Assessment of left atrial functions in active rheumatoid arthritis patients using different echo-Doppler modalities

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Article

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Abstract

Background: left atrium (LA) plays an important role in maintaining optimal cardiac output. Rheumatoid arthritis (RA) has been considered an independent cardiovascular risk factor that can affect all cardiac chambers and functions, especially in active disease.

Aim of the study: To evaluate the effect of the activity of rheumatoid arthritis disease on left atrial functions using different echo-Doppler modalities.

Methods: Sixty-five patients with RA without evidence of previous cardiovascular disease and 36 healthy control subjects were included. Echo-Doppler examination was done with measurements included LV dimensions, ejection fraction, trans-mitral Doppler flow and tissue Doppler velocities , LA dimensions, volumes, phasic LA peak strain and LA global longitudinal strain.

Results: 39 patients had an active disease while 26 were in remission. The two patients' groups had higher values of LV internal dimensions, LA volumes, and early diastolic peak strain as a surrogate of the conduit function compared to the control group. On the other hand, they had lower values of LV-EF, FS, mitral E/A ratio & Em and lower values of parameters of reservoir & contractile function, compared to the control subjects. There were no significant differences between the 2 patients' groups in all measures except for a significantly lower value of LA GLS in active RA compared to patients in remission ($p=0.001$). The LA-GLS correlated significantly with RA disease activity score ($r=0.60$, $p<0.001$).

Conclusion: LA function is impaired in RA and this impairment correlates with the disease activity. The LA-GLS is superior in the detection of subclinical left atrial dysfunction.

Key Messages

- Left atrium plays an important role in maintaining optimal cardiac output.
- Rheumatoid arthritis patients are exposed to cardiovascular risks that can affect cardiac functions, especially in active disease.
- This study was conducted to evaluate the effect of the activity of rheumatoid arthritis disease on left atrial functions using different echo-Doppler modalities.
- We found that LA function is impaired in RA and this impairment correlates well with the disease activity, with the LA-GLS is superior in the detection of subclinical left atrial dysfunction.
- A special interest should be given to the heart of RA patients to minimize cardiac complications and disability or even death.

Introduction

Rheumatoid arthritis (RA) is a systemic autoimmune inflammatory disease characterized by the production of autoantibodies and the deposition of immune complexes [1]. Long-term inflammatory

burden and immunological abnormalities can cause substantial harm to several organs, including the heart, via various pathways [2]. RA patients have a 2-fold higher risk of developing and dying from heart failure than the general population [3], and RA patients have a 2-fold higher risk of developing and dying from heart failure than the general population. Increased left ventricular end diastolic pressure (LVEDP), increased strain on the LA with induced LA remodeling, and heart failure development are all linked to RA disease activity [4, 5]. The majority of RA patients who arrive with HF have decreased diastolic function but a normal ejection fraction. [6,7[

Because of measuring problems, LA function is understudied. Only the LA diameter is usually measured in standard echocardiography. Tissue Doppler imaging's accuracy in measuring LA is limited, thus it is only used in clinical and research contexts [8]. Tissue Doppler imaging (TDI) and speckle tracking echocardiography (STE) can be used to assess noninvasively any of these different functions (Peak atrial strain during ventricular systole (S), Late peak strain just before the active atrial contractile phase (CT), and Early diastolic peak strain (E) as a surrogate of the conduit function) [10]. Speckle tracking echocardiography (STE) provides for the measurement of LA function as well as the detection of LA dysfunction prior to the use of conventional echocardiography.

The goal of this study was to evaluate the effect of RA disease activity on LA global longitudinal strain (LA-GLS) and phasic left atrial function using speckle-tracking echocardiography (STE).

Patients And Methods

Patients who attended the outpatient clinic of the Rheumatology Department at Al-Zahraa University Hospital and were diagnosed with rheumatoid arthritis according to the 2010 ACR-EULAR criteria and had no evidence of cardiovascular disease were included in this cross-sectional prospective study [11].

From January to June 2018, the study comprised 65 patients with RA and 36 healthy control volunteers who were age and sex matched.

