time to peak systolic strain rate (t-SRsys) was measured as the time from the peak R-wave of the ECG trace to SRsys.
Visual assessment of wall motion score from grey-scale B-mode cine loops was performed by an expert investigator. Myocardial wall segments were scored according to American Society of Echocardiography (ASE) recommendations: normal = 1, hypokinetic = 2, akinetic = 3, and dyskinetic = 4.

Data and statistical analysis:
The comparison between visual impression of DSE and 2D GLS was analyzed by assigning segments in the mid- and basal anterior septum and anterior wall, mid-septum and apex to the left anterior descending artery. The basal and mid-segments of the posterior and the lateral walls were considered to be in the territory of the circumflex artery and the basal and mid-segments of the inferior wall were allocated to the right coronary artery. This approach is in accordance with that adopted by the American Society of Echocardiography.[13]
Data were analyzed using SPSS for Windows 12.0. Mean and standard deviation were used to describe continuous variables. Data were tested for normal distribution. Post-systolic strain index and Post-systolic strain rate index were positively skewed and were therefore log-transformed prior to analysis. Results are shown in natural units. Unpaired t-tests were also used to compare between visual impression of DSE and 2D GLS in same patient. The test results are presented as two-tailed values and if $P < 0.05$ then it is marked as statistically significant.

RESULTS

A total of 22 patients consented to participate in the study. Two patients had inadequate echo windows at baseline and were excluded. Therefore, the study population was composed of 06 women and 14 men with a mean (SD) age of 52 (2.0) years. 17 patients had history of ST-elevation myocardial infarction. Cardiovascular risk factors included diabetes (n=15), hypertension (n=10), hypercholesterolaemia (17), family history (9), current smoker (6), and ex-smoker (7).

Regional wall motion was observed and 2D GLS was obtained 2 times, earlier at baseline and later at peak of DSE. Unpaired t-tests was done comparing myocardial motion in different segments supplied by coronary vessels territory with 2D GLS at rest and peak stress. On DSE, 6 patients had viable LAD, 9 had viable LCX and 6 had viable RCA. 9 had nonviable LAD, 2 had nonviable LCX and 3 had nonviable RCA [Table 1].

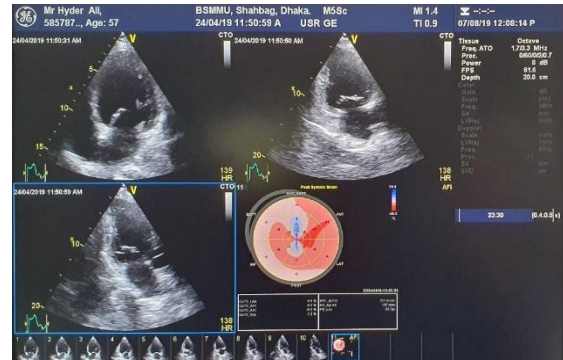**Table 1: DSE findings of the patients with viability of different arterial teritory**

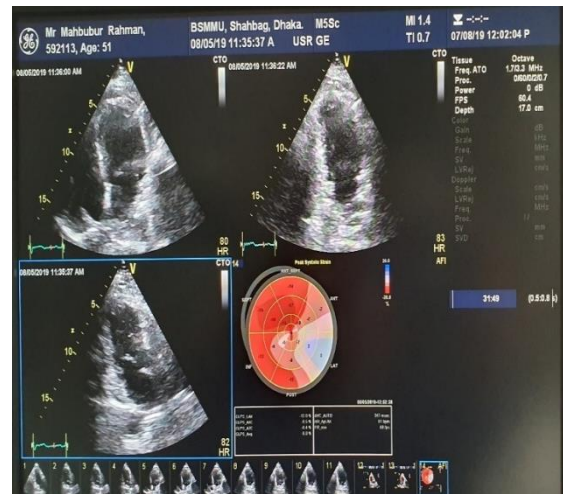| (N=20)	LAD	LCX	RCA
Normal	5	9	11
Viable	6	9	6
Nonvaible	9	2	3
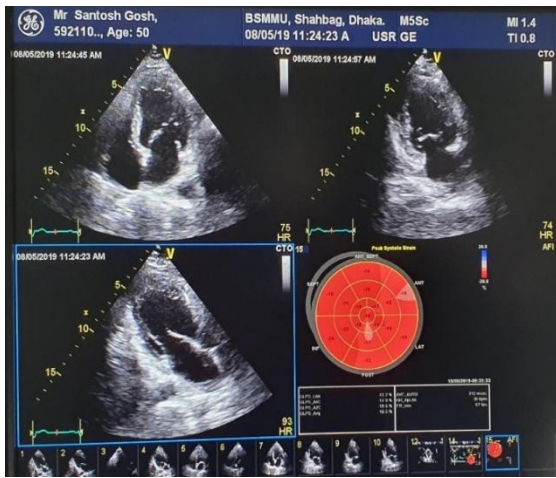
Figure 1: 2D GLS at rest in 'A' patient
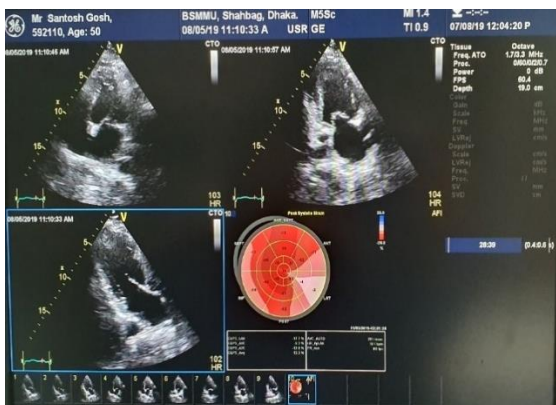
Figure 2: 2D GLS at peak stress in 'A' patient

