Early detection of left ventricular systolic dysfunction in asymptomatic patients with rheumatoid arthritis using global longitudinal strain assessment

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Abstract: Background: The higher mortality rate of patients with rheumatoid arthritis (RA) has been linked to cardiovascular (CV) disease. It is well known in literature that RA is associated with enhanced atherosclerosis and impaired endothelial function early after the onset of the disease. CV disease represents one of the leading causes of subclinical cardiac involvement. Recently, 2D speckle tracking echocardiography (STE) has emerged as cardiac imaging that allows non invasive and angle independent measurement of global and regional left ventricular (LV) myocardial strain. **The aim of this** study was to evaluate the left ventricular function by speckle tracking echocardiography in asymptomatic patients with rheumatoid arthritis with short disease duration and without known CV diseases. **Patients and Methods:** We studied 50 RA patients mean ± SD age (46±12 years) without clinical evidence of CVD compared to 33 age matched (44.7 ±9.3 years) healthy control with (88%) women in each group. Both patients and control groups underwent laboratory assessment stress electrocardiogram to exclude myocardial ischemia and echocardiographic study using conventional, tissue Doppler imaging (TDI) and STE. Global LV longitudinal strain was obtained from apical 3, 4- and 2 chambers view and analyzed using available software. **Results:** The conventional echo- Doppler parameters were comparable between RA and control group except for significant difference in interventricular septal thickness in RA patients compared to control (9.65± 1.80 mm vs. 8.53± 1.23 mm, $p<0.05$). TDI showed a significant reduction of S′, E′ with higher E/ E′ ratio in RA patients compared to control (6.39 ±1.13 cm vs 7.17 ±0.64 cm, mean E′ ±SD= 8.72±1.91 cm vs. 11.04± 1. 35 cm,, mean E/ E′ ±SD=8.99±2.49 vs 6.77±1.4 $p<0.05$ respectively). LV global longitudinal strain by STE was significantly reduced in RA compared to controls (17.22 ±1.46% vs. 21.98 ±2.48%, $p <0.05$) respectively, a significant negative correlation was found between global LV strain and antiCCP (marker of disease severity) ($r= -0.054$, $p<0.01$). **Conclusions:** RA patients without known CVD have impaired LV systolic longitudinal strain measured using STE compared to healthy subjects. These findings suggest that subclinical myocardial disease may be present in RA patients prior to the development of symptomatic CVD. Strain imaging may represent an effective tool for detection of subclinical CVD, and identifying RA patients at increased risk for developing heart failure (HF).

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1. Introduction

Rheumatoid arthritis (RA) is a systemic autoimmune disease affecting about 1% of the general population. It is characterized by chronic inflammation and enhanced atherosclerosis. RA is associated with increases in both morbidity and mortality compared with the general population. RA increases the risk of cardiovascular (CV) mortality by up to 50% compared with the general population and CV disease (CVD) is the leading cause of death in RA patients **(1)**.

The excess of cardiovascular (CV) mortality and morbidity could be explained by the chronic inflammation, disease duration, disease activity, immunosuppressive therapy, in addition to traditional CV risk factors **(2)**. In particular chronic inflammation, accelerated atherosclerosis and functional abnormalities of the endothelium suggest a subclinical CV involvement beginning rapidly soon after the onset of the disease at younger age than in general population and progressing with the disease duration **(3)**.

Being associated with unfavorable prognosis, it becomes mandatory to detect subclinical cardiac involvement in asymptomatic RA patients for adequate long term treatment, in particular early detection of subtle cardiac injury and therapeutic intervention in this subclinical stage may potentially limit long term morbidity and mortality in these patients **(4)**.

The European League Against Rheumatism (EULAR) recommendations for the management of CV risk in RA highlight the critical importance of adequate disease control in lowering CV risk. Annual CV risk assessments are recommended for patients with RA, with the risk assessment repeated when modifying anti-rheumatic drugs (MARDs) therapy is changed [1].