Informed consent was taken from all participants. The study protocol was authorised by a local ethical committee [Ethics Committee of Faculty of Medicine for Girls, Al-Azhar University, Nasr City, Cairo, Egypt, Registered at Central Administration of Research & Development; Egyptian Ministry of Health: Reg No. RHBIRB2018122001].

We obtained informed ethical consents from all patients to participate in this study, as well as its publication according to the recommendations of the above-mentioned committee.

Evidence of coronary artery disease (CAD) as detected by clinical history, ECG or echocardiographic wall motion abnormalities, valvular or congenital heart disease, diabetes mellitus, hypertension, advanced renal or hepatic diseases, and inadequate image quality all excluded patients from this study.

The disease activity score (DAS28) was computed by counting the number of swollen and tender joints as well as the erythrocyte sedimentation rate in 28 joints (ESR). [12]

Patients were classified in remission if their DAS28 was less than 2.6, and active disease was defined as DAS28 greater than 2.6. As a result, patients were separated into two groups: active RA patients (39 patients) and remission RA patients (39 patients) (26 patients).

All participants underwent a history and physical examination, with a focus on the duration of the disease and the drugs they were taking at the time. Total serum cholesterol, serum creatinine, C-reactive protein (CRP), ESR, rheumatoid factor (RF), neutrophil lymphocytic ratio (NLR), and platelet lymphocytic ratio (PLR) were all tested.

Ultrasound equipment GE- Vivid 7 system (GE- Ultrasound, Horten, Norway) with M3S (3.5MHz) matrix probe and echo Pac version 8.0 were used for echocardiography. The American Society of Echocardiography (ASE) and the European Association of Cardiovascular Imaging (EACCI) criteria for echo-Doppler for Cardiac Chamber were followed. Adults' Echocardiography Quantification (13)

Echo examination was performed in the left lateral decubitus. Averages of three consecutive cycles were used for all echo data. Images were recorded from parasternal and apical windows and the following parameters were obtained:

I- Conventional echo Doppler measurements including:

o Left ventricular dimensions and functions .

o Trans- mitral Doppler flow velocities including early (E) and late(A) diastolic velocities, E/A ratio.

o LA anteroposterior diameter measured from 2D parasternal long axis view targeted M-mode.

o LA superior-inferior and medio-lateral diameters measured from the apical 4 chamber view.

o LA volumes were estimated by area length method, averaged from apical 4 and 2 chamber views measurement.

- LA volume included:

• Maximal LA volume [Vmax] measured at the end of systole just before mitral valve opening at the end of the T wave on ECG.

• Minimal LA volume [Vmin] was measured at end diastole just at the closure of the mitral valve.

• Pre contractile LA volume (LAV pre-A] measured at P-wave onset on ECG just before atrial contraction.

• LA volume index (LAVI) was calculated for each of the above volumes as LA volume divided by body surface area [14].

II- TDI measures

II- TDI (Total Daily Intensity)

We used two apical views for the TDI velocity and TDI derived strain measurements (4&2 chamber views). Three complete cardiac cycles during end expiration were recorded and archived in a cine-loop format for data collection. To achieve a frame rate of more than 80 frames per second, the image sector width was adjusted as tiny as possible. To avoid aliasing in the image, special attention was made to the colour Doppler velocity range setting.

The sample volume was placed at postroseptal and lateral sites in the apical 4-chamber view, inferior and anterior sites in the apical 2-chamber view, to measure peak systolic myocardial velocity (Sa), early diastolic myocardial velocity (Average Ea), and late diastolic myocardial velocity (Average Ea), and late diastolic myocardial velocity (Average Ea (Average Aa). E/Ea was estimated as the ratio of E velocity from pulsed-Doppler echo to Ea from TDI.

Because of its thin-walled nature, the TDI of the LA was tested by putting sample volume at the mid atrial segment of interest, usually approximately 2 mm for measuring velocity and preferably not more than 12 mm for strain[15].

With little gain and lower filter settings, the velocity range was tuned at 20 to 30 cm/s[16].