Figure 3: 2D GLS at peak stress in 'B' patient

Figure 4: 2D GLS at peak stress in 'C' patient
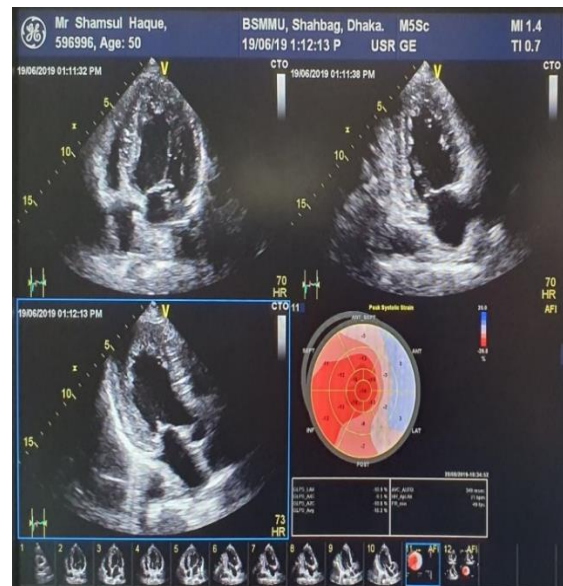
Figure 5: 2D GLS at peak stress in 'D' patient

Difference in SRps in myocardial segments supplied by LAD at baseline peak stress in patients who have normal and nonviable LAD (-21% to. -23%, p=0.98) and (-6%to – 7%, p= 2.87) which were not significant. At peak exercise there was a trend towards greater SRps in viable territory of LAD in

compared with baseline and peak stress (-11% to -16%, P = 0.05) which was significant. [Table 2]

Table 2: Comparison of DES findings and 2D GLS at base line and peak stress in LAD territory.

Findings of LAD territory at peak DSE (N=20)	2D GLS baseline (Average)	2D GLS at peak (average)	p-value
Normal (n=5)	-21%	-23%	0.98
Viable (n=6)	-11%	-16%	0.05
Nonviable (n=9)	-6%	-7%	2.87

There was no significant difference in SRps in myocardial segments supplied by LCX at baseline and peak stress in patients who have normal and nonviable LCX (-20% to. -21%, p=0.82) and (-5% to − 5%, p=1.18). At peak exercise there was a trend towards greater SRps in viable territory of LAD with baseline and peak stress (-12% to -15%, P = 0.06). [Table 3]

Table 3: Comparison of DES findings and 2D GLS at base line and peak stress in LCX territory.

Findings of LCX territory at peak DSE (N=20)	2D GLS baseline (average)	2D GLS at peak (average)	p-value
Normal (n=9)	-20%	-21%	0.82
Viable (n=9)	-12%	-15%	0.06
Nonvaible (n=2)	-5%	-5%	1.18

There was no significant difference in SRps in myocardial segments supplied by RCA at baseline and peak stress in patients who have normal and nonviable RCA (-23% to. -24%, p=1.72) and (-4% to − 5%, p=2.10). At peak exercise there was a trend towards greater SRps in viable territory of RCA with baseline and peak stress (-10% to -15%, P = 0.04). [Table 4]

Table 4: Comparison of DES findings and 2D GLS at base line and peak stress in RCA territory.

Findings of RCA territory at peak DSE (N=20)	2D GLS baseline (average)	2D GLS at peak (average)	p-value
Normal (n=11)	-23%	-24%	1.72
Viable (n=6)	-10%	-15%	0.04
Nonvaible (n=3)	-4%	-5%	2.10

2D longitudinal strain rate increased in viable territory at peak stress and there was no significant change in normal and nonviable territory. There were no statistical significant differences in other measured strain or strain rate parameters either at baseline or at peak stress during DSE procedure. There were no significant differences in the other deformation parameters.