Speckle tracking echocardiography(STE) is a peculiar technique of 2- dimensional (2D) echo images analysis recently introduced to allow the study of myocardial deformation[4]. Differently from Tissue Doppler imaging (TDI), STE is an angle- independent technique which may allow an accurate assessment of segmental myocardial deformation by gray – scale based imaging analysis frame by frame. Moreover, the lack of angle-dependency is of great advantage because myocardial strain could be tracked in 2D, along the direction of the wall and not along the ultrasound beam [4].

Recently, *Sitia et al.*, [5] demonstrated that left ventricular (LV) longitudinal systolic strain was reduced in RA patients after mean disease duration of 34 months despite the normal standard echocardiographic study [5].However; they investigated a rather small number of RA patients and almost 3 years after disease's onset. Furthermore, *Fine et al.,* [6] recently found global longitudinal systolic strain (GLS) to be reduced in patients with long-standing RA compared to controls. It would be of great interest to detect even earlier evidence of subtle cardiovascular injury.

The purpose of this study was to evaluate the left ventricular function by speckle tracking echocardiography in asymptomatic patients with rheumatoid arthritis with short disease duration and without known CVD.

2. Patients and methods

1. Study population

The study cohort consisted of 50 consecutive patients, the mean age was 45.8±9.6 years, with well-established diagnosis of rheumatoid arthritis attending Al-Zahraa University hospital (Cairo, Egypt); Rheumatology outpatient clinic between January 2015 to August 2015, compared to 33 age and sex matched healthy subjects with mean age 44.7±9.3 years as a control group. All enrolled patients had a documented RA. To maintain homogeneity of the study cohort all hypertensive and/or ischemic patients were excluded from subsequent analyses.

Ischemic heart disease was excluded in all patients by a negative stress electrocardiogram (ECG) conducted at Al-Zahraa hospital- Cardiology – department. All patients underwent treadmill exercise stress according to the standard Bruce protocol. Testing was symptom-limited unless prematurely terminated for reasons recommended in the updated guidelines of exercise testing [7].

All patients with advanced comorbidities that might alter left ventricular functions (e.g. advanced liver failure, chronic kidney disease, severe obstructive pulmonary disease, hypo- or hyperthyroidism, clinical history and signs or symptoms of cerebrovascular events, use of vasoactive drugs or patients with cardiac rhythm abnormalities) were excluded from this study. Also, we exclude patients with echocardiographic data of significant valvular heart disease, pericardial disease, congenital heart disease or technically poor acoustic window precluding satisfactory 2D echocardiographic imaging of LV.

All patients included in this study were recruited from Rheumatology outpatient clinic at Al-Zahraa University hospital, Cairo, Egypt. All Patients were fulfilled the American College of Rheumatology (ACR) revised criteria for diagnosis of RA and according to the 2010 ACR-EULAR criteria. Disease activity was assessed using 28-joint disease activity score (DAS-28). Disease duration ranged between 12-60 months; with mean disease duration 38.04±16.82 months.

The DAS-28 is a disease activity index developed after the extended original DAS score. It consists of a 28 tender joint count (range 0-28), a 28 swollen joint count (range 0-28), ESR, and an optional general health assessment on a visual analogue scale (range 0-100). Because of the use of reduced and non-graded joint counts, the DAS-28 is easier to complete than the original DAS. The DAS-28 has a continuous scale ranging from 0 to 9.4. The level of disease activity can be interpreted as low (DAS-28 < 3.2), moderate (3.2<DAS-28 < 5.1), or high (DAS-28 > 5.1). DAS-28< 2.6 corresponds to being in remission according to the ACR criteria [8, 9].

All patients received anti-rheumatic therapy (biological or non-biological DMARDs or steroids. The protocol study was approved by our local Ethical Committee and all subjects gave written informed consent.