III- Left atrium 2D Speckle tracking echocardiography examination:

To allow for strong delineation of the endocardial border and frame-to-frame tracking, 2D-STE was done on grey scale images with good image quality. The frame rate was set to 60-80 frames per second. The QRS onset was employed as a reference point, and the left atrium was analysed using a commercially available LV strain software package. The non-foreshortened apical 4-chamber view yielded 2D speckle tracking analysis of LA global longitudinal strain (LA-GLS) and left atrial peak longitudinal strain (LA-PLS) [17]. The region of interest was expanded to embrace the whole myocardium of the left atrium. If necessary, manual corrections were made to improve tracking outcomes.

Analysis of the LA strain curve was done to measure:

1. Peak atrial strain during ventricular systole (εS) measured just before mitral valve opening and it is considered as a surrogate of the reservoir function.

2. Late peak strain just before the active atrial contractile phase (εCT) begins, at the onset of the P wave on the electrocardiogram, as a surrogate of the contractile function.

3. Early diastolic peak strain (εE) as a surrogate of the conduit function. It is measured as the difference between the (εS) and (εCT) [Fig.1, Fig.2]

Statistical analysis

The information was gathered, reviewed, tallied, and statistically assessed. The mean and standard deviation were used to express quantitative data. The unpaired Student t-test was performed to determine whether there was a statistically significant difference between two samples' means. To find statistically significant relationships between qualitative variables, the X2–test was performed. When the P value was less than 0.05, the result was regarded significant, and when it was less than 0.01 it was called very significant.

Results

This study included 101 participants, 65 patients with RA (mean age 45.93 ± 4.18 years) and 36 age matched control subjects (46.37 ± 7.32 years) (p = NS). The mean disease duration was 9.29 ± 4.28 years and the mean DAS28 was 3.45 ± 0.91.

Thirty-nine patients had active disease and constituted the first group (active RA) and 26 patients were in remission and constituted the second group (Remission RA).

Baseline demographic and clinical characteristics are matching between those with active disease, in remission and the control group in age and sex. Majority of our patients were females as the incidence of RA is more in females.

The disease duration was matched in patients with active disease and those in remission and there was a significant difference as regard DAS28 as it the main topic for classification.

RA patients (active and remission) had significantly higher values of CRP, ESR, and triglyceride compared with the control group with more elevation of CRP, ESR and neutrophile in active RA group compared with the remission RA group (active vs. control, P = 0.000; remission vs. control, P = 0.001; and active vs. remission, P = 0.01). On the other hand there were significantly lower values of red blood cells count, hemoglobin level and lymphocyte in RA groups (active and remission) than control group with significantly lower lymphocytic count in active RA compared with the remission, this explained by the effect of chronic inflammatory state on erythropoiesis. As regard both (PLR and NLR) there were statistically significantly higher in disease activity and remission when compared to control group with no statistically significant difference between the disease groups (active and remission). No significant difference was found between the two groups in respect to WBCs, platelet count and INR.

Both active RA patients and those in remission had significantly higher LV dimensions, wall thickness, and significantly lower EF % and FS % compared to the control group with no significant differences in these parameters between active and remission group.

In trans-mitral Doppler flow and TDI parameters there were no significant difference among the active and remission groups as regard MV-E velocity, MV-A velocity, MV-E/A ratio, average LV Em, average LV Am and LV E/Em. Although there is a significant higher MV-A velocity, MV-E/A average LV Am and LV E/Em and lower average LV Em between the patients (either active or in remission) and control group.

LA diameters (anteroposterior and superior inferior), LA volumes (maximum, minimum and pre) and LA volume index (maximum, minimum and pre) did not differ among different disease severity groups although the difference is significant when comparing active rheumatoid arthritis versus control or rheumatoid patients in remission compared to control group (table 1).

LA functions (reservoir, conduit and contractile function) did not differ among different disease severity groups although the difference is significant when comparing active rheumatoid arthritis versus control or rheumatoid patients in remission compared to control group.(table2).

There is highly significant lower value of LAGLS and 2D-peak LAS in rheumatoid arthritis patient (in remission or active disease state) compared to control group as in figure (3) and this difference also is highly significant regarding LA GLS but not 2D-peak LAS regarding diseases severity state (active versus remission) (Table 2) .

There was a significant negative correlation between RA disease activity score level and LAGLS (r=-0.60, p value = 0.001)

Discussion

When compared to the general population, rheumatoid arthritis, regardless of disease activity, is related with increased mortality and morbidity. Even with maintained LV systolic function, CVDs are the major cause of death in rheumatoid arthritis [18].

