

ABSTRACT

Background: Early detection of subclinical left ventricular (LV) systolic dysfunction is crucial and could influence patients' prognosis by aiding the clinician to candidate patients for better management.

Objective: To detect early LV systolic dysfunction in asymptomatic patient with chronic aortic regurgitation by two dimensional speckle tracking echocardiography.

Methods: Sixty one asymptomatic patients with chronic aortic regurgitation, with no ischemic heart diseases (by coronary angiography) or conductive heart diseases, no diabetes mellitus, no hypertension, and no other valvular heart diseases (group 1) and fifty age and sex-matched healthy subjects (group 2) were enrolled into the study. Group (1) was further classified into 3 sub-groups according to 4 chosen parameters from the published guidelines of American Society of Echocardiography (ASE) into: Mild AR, Moderate AR, and Severe AR.

All patients and controls underwent echocardiographic examination including conventional echocardiography, tissue Doppler study and Two Dimensional (2-D) Speckle Tracking Echocardiography.

Results: GLS showed the highest sensitivity and specificity in detection of subtle LV systolic dysfunction in moderate AR. In moderate AR, a cut

off value of $> (-19.62)$ has sensitivity and specificity of 91.3% and 95.5% respectively, with Positive Predictive Value (PPV) and Negative Predictive Value (NPV) of 87.5% and 96.9% respectively, Area under curve (AUC) of 0.981. In all types of AR, GLS had higher NPV than PPV which makes it a powerful screening tool for early detection of subtle LV systolic dysfunction.

Conclusion: Global Longitudinal strain measured by 2-D speckle tracking echocardiography is an excellent tool for early detection of subtle LV systolic dysfunction in asymptomatic patients with chronic AR.

Keywords: Aortic Regurgitation, Global Longitudinal Strain, Ejection Fraction.

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Received at 13/6/2017

Accepted at 4/12/2017

INTRODUCTION

Aortic regurgitation (AR) is a common form of valvular heart disease ⁽¹⁾ Natural history studies have shown that this results in left ventricular (LV) dilation and,

ultimately, systolic dysfunction, which is transiently reversible but then becomes permanent ⁽²⁻³⁾.

Quantitation of Aortic Regurgitation I-Doppler Parameters: ^(4, 5,6,7,8)

Aortic Regurgitation	Mild	Moderate	Severe
Jet density- CW	Incomplete or faint	Dense	Dense
Jet deceleration rate CW (PHT, msec)	Slow >500	Medium 500-200	Steep <200
Diastolic flow reversal in descending orta PW	Brief ,early diastolic reversal	Intermediate	Prominent holodiastolic reversal

II- Quantitative Parameters (4,9,10,11,12,13,14,15)

VC width, cm	<0.3	0.3-0.60	>0.6
Jet width/LVOT width,%	<25	25-45 46-64	≥65
Jet CSA/LVOT CSA, %	<5	5-20 21-59	≥60
RVol, mL/beat	<30	30-44 45-59	≥60
RF, %	<30	30-39 40-49	≥50
EROA, cm²	<0.10	0.10-0.19 0.20-0.29	≥0.30

* AR, Aortic regurgitation; CSA, cross sectional area; CW, continuous wave Doppler; EROA, effective regurgitant orifice area; LV, left ventricle; LVOT, left ventricular outflow tract ; msec, millisecond; PHT, pressure half-time; PW, pulsed wave Doppler; R Vol, regurgitant volume; RF, regurgitant fraction; VC, vena contracta

METHOD**LV Global Systolic Function:**

● Mitral Annulus Plane Systolic Excursion (MAPSE) and Average myocardial tissue velocity in systole (s): M-mode interrogation is undertaken of the lateral mitral annulus, and annular excursion toward the transducer is then calculated. There is a relatively linear correlation between the magnitude of systolic annular excursion and global systolic function. This same principle is used in Doppler tissue imaging of the annulus for determination of systolic excursion as a marker of ventricular function to measure average systolic myocardial tissue velocity (s').^(16,17)