2. Laboratory assessment

Blood samples were collected after an overnight fast in all patients and controls and were analyzed for total cholesterol, triglycerides, fasting blood glucose, serum creatinine, white blood cell and platelet cell counts. The erythrocyte sedimentation rate (ESR) was calculated. C-reactive protein (CRP) was measured using routine methods for all patients. Anti-cyclic citrullinated peptide (anti-CCP) antibodies were tested for the patients.

3. **Electrocardiography (ECG):**

The patients and controls underwent a standard 12 lead – surface ECG recording, the recording were reviewed for abnormalities such as rhythm disturbance, T-wave or ST wave abnormalities suggesting myocardial ischemia or presence of bundle branch blocks which is a contraindication for stress ECG**.**

4. **Echocardiography**

A) Standard Echocardiography:

All echocardiographic examinations were performed by a single operator. Transthoracic echocardiographic (TTE) images were recorded using (VIVID 5 GE system) with tissue Doppler imaging (TDI) capability. All cases were examined using multifrequency (2.5- 3.5 MH) Matrix probe (M3S) with simultaneous ECG recording to allow timing of flow with patients lying down in the left lateral decubitus position. Comprehensive trans-thoracic M-mode, 2 Dimensional (2D), and Doppler were done in standard views (parasternal long axis, parasternal short axis, apical four and two chamber views) to measure left ventricular (LV) dimensions, LV volumes, left atrial diameter and volumes. The LV ejection fraction was calculated by a modified biplane Simpson's method from apical 4- and 2 chambers views.

Doppler indices of LV diastolic function were measured using standard techniques [(10)]. The transmitral early (E wave) and atriogenic (A wave) diastolic velocities, E/A ratio and deceleration time (DT) were recorded.

B) Tissue Doppler Imaging (TDI)

The tissue Doppler velocity profiles were derived from the apical 4- and 2-chambers view with Doppler sample volume placed at septal, lateral, anterior and inferior mitral valve annuli. Images were acquired with high frame rate (>100 frame/s) reducing background noises as possible.

In order to obtain a clear tissue signal, three consecutive cycles were recorded and stored for subsequent offline analysis; we considered the average of 3 measurements for all TDI parameters. The following parameters were measured for each site: Average peak systolic mitral annular velocity (S′) the markers of longitudinal LV systolic function [(11)] (S′), early diastolic annular velocity (E′) and late diastolic annular velocity (A′) and E/E′ which is the ratio of average peak early transmitral diastolic velocity measured by Doppler (E) and (E′) is the average peak early diastolic mitral annular velocity measured by TDI.

C) Speckle tracking analysis

Speckle tracking analysis was performed off-line with QRS onset as the reference point applying a commercially available LV strain software package to the left ventricle (**EchoPAC version 110.1.2).** Using dedicated software package Automatic Function Imaging (AFI), 2D images were obtained from the apical long, two and four chamber views, using high frame rates (60–90 frame/s) and storing three cardiac cycles in cine-loop format for off-line analysis to assess LV longitudinal strain by tracing the endocardial border on an end-diastolic frame and the software automatically tracked the border on the subsequent frames. Adequate tracking can then be verified in real time and corrected by adjusting the region of interest or manually correcting the border. The LV was divided into 17 segments and automated measurements of segmental systolic longitudinal strain values then global LV longitudinal strain (LV-GLS) were calculated.

Statistical Analysis

Data were presented as mean ± standard deviation (SD) and analyzed by SPSS 16. Difference between two groups was compared by unpaired Student *t*-tests. $p < 0.05$ was considered statistically significant. Association of two sets of data was evaluated with Pearson test for correlation analysis.

3. Results

Clinical and biochemical characteristic

The Baseline characteristics of the studied population are summarized in table (1). The study population consisted of 50 RA patients; 6 males (12%) and 44 female (88%) with their mean age ±SD (45.8 ±9.6 years) compared to 33 healthy subject; (4 males (12.1%) and 29 female (87.9%) with their mean age ±SD (44.7 ±9.3 years).