In this investigation, non-invasive echo-Doppler parameters (conventional, tissue Doppler, and STE) were used to assess LA function in RA patients with and without disease activity. When RA patients were compared to age and gender matched controls, the LA deformation dynamics were deteriorated, with higher reduction of both LA-GLS and LA-PLS in disease activity versus remission. The severity of left ventricular diastolic dysfunction was linked to the amount of LA dysfunction (LVDD).

In contraction and relaxation, the left atrium serves at least three key physiologic roles. The left atrium functions as a 'reservoir' that absorbs blood from the veins during ventricular systole and iso-volumic relaxation. The left atrium acts as a 'conduit' for blood flow into the ventricle during early ventricular diastole. Finally, during the late phase of ventricular diastole, the left atrium's 'booster pump function' augments ventricular filling. Left atrial dysfunction has been linked to a number of conditions, including hypertension and ischemic stroke. We excluded patients with pre-existing illnesses from this study in order to assess the influence of RA on LA function, whether active or in remission.

Although a significant prevalence of left ventricular diastolic dysfunction (LVDD) has been described in rheumatoid arthritis, it is difficult to quantify and has inter observer variability due to its reliance on evaluation of numerous diastolic dysfunction parameters [13].

Left atrial volumes and functions are major predictors of unfavorable cardiac events and are used as markers for the degree and chronicity of left ventricular diastolic dysfunction [9].

In a range of cardiovascular diseases, the severity and chronicity of LVDD is an accepted surrogate measure for maximum left atrium volume [13], in addition to size,

The structural and functional adaptive alterations of LA that characterize LV diastolic function are determined by LA function. If systolic function is retained, the LA contributes one-third of cardiac output during exercise, as a result [15]. Patients with impaired LV systolic and diastolic function showed higher LA adaptive functional changes [13].

In this study, rheumatoid arthritis patients had a higher lipid profile than controls, which could be explained in part by higher inflammatory markers like CRP and ESR.

Although there were differences in heart dimensions and LV systolic function characteristics across the groups studied, they were all within the normal range. Diastolic parameters, on the other hand, were found to be impaired in rheumatoid arthritis patients by conventional echocardiography and TDI parameters with no significant difference in disease activity state, implying that rheumatoid arthritis and possibly other rheumatologic diseases can affect LV diastolic function.

In the current study, rheumatoid arthritis patients had significantly higher LA volumes and indices than controls, with no statistical difference in disease activity. In rheumatoid arthritis patients, there was also a decrease in LA reservoir and contractile activity, as well as an increase in conduit function.

This is in line with a study published in 2020 that found a significant variation in left atrial volumes between patients and controls, with no link to disease activity. On the other hand, regardless of disease activity or duration, this study found an inverse relationship between tissue Doppler parameter velocities (Em, Am, Sm) and the rheumatoid factor. They just looked at LA GLS and discovered a significant difference between patients and controls, but they didn't look at disease activity levels [19]. No previous study that we are aware of in the literature compared LA GLS or LAS with different RA activity states.

Another study used another metric (the LA expansion index) as a predictor of AF occurrence and discovered that the LA expansion index outperformed the LA volumes in terms of predictive efficacy. Unfortunately, this index was not included in the current study.

With the growing use of 2D-speckle tracking echocardiography in clinical practise to pick up subclinical abnormalities, left atrium mechanics computed from monitoring deformation of LA myocardium using strain and strain rate (SR) imaging is a new tool in cardiac imaging.[20]

In this study, rheumatoid arthritis patients had a significant reduction in LA GLS and 2D-peak LAS, and this difference was significant between active and remission cases in terms of LA GLS only. Furthermore, the current investigation found a strong negative association between the LA GLS and the rheumatoid arthritis disease activity score. The severity of left atrial stiffness could explain this finding. As our investigation revealed, rheumatoid arthritis activity score can predict subclinical LA dysfunction.

Another study looked at the effects of interleukin inhibitors on myocardial deformation and vascular function in RA patients and discovered a considerable improvement in LV GLS after therapy with interleukin inhibitors, particularly in patients with coronary artery disease [21]. Their findings back up our observations that disease activity is proportional to decreasing myocardial function, whether in the LV or LA.