● Ejection Fraction:

EF is calculated from EDV and ESV estimates, using the following formula: $EF = (EDV - ESV) / EDV$. Where EDV is the end diastolic volume, ESV is the end systolic volume. The biplane method of disks (modified Simpson's rule) is the currently recommended 2D method to assess LV EF.^(18, 19)

● Global Longitudinal Strain (GLS): Lagrangian strain is defined as the change in length of an object within a certain direction relative to its baseline length: $Strain (\%) = (L1 - L0) / L0$ ²⁰ where L1 is the length at time t, and L0 is the initial length at time 0. The most commonly used strain-based measure of LV global systolic function is GLS. It is usually assessed by speckle-tracking echocardiography (STE)^(22, 23, 24, 25)

The negative nature of GLS can lead to confusion when describing increases or decreases in strain. It is recommended that all references to strain changes specifically mention an increase or decrease in the absolute value of strain, to avoid confusion.²³

A Cross Sectional Study was done in the period from 7th May 2016 to 30th April 2017 in the Department of Echocardiography in Al-Yarmook Teaching Hospital, Iraqi Center of Heart Diseases, and Baghdad Teaching Hospital.

The study population consisted of 111 individuals, 61 patients with isolated AR referred as (group 1); and 50 healthy persons (control group) referred as (group 2).

● Inclusion criteria were: Asymptomatic patient with chronic aortic regurgitation, with NYHA class I (New York Heart Association Classification of Heart Failure).

● Exclusion criteria were:

- 1- Ischemic heart disease (excluded by coronary angiography).
- 2- Arrhythmia and conduction defects.
- 3- Hypertension.
- 4- Diabetes mellitus.
- 5- Other valvular heart diseases.
- 6- Previous cardiac surgery.
- 7- Any other chronic systemic diseases.

All 61 patients (group 2) were further divided into three groups (Mild, Moderate and Severe AR); according to the following chosen echocardiographic parameters depending on the published guidelines of ASE⁽¹²⁾

- 1- Vena contracta width.
- 2- Regurgitant volume.
- 3- Pressure-half time.
- 4- Jet width/LVOT width.

The control group consists of 50 healthy volunteers, (men, and women) from the same area who were recruited as control subjects. All control subjects identified themselves as healthy volunteers.

Conventional echocardiography, tissue Doppler and speckle tracking echocardiography were performed to all patients and controls using

Echocardiography machine; Vivid E9 (GE, Healthcare).

Transthoracic echocardiographic images were acquired at rest with the patient in the left lateral decubitus position by the same echocardiographer. The conventional echocardiography images were taken in parasternal and apical views and the standard LV measurement included: Left Ventricular End Diastolic Diameter (LVEDD), Left Ventricular End Systolic Diameter (LVESD), interventricular septum thickness (IVST) and posterior wall thickness (PWT) using 2D and M-mode measurement. EF%, EDV, ESV were measured using Simpson's method. MAPSE was measured by M-mode interrogation of the lateral mitral annulus, and annular excursion toward the transducer is then calculated. LV mass was derived from the Devereux-modified cube formula: $LV\ Mass = 0.8 \cdot 1.04 \cdot [(IVS+LVID+PWT)^3 - LVID^3] + 0.6g$ ¹⁸

Where IVS is interventricular septum; LVID is LV internal diameter, and PWT is inferolateral wall thickness.

To assess AR severity, transmitral and aortic flows were recorded using pulsed Doppler echocardiography. Vena contracta width (VCW) was measured using color Doppler in the parasternal long axis view. Continuous wave Doppler through aortic valve in the five chamber view was used to measure PHT. Jet width /LVOT width was measured using color Doppler in the parasternal long axis view. Average septal and lateral (s') was taken using tissue Doppler image through septal and lateral wall of LV to

measure average myocardial tissue velocity. The frame rate was adjusted at 80 frames/s, and the cine-loop of 3 consecutive beats was stored for offline speckle-tracking analysis. Images were acquired at end-expiration. Apical 3-chamber, 4-chamber and 2-chamber views were used for longitudinal strain Analysis.