Both groups were comparable regarding age, sex, blood pressure, serum lipid levels, fasting blood sugar and blood urea nitrogen, however the RA patients had higher creatinine and inflammatory markers (ESR, WBCs and CRP) levels when compared to healthy control.

Conventional Echo-Doppler evaluation:

Conventional TTE examination showed that both RA and healthy controls are comparable regarding normal LV diameters, volumes and systolic function. We found that IVSD was thicker in RA patients when compared to healthy controls (9.65± 1.8 mm vs. 8.53± 1.23 mm, $p<0.05$) while no significant differences were found in conventional Doppler parameters (E, A, E/A and DT) between the RA and healthy controls as shown in (Table 2).

Tissue Doppler Parameters

A highly significant reduction of the average systolic mitral annular wave velocity obtained from 4 annular sites (S′) was found in RA patients compared to healthy control (6.39 ±1.13 cm vs 7.17 ±0.64 cm, $p< 0.05$ respectively) as well as average of early mitral annular diastolic wave velocity obtained from 4

annular sites (E′) was significantly reduced in RA patients compared to control (8.72±1.91 cm vs. 11.04± 1. 35 cm, p<0.05) figures (1 A and B). Also a higher E/E′ ratio was found in RA when compared to healthy controls although both groups were comparable in average A′ wave velocity, as summarized in (Table 3).

Table 1: Demographic, Clinical and Biochemical characteristic of the study population

Variables	RA (n= 50)	Control (n=33)	P value
Age (years)	45.8 ±9.6	44.7 ±9.3	NS
gender n(%) female	44 (88%)	29 (87.9%)	NS
SBP (mmHg)	114.8±13.5	110.7±12.6	NS
Cholesterol (mg/dl)	186.34±4.453	176.60±45.5	NS
Triglyceride (mg/dl)	115.44±39.97	119.76±20.69	NS
Blood urea (mg/dl)	29.7±6.12	26.76±7.68	NS
Creatinine (mg/dl)	**0.87±0.25**	**0.69±0.16**	**<0.05**
Glycaemia (mg/dl)	85.1±13.4	79.4±15.06	NS
CRP(mg/dl)	**19.83±11.25**	**1.55±1.20**	**<0.05**
ESR (mm/h)	**50.32±20.38**	**10.61±6.40**	**<0.05**
DAS-28	4.04±0.82	-	
Anti CCP (UI)	54.61±34.76	-	
Disease duration (M)	38.04±16.82		

CRP= C-reactive protein, ESR== erhytrocyte sedimentation rate, DAS-28= disease activity score, Anti-CCP= anti-cyclic citrullinated peptide antibodies. Values are expressed as mean ±SD.

Table (2) conventional echocardiographic and Doppler parameters to the study groups

Variables	RA (n= 50)	Control (n=33)	P value
EF (%)	68.90 ±7.10	68.30 ±5.34	NS
IVST(mm)	**9.65±1.80**	**8.53± 1.23**	**<0.05**
PWT (mm)	9.08±1.73	8.72±1.24	NS
LVEDD (mm)	48.84±5.61	46.75±5.54	NS
LVESD(mm)	29.96±5.21	28.93±4.10	NS
LVEDV (ml)	76.16±23.6	68.11. ±21.23	NS
LVESV (ml)	33..31±16.10	25.6 6±8.79	NS
Average peak E wave (cm/s)	75.58±14.94	75.39±16.73	<0.05
Average peak A wave cm/s)	60.08±13.20	59.27±11.08	NS
Average E/A	1.2±0.21	1.3 ±0.32	NS
DT (ms)	192. 24±32.41	185.86±42.75	NS