Conclusion

LA function is impaired in rheumatoid arthritis patients and this impairment correlates with the disease activity score (DAS28). The LA-GLS is superior in detection of subclinical left atrial dysfunction.

We recommended further studies using other modalities MRI to delineate ventricular and atrial tissue characterization and the presence & degree of fibrous tissue in the myocardial of patient having rheumatoid arthritis.

Declarations

Competing interests:

- The author confirms that there are no any potential conflicts of interest.

Contributorship:

1-Eman Zaki (EZ)

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4-Eman roshdy (ER)

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7-Adel Elbeialy (AE)

The codes, supervised the research:

EZ, BE, HA, ER, SS, MA, AE performed the experiments.

AE, EZ, BE, ER, SS wrote and revised the manuscript.

AE is the corresponding author

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Funding, grant/award info:

- I confirm also that there are not any financial support or other benefits from commercial sources for the work reported on in the manuscript, or any other financial interests that I may have, which could create a potential conflict of interest or the appearance of a conflict of interest with regard to the work.

Ethical approval information:

- This study was carried out according to regulations and approval of Ethics Committee of Faculty of Medicine for Girls, Al-Azhar University, Nasr City, Cairo, Egypt, Registered at Central Administration of Research & Development; Egyptian Ministry of Health: Reg No. RHBIRB2018122001
- Informed ethical consents were obtained from all patients to participate in this study, as well as its publication according to the recommendations of the above-mentioned committee.

Data sharing statement:

- I confirm hereby that the manuscript has not been submitted or is not simultaneously being submitted elsewhere, is not at the time of submission under consideration by another journal or other publication, and that no portion of the data has been or will be published elsewhere while the manuscript is under review by the journal, unless rejected or withdrawn by the author. Also we confirm that no portion of the data has been or will be published elsewhere while the manuscript is under review by the journal.

Data Availability:

- The datasets used and/or analyzed during the current study available from the corresponding author on reasonable request.

Patients and Public involvement

- I confirm here that all patients are fully anonymized and unidentifiable in any way, and they gave us informed written consent that they agree to publish this research in its present form.

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Tables

Table (1): Comparison between active RA, remission RA and control group as regard left atrium diameters and volumes.

Variable	Active RA (n=39)	Remission (n=26)	Control (n=36)	Active VS control P value	Remission Versus control P value	Active VS Remission P value
LA antero-post diam(mm)	36.64±4.89	36.57±6.70	33.02±1.97	**0.001	0.01	NS
LA sup-inf diam (mm)	40.0±7.88	37.26±7.99	34.17±2.26	**0.001	NS	NS
LA med-lat diam(mm)	36.15±7.57	31.96±6.97	32.40±3.30	0.01	NS	NS
LAV Max (ml)	50.71±21.39	51.50±19.52	34.34±3.66	**0.001	**0.001	NS
LAVI Max(ml/mm^2)	26.871±10.01	26.33±9.79	17.67±1.69	**0.001	**0.001	NS
LAV Min (ml)	24.15±13.37	23.61±11.87	11.85±1.98	**0.001	**0.001	NS
LAVI Min (ml/mm^2)	13.16±6.40	13.17±6.40	5.76±.0.95	**0.001	**0.001	NS
LAV Pre (mm)	31.12±14.96	29.84±11.44	17.97±1.93	**0.001	**0.001	NS
LAVI Pre (ml/ mm^2)	17.13±7.02	15.53±6.06	9.88±1.07	**0.001	**0.001	NS

* Significant difference (p value<0.05), ** Highly significant difference (p value<0.001).

Table (2): Phasic left atrium Speckle tracking echocardiography and left atrial deformation in relation to disease activity compared with the control group.