DISCUSSION

This study has demonstrated a potential role for local myocardial deformation indices in the objective assessment of DSE by 2D GLS. There was no significant difference in SRps or SRps/sys between the myocardium supplied by particular coronary artery at baseline and peak stress in DSE. Thus exercise echo, but not conventional B-mode stress echocardiography, could document successful treatment of ischaemia by PCI. Strain rate imaging has been established as an objective marker of ischaemia during dobutamine stress echocardiography in animal models and in patients with chest pain.[14,15] Although exercise is a more physiological stressor than dobutamine and allows assessment of exercise capacity with reliable electrocardiograph data, it is constrained by suboptimal image quality at peak stress which impairs analysis of deformation parameters.[6,7] Treadmill stress is also hampered by the delay in image acquisition after achieving peak exercise. This was confirmed by the present study which demonstrated that poor endocardial border definition immediately after peak stress not only prevented meaningful B-mode visual assessment in many patients but also yielded the least number of analyzable myocardial deformation waveforms. In contrast, regional temporal events during the cardiac cycle, which can be accurately tracked by the high frame rate of SRI, are less sensitive to acoustic noise and not influenced by the insonation angle.[16] These phase changes are easier to measure and may be the reason that t-SRsys was the only measured parameter to reveal significant differences at peak stress in segments that were presumably more ischaemic prior to revascularization. While this was not accompanied by detectable differences in B-mode visual assessment pre- and post-PCI, significant reductions in SRps and SRps/sys were demonstrated following revascularization.

The development of ischaemia is associated with a progressive reduction in systolic contraction with a concomitant increase in post-systolic contraction.[17,18] The short duration (40–110 ms) and small amplitude of post-systolic contraction may mean that subtle degrees of asynchrony between ischaemic and non-ischaemic regions cannot be detected by the temporal resolution of the human eye (90 ms).[5] Furthermore, visual evaluation may erroneously interpret the development of post-systolic contraction as true systolic contractility and fail to recognize that a significant portion of deformation was occurring after aortic valve closure. SRI may overcome these limitations by offering a frame rate sufficient to resolve the timing and distinguish the true peak magnitude of brief local mechanical events.[19] The present study suggests that SRI may improve the detection of exercise-induced ischaemia by the analysis of data acquired

in recovery despite the absence of appreciable differences in conventional B-mode visual assessment. This is an important finding and raises the possibility of a greater applicability of this imaging modality. Post-systolic changes in myocardial deformation were shown to persist for at least 30 min following stress test. However, additional studies with other stress modalities such as supine bicycle are needed to compare exercise and dobutamine stress echocardiography in this setting. The time course demonstrated that post-systolic contraction developed at peak stress, persisted into recovery and was significantly reduced following revascularization in segments supplied by target vessels in conjunction with an improvement in symptoms. Although the pathophysiology remains to be fully established, this suggests that post-systolic contraction may represent myocardial stunning in response to ischaemia and is supported by previous work demonstrating similar findings during the recovery period following dobutamine stress in a canine model.[20] These data suggest that SRps and SRps/sys may be able to predict an improvement in myocardial contractility and are potential markers of functional recovery following PCI. Although significant differences in SRps and SRps/sys were demonstrated, the utility of these parameters as a clinical measure of ischaemia was limited by the overlap in values between segments in the territory of the target and nontarget vessels, such that no cut-off values for the diagnosis of ischaemia could be derived. Although a relatively small number of patients was recruited, the study involved data analysis from myocardial segments both in visual impression and 2D GLS findings. More patients would be required to determine whether this technique could enable accurate diagnosis of ischaemia and to calculate the sensitivity and specificity. Williams et al.[21] measured tissue Doppler and deformation parameters at rest and following treadmill exercise stress only in the basal anterior segments in patients with significant proximal LAD disease and controls with normal coronary angiography. In contrast to the present study, patients had significantly lower systolic and diastolic tissue velocities, strain and strain rates at peak exercise which was almost similar to visual findings of DSE by the operator. We adjudged all segments supplied by the target artery to be in the 'at risk' territory without considering the relationship between location of the culprit lesion and local myocardial function but these segments may not all be equally susceptible to the effects of ischaemia. Although the estimation of the segmental extent of coronary artery disease is difficult, it may be accomplished using the coronary artery jeopardy score.[22] Respiratory motion artefact reduced the number of satisfactory traces obtained from the anterior segments. Thus, adequate waveforms were only possible in eight segments but it is important that this is documented so that future studies can concentrate on certain key segments. Although this is a limitation, all three coronary vascular territories were still represented and the detection of significant changes in myocardial deformation indices was not prevented. Therefore, this study reveals a number of factors in terms of study power and design that are required to be addressed in order to refine future research to establish the sensitivity and specificity of myocardial deformation indices in the detection of ischaemia by GLS which is an objective study.

CONCLUSION

There is no significant difference in viability in DSE and t-SRsys at peak stress. This suggests that SRI offers an opportunity to improve the detection of dynamic regional abnormalities by echocardiography in response to dobutamine stress echo at the peak stage. Larger studies are required to establish the sensitivity and specificity of this technique in order to determine the objective evidence of DSE in the diagnosis of ischaemia by 2 D GLS.

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