EF=ejection fraction; IVST=interventricular septal wall thickness; PWT=posterior wall thickness; LVEDD=left ventricular end diastolic dimension, LVESD=LV end systolic dimension, LVEDV =LV end diastolic volume, LVESV=LV end systolic volume, E =early diastolic wave velocity, A =late diastolic wave velocity, E/A= ratio of early to late diastolic trans mitral flow velocity, DT=deceleration time (values given as means± SD)

Table (3) Tissue Doppler parameters to the study groups

Variables	RA (n= 50)	Control (n=33)	P value
Av. S′ (cm/s)	**6.39 ±1.13**	**7.17 ±0.64**	**<0.05**
Av.E′ (cm/s)	**8.72±1.91**	**11.04± 1. 35**	**<0.05**
Av. A′ (cm/s)	**6.97±1. 34**	**7.24±1.37**	NS
Average E/E′	**8.99±2.49**	**6.77±1.4**	**<0.05**

Av.S_a=average of systolic mitral annular wave velocity at 4 annular sites, Av. E′ =average of early mitral annular diastolic wave velocity at 4 annular sites, Av.A= average of late mitral annular diastolic wave velocity at 4 annular sites. E/ E′ ratio of early transmitral diastolic flow velocity obtained by conventional Doppler to early mitral annular diastolic wave velocity obtained by TDI (values given as means± SD)

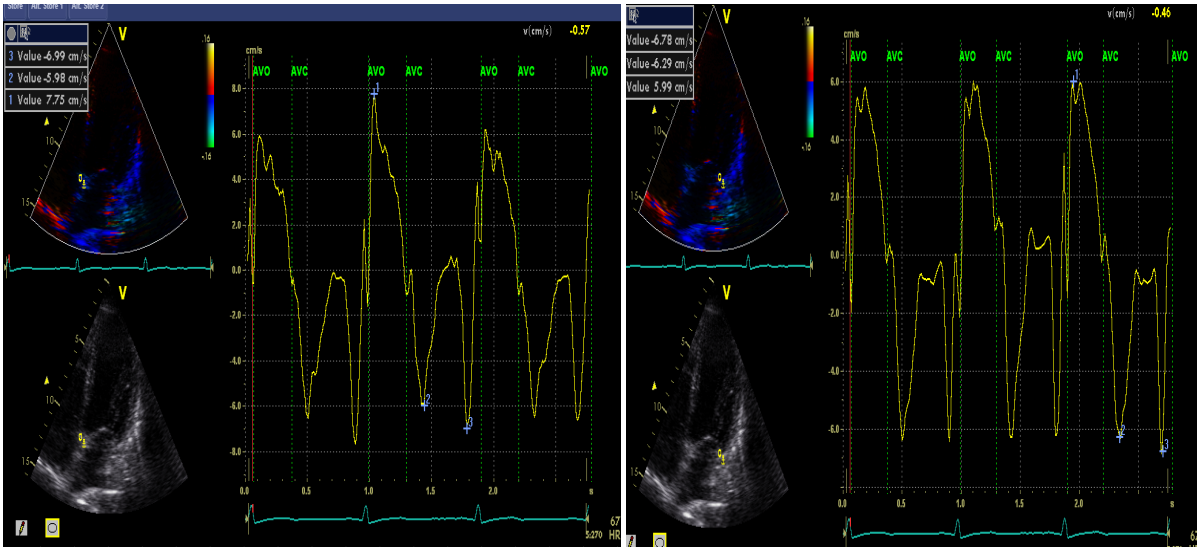

Figure (1): TDI derived systolic, early and late diastolic annular velocity at (A) septal and (B) lateral sites in RA patient

Speckle tracking echocardiography

Speckle tracking analysis (Table 4) showed that LV global longitudinal strain was significantly reduced in RA patients compared to control (Fig 2 A and B).