Variable	Active RA (n=39)	Remission (n=26)	Control (n=36)	Active VS control P value	Remission Versus control P value	Active VS Remission P value
Reservoir function % (εS)	59.77±8.43	57.160±8.43	67.69±2.15	**0.001	**0.001	NS
Conduit function % (εS - εCT)	77.19±20.65	82.30±18.74	61.71±7.86	**0.001	**0.001	NS
Contractile function % (εCT)	27.04±19.30	24.72±19.20	57.50±16.70	**0.001	**0.001	NS
LA GLS	11.81±1.5	13.87±1.32	25.51±2.34	**0.001	**0.001	**0.001
2D-Peak LAS(%)	19.02±5.43	20.96±2.10	30.74±2.10	**0.001	**0.001	NS

LAGLS (%): left atrial global longitudinal strain percentage, 2D-Peak LAS(%): 2- dimension peak left atrial strain percentage

Figures

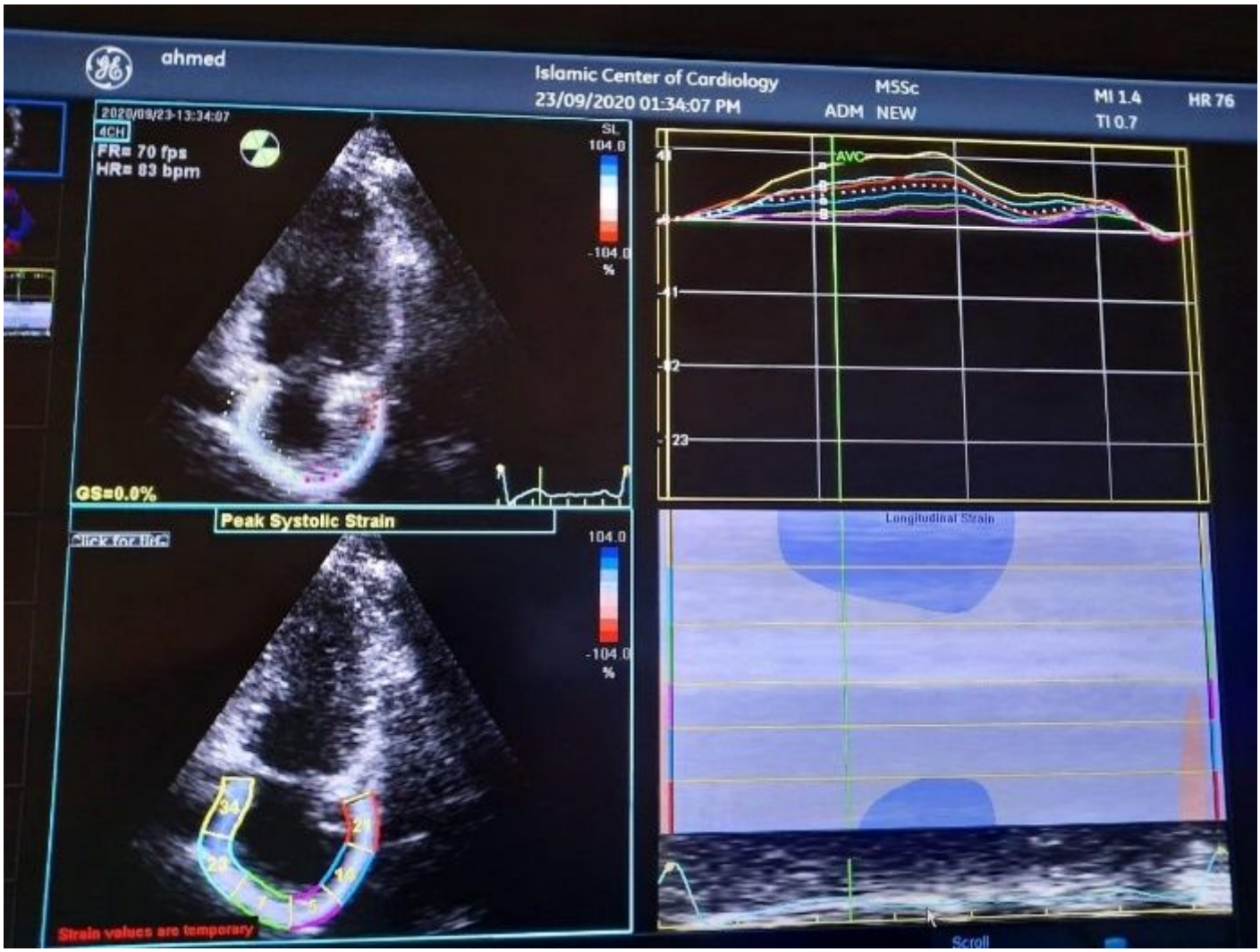

Figure 1

apical 2-chamber view of left atrial global longitudinal strain by speckle tracking echo