In each echocardiographic view, the myocardium was automatically divided into 6 segments. The global longitudinal strain was calculated by averaging the peak systolic values of all the 18 segments, derived from the three apical views (six segments in each apical view): the septal, anteroseptal, lateral, anterior, posterior and inferior LV walls.

SPSS 20. software package was used to make the statistical analysis, p value was considered when appropriate to be significant if less than 0.05.

RESULT

Apart from SBP, DBP and HR, there was no statistically significant difference in age, sex, weight, and height between AR patients and control (Table 1). Table 2- shows conventional echocardiographic parameters in AR according to severity as compared to control .Except for EF% (in which EF decreased significantly in severe AR), the value of the rest of the variables in table 3 increase as the severity of AR increase.

Table 1: Demographic and clinical data of the study population (n=111)

	Normal	Mild	Moderate	Severe	P value
Number	50	16	23	22	-
Age (years)	47.8 ± 14.7	51.2 ± 10.5	50.0 ± 16.3	48.2 ± 14.0	0.832
Sex					
Male (53)	24 (48.0%)	6 (37.5%)	12 (52.2%)	11 (50.0%)	0.825
Female (58)	26 (52.0%)	10 (62.5%)	11 (47.8%)	11 (50.0%)	
Weight (kg)	74.9 ± 7.6	69.6 ± 4.1	74.3 ± 6.9	73.7 ± 6.4	0.068
Height (cm)	172.8 ± 5.7	172.8 ± 8.2	175.0 ± 6.6	172.7 ± 6.3	0.509
SBP	128.6 ± 5.7	129.7 ± 5.3	132.1 ± 4.6*	132.6 ± 5.0*	0.009
DBP	73.3 ± 6.1	72.9 ± 6.7	73.3 ± 7.2	80.5 ± 7.0*	<0.001
HR	62.4 ± 5.1	62.3 ± 4.5	65.8 ± 5.1	68.0 ± 5.1*	0.003

DBP, Diastolic Blood Pressure; HR, Heart Rate; SBP, Systolic Blood Pressure

Table 2: echocardiographic data of the study population (n=111)

	Normal	Mild	Moderate	Severe	P value
Number	50	16	23	22	-
IVS thickness	0.77 ± 0.10 ^a	0.82 ± 0.09 ^a	0.82 ± 0.08 ^a	0.97 ± 0.15 ^{***b}	<0.001
Posterior wall thickness	0.81 ± 0.10 ^a	0.87 ± 0.09 ^a	1.02 ± 0.07 ^{***b}	1.12 ± 0.10 ^{***c}	<0.001
LV mass	128.8 ± 30.3 ^a	129.7 ± 23.1 ^a	184.1 ± 29.4 ^{***b}	284.7 ± 62.5 ^{***c}	<0.001
LVEDD	4.85 ± 0.49 ^a	4.65 ± 0.28 ^a	5.36 ± 0.35 ^{***b}	6.25 ± 0.55 ^{***c}	<0.001
LVEDS	2.82 ± 0.48 ^a	3.03 ± 0.22 ^a	3.89 ± 0.36 ^{***b}	4.45 ± 0.52 ^{***c}	<0.001
LVED volume	103.6 ± 16.2 ^a	110.4 ± 10.5 ^a	142.2 ± 25.8 ^{***b}	234.8 ± 58.3 ^{***c}	<0.001
LVES volume	34.9 ± 7.7 ^a	39.3 ± 5.1 ^a	46.8 ± 8.4 ^a	51.1 ± 28.5 ^{***b}	<0.001
EF%	66.5 ± 4.1	64.4 ± 3.5	67.0 ± 2.01	57.3 ± 4.4 ^{***}	<0.001
LA Dimension	35.7 ± 2.0	36.0 ± 2.5	38.3 ± 3.3 ^{***}	42.8 ± 4.0 ^{***}	<0.001
Ascending Aorta D	2.93 ± 0.30	2.82 ± 0.21	3.00 ± 0.25	4.37 ± 0.49 ^{***}	<0.001