Table (4): comparison of LV-GLS between RA patients and control group

Variables	RA (n= 50)	Control (n=33)	P value
LV.GLS (%)	**17.22 ±1.46**	**21.98 ±248**	**<0.05**

LV.GLS =left ventricular global longitudinal strain obtained by2-D -STE

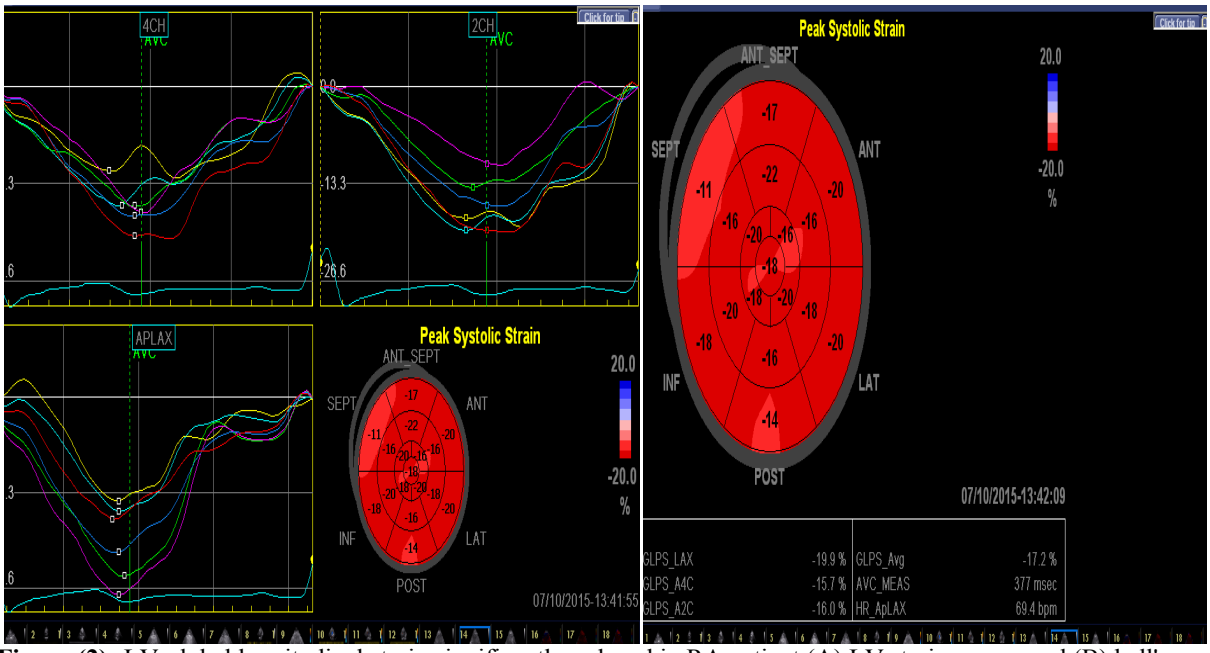

Figure (2): LV-global longitudinal strain significantly reduced in RA patient (A) LV strain curves and (B) ball's eye of 17-segments

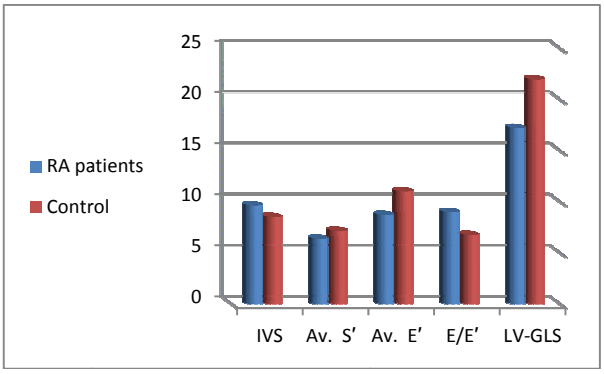

Figure (3): comparison of echo-Doppler parameters including TDI and STE between RA patients and control groups

Correlation between left ventricular function and antiCCP

By using conventional M-mode measurement of LV ejection function (EF), we found no significant correlation with the antiCCP level among RA patients. On the other hand, using more sensitive modality for evaluating of LV systolic function (by measuring LV-GLS), we found a significant negative correlation between LV- GLS and antiCCP ($r= -0.054$, $p<0.01$) among RA patients.