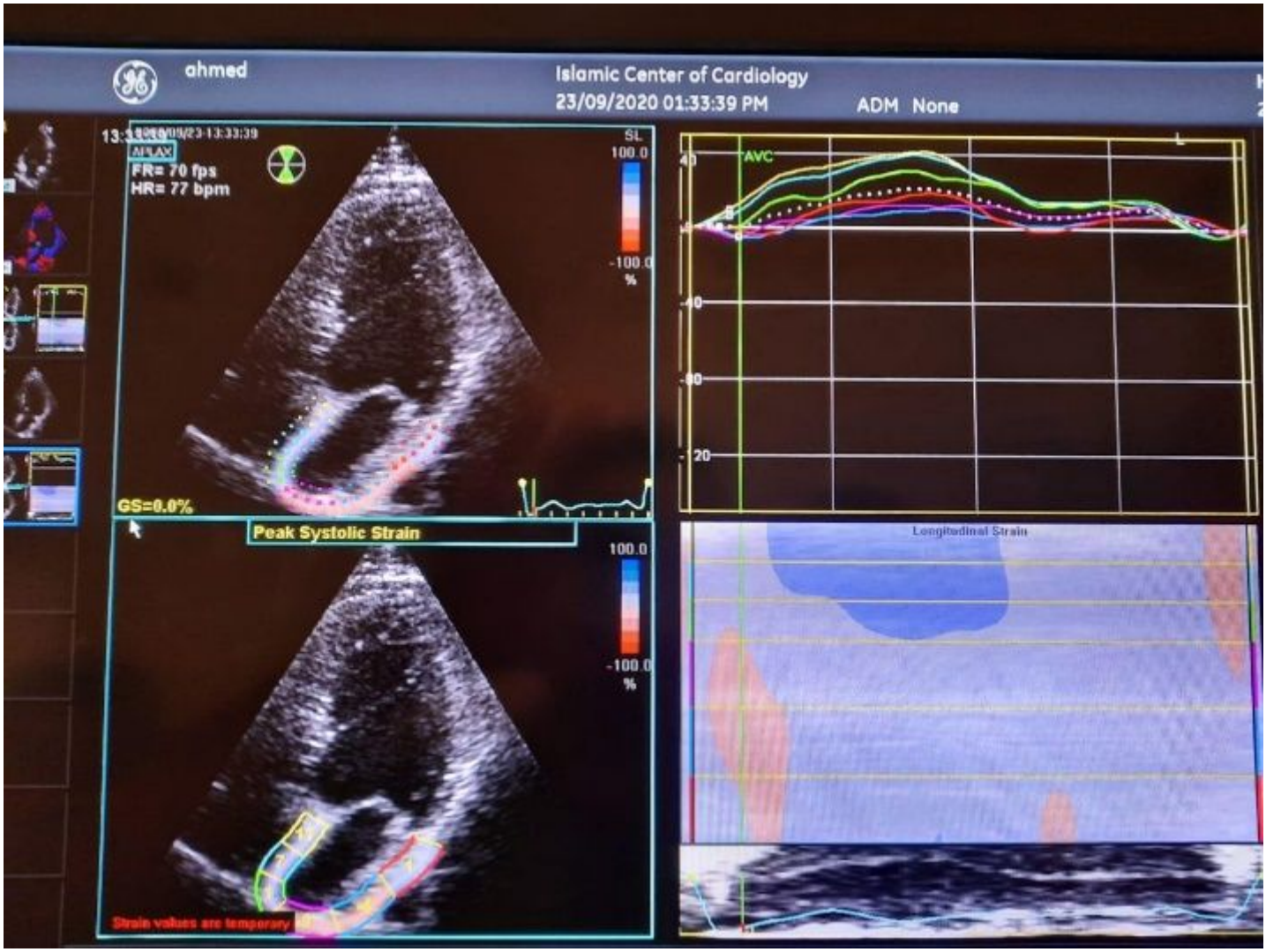

Figure 2

apical 4-chamber view of left atrial global longitudinal strain by speckle tracking echo