Table (3) displays the systolic parameters used in control and AR patients as follows: Absolute GLS value showed statistically significant decrease in moderate and severe AR; P value <0.001. However, s' and EF % showed only a statistically significant decrease in severe AR versus control. Table (4) presents the linear

regression analysis of different variables versus GLS according to severity of AR. In severe AR, EF and MAPSE showed significant negative relationship (β) with numerical value of GLS (that is reflected as positive relationship with absolute GLS value) with a P value of < 0.001.

Table 3: Change in Global Longitudinal Strain values as compared to other systolic echocardiographic parameters of the study population (n=111)

	Normal	Mild	Moderate	Severe	P value
Number	50	16	23	22	-
Average mitral annular s'	11.62 ± 1.42	11.64 ± 1.40	10.59 ± 1.03	6.91 ± 0.90*	<0.001
Global longitudinal Strain %	-22.42 ± 1.88	-20.88 ± 1.39	-7.73 ± 1.27	-15.07 ± 1.96**	<0.001
Average MAPSE	1.27 ± 0.13	1.28 ± 0.07	1.28 ± 0.08	1.24 ± 0.15	0.534
EF%	66.5 ± 4.1	64.4 ± 3.5	67.0 ± 2.01	57.3 ± 4.4 ^{***}	<0.001

Table 4: Linear regression analysis of different variables versus GLS in different types of AR:

Variables	Mild AR		Moderate AR		Severe AR	
	B	P value	B	P value	B	P value
IVS thickness	0.010	0.485	0.054	0.403	0.029	0.448
Post. wall thickness	0.160	0.278	0.134	0.271	0.146	0.258
LV mass	0.145	0.181	0.121	0.067	0.130	0.152
LVEDD	0.197	0.132	0.125	0.569	0.983	<0.001 [S.]
LVEDS	0.211	0.057	0.077	0.727	0.985	<0.001 [S.]
LVED volume	0.150	0.175	0.932	<0.001 [S.]	0.982	<0.001 [S.]
LVES volume	0.006	0.492	0.140	0.135	0.967	<0.001 [S.]
EF%	-0.106	0.125	-0.153	0.243	-0.869	<0.001 [S.]
Average MAPSE	-0.186	0.245	-0.222	0.310	-0.972	<0.001 [S.]
LA Dimension	0.150	0.289	0.121	0.067	0.971	<0.001 [S.]
Ascending Aorta D	0.076	0.780	0.960	<0.001 [S.]	0.971	<0.001 [S.]

IVS, interventricular septum ; *LVEDD*, left ventricular diastolic diameter ; *LVEDS*, left ventricular systolic diameter

Figure (1) reveals this relation according to severity of AR. EF showed statistically significant relationship in severe AR (but not in mild and moderate AR), which means that it was unable to detect early LV systolic dysfunction as compared to GLS. Table (5) explains the predictive characteristics of systolic parameters used for detection of early Left ventricular systolic dysfunction in asymptomatic AR patient. From the AR study sample, a GLS cut off value of $>-19.62\%$ yielded a sensitivity and specificity of 75.4% and 99% respectively, both of which are higher as compared to EF and s' . The area under curve (AUC) being 0.928, which reflected an excellent test.

This means that it was the most diagnostic and better confirmatory and screening tools for early detection of subtle reduction in LV systolic function. Finally; table (6) and figure (2) analyses the predictive characteristics of GLS for different types of AR according to severity. In the recent study, a GLS cut off value of $>-19.62\%$ for moderate AR showed sensitivity and specificity of 91.3%, 95.5% for moderate AR with an AUC of 0.981 (excellent test). This cut off value showed the best positive and negative predictive values being 87.5% and 96.9% respectively. This means that GLS was both confirmatory and exclusive tool in the early diagnosis of LV systolic dysfunction.

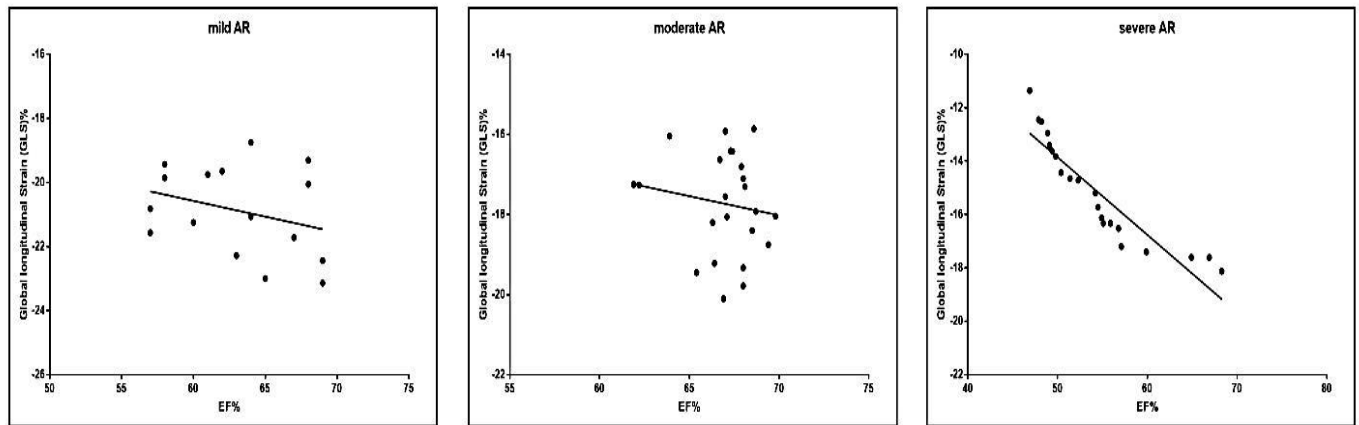


Figure 1: Relationship between EF % versus GLS in patients according to severity of AR.

Table 5: Predictive characteristics of echocardiographic variables for the detection of left ventricular systolic dysfunction in asymptomatic patients with chronic aortic regurgitation

	Cut off	Sensitivity	Specificity	AUC	P value
GLS%	>-19.62	75.4%	99%	0.928	<0.0001
Average mitral annular s'	≤ 9.65	57.4	94%	0.815	<0.0001
EF	≤ 57.1	31.1%	98.0%	0.680	<0.0001
MAPSE	-	-	-	0.519	0.729

Table 6: Predictive characteristics of GLS for the detection of left ventricular systolic dysfunction in asymptomatic patients with chronic aortic regurgitation (According to severity)

	Cut off	Sensitivity	Specificity	PPV	NPV	AUC	P value
Mild AR	>-22.54	87.5%	54.0%	37.8%	93.1%	0.739	0.0004
Moderate AR	>-19.62	91.3%	95.5%	87.5%	96.9%	0.981	<0.0001
Severe AR	>-18.2	100%	83.2%	84.5%	100%	0.963	<0.0001

AUC, area under curve; NPV, negative predictive value; PPV, positive predictive value.