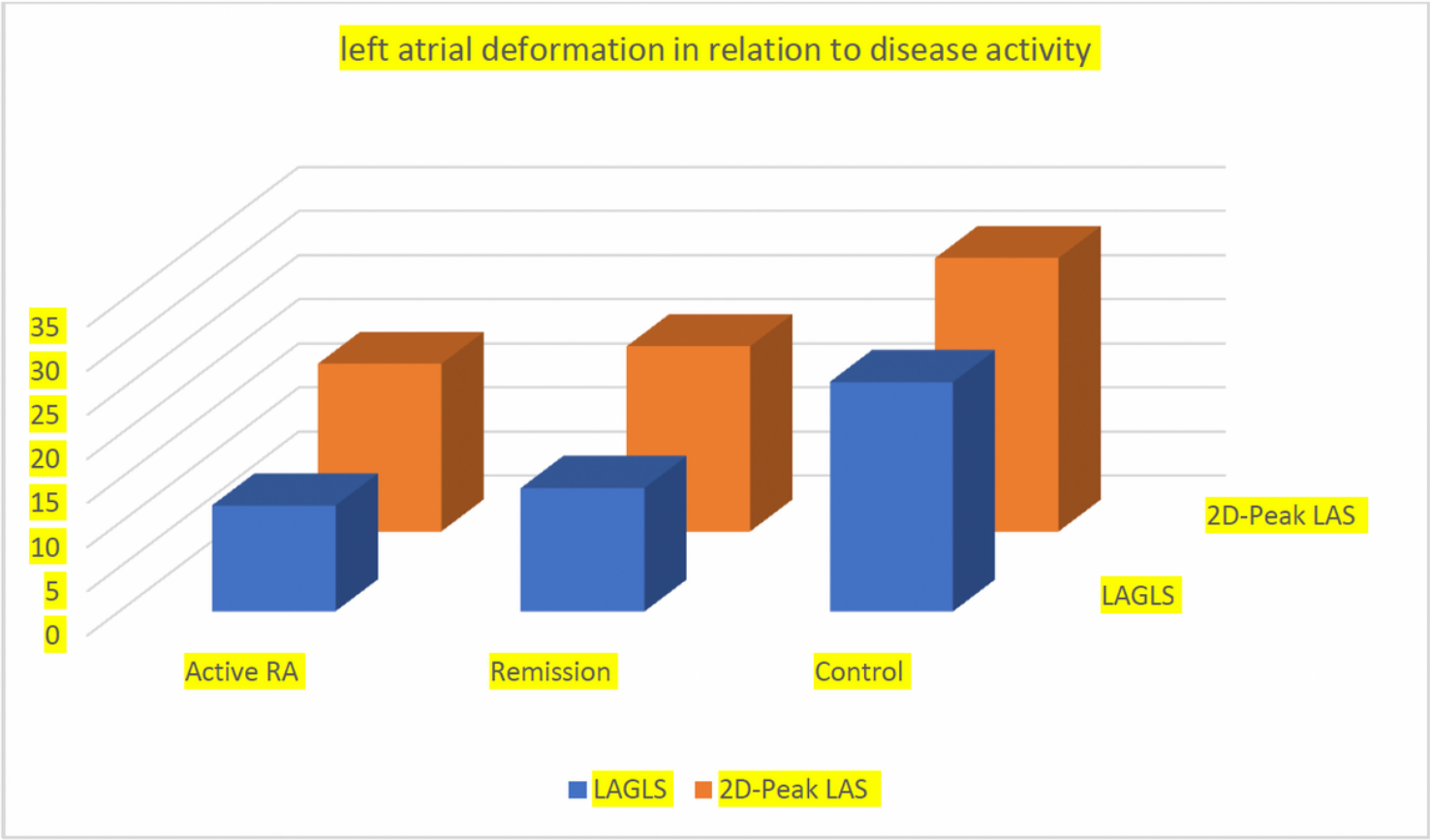

Figure 3

comparison between the studied groups as regard LAGLS and 2D-peak LAS