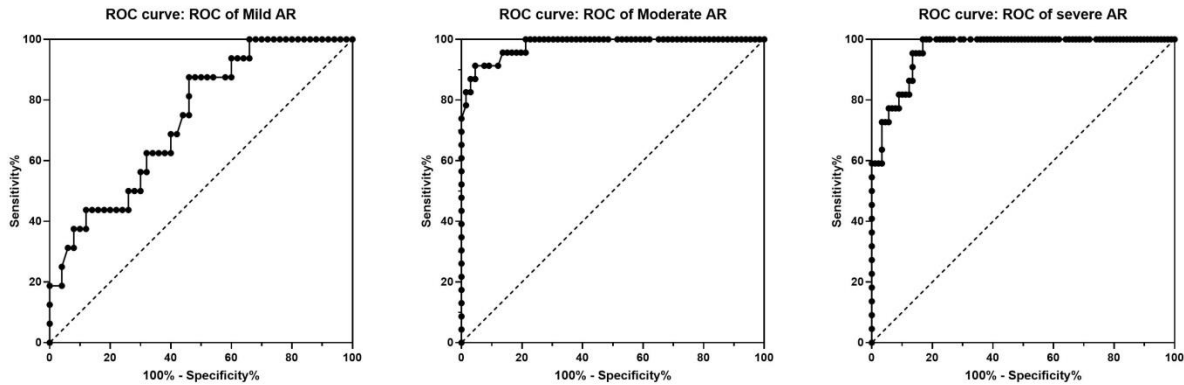


Figure (2): Receiver Operating Characteristic Curve (ROC) curve analysis to predict the GLS validity to discriminate the degree of AR.

DISCUSSION

The current study showed that apart from SBP, DBP and HR; there was no significant statistical relationship of age, sex, body weight or height with severity of AR.

In a study reported by Vaida Mizarienė et al (study 2012)²⁶, it was only systolic blood pressure which showed statistically significant change with severe AR, which is close to the results of this study.

Absolute Global longitudinal strain value showed statistically significant reduction in moderate and severe AR. Although average MAPSE was reduced with increase in severity of AR, that change was not statistically significant. EF and average mitral annular s' were reduced with increasing severity of AR. However; measurement ensued significant results only in severe AR.

In their study, Marciniak et al²⁷ reported that only severe AR that showed significant change in EF. In their study, they did not measure global longitudinal strain, instead; they measured peak systolic strain for interventricular septum and LV lateral wall. Their study showed a significant reduction in absolute peak systolic strain value in interventricular septum and LV lateral wall in moderate and severe AR. These findings are close to the finding in the recent study. Both EF and MAPSE have statistically significant negative relationship with numerical value of GLS in severe AR.

Vaida Mizarienė et al²⁴, studied this relationship for EF with GLS in patients with severe AR.

The results were concordant to the recent study with a P value of 0.001.

The recent study focused on sensitivity and specificity of the GLS and compared them with that of EF, average mitral annular s' and MAPSE. In all types of AR, GLS has more sensitivity and specificity to detect early LV systolic dysfunction. The study also calculated the positive predictive value (PPV) and negative predictive value (NPV) for each type of AR. Moderate AR showed PPV and NPV of 87.5% and 96.9% respectively. In severe AR, the PPV and NPV of 84.5% and 100% respectively.

In 2015, See Hooi Ewe et al²⁸, studied left ventricular systolic dysfunction in asymptomatic patient with AR as a whole without grading severity. This was a retrospective study which used only apical 4 chamber view to measure the GLS. GLS cut off value of -15.1% has a sensitivity of 35% and specificity of 87% (PPV of 75% and NPV of 54%). The latter reduced sensitivity may be attributed to the use of single view to measure GLS. This means that other segments which should be measured in Apical three and two chamber views are missed and thus might lead to this lower sensitivity.

Limitations of the study:

Other types of strain such as radial and circumferential strain were not measured because of unavailability of the software in the used echocardiographic machine. The values of latter types of strain may be more informative.

CONCLUSION

The study showed that GLS was the most sensitive and specific to detect early systolic dysfunction in chronic AR. Thus it can be a gold standard for assessing subtle LV systolic dysfunction in asymptomatic patients with chronic AR and preserved EF.

The study concluded that all parameters have negative relationship with absolute value of GLS, except for EF and MAPSE which have positive relation.

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