Correlation between left ventricular function and disease duration:

No correlation was found between left ventricular systolic function either by conventional echocardiography (EF) or by GLS and disease duration

4. Discussion

CVD represents a significant source of morbidity and mortality among RA patients, accounting for 50% of all deaths [12, 2]. This risk is independent of traditional CVD risk factors or the presence of CAD [13, 14]. The considerable disease burden highlights the importance of early recognition of patients at risk for developing clinical HF, which could facilitate better prognostic assessment and potentially earlier therapeutic intervention to improve outcomes [6].

While it has been demonstrated that RA patients have a higher prevalence of LV diastolic dysfunction as measured by echocardiography compared with age and gender matched subjects without RA [15, 16], the mechanism underlying this observation remains unclear [14]. Plasma markers such as B-type natriuretic peptide (BNP) have been shown to be less effective for CVD screening in RA [17]. These reports indicate a need for better strategies for evaluating RA patients for subclinical CVD.

The mechanism of CVD in RA remains an area of ongoing research. There is considerable evidence suggesting that chronic inflammation contributes to impairment of endothelial and microcirculatory function, leading to the early onset of atherosclerosis in RA patients [18, 19]. This perfusion impairment may lead to both systolic and diastolic dysfunction.

Furthermore, prolonged inflammation may lead to oxidative stress, myocyte dysfunction, [20, 21] and to a cytokine-induced increase in fibroblast activity causing myocardial collagen deposition and interstitial fibrosis [1]. These processes may be potentially mitigated by early RA treatment if an appropriate patient selection tool is recognized. Strain imaging has proven to be a valuable non-invasive tool for identifying subclinical CVD in other forms of HF [21] and the findings from this study suggest the same may be true for RA.

In this study we thought to evaluate left ventricular function by STE in asymptomatic RA patients without known CVD with short disease duration.

In the current study we found no significant differences in LV diameters, volumes and left ventricular ejection fraction (EF) between the RA and healthy controls.

Consistent to our results, *Sitia et al.,*[5] who evaluated the left ventricular function in 22 RA patients with short disease duration by echocardiography they found that RA patients had normal LV diameters and volumes, and systolic function with no statistically significant differences compared to healthy controls by conventional echocardiography.

Fine et al., [6] studied 87 patients with RA and concluded no significant differences between RA patients and the control group in left ventricular dimensions or LV ejection fraction.

Concordant to our results, *Cioffi et al.,*[22] studied the prevalence and factors related to left ventricular dysfunction in asymptomatic patients with RA by echocardiography. They found that no significant difference between RA patients and control group regarding LV ejection fraction. However, they reported that RA patients had smaller LV volumes compared to control, (LV end diastolic volume was 46 ± 11 ml in RA vs. 52 ± 13 ml in control group, $p< 0.001$).

Similarly, *Hanne et al.,* [23] compared the cardiac function in 85 adult patients with RA to those of healthy control. They concluded that both RA patients and control were comparable concerning the variables of LV systolic function as LV end diastolic dimension (LVEDD) and LV EF [23].

Also, Montecucco et al., [24] were reported no differences in LVEDD and systolic function between RA patients and controls [24].

Discordant to our results Oguz, *et al.*,[25] and Bharti *et al.*,[26] demonstrated an impairment of LV systolic function, reflected by a reduced EF in adolescents with RA [25, 26]. Further, Bharti, *et al.*, [26] and Alkady, *et al.*, [27] have reported a larger LVEDD in children with *RA* compared with controls [26, 27] despite that all values were within normal limits in these studies [25, 26, 27].

In our study we found a significant difference in interventricular wall thickness in RA patients compared to control group (9.65± 1.80 mm vs. 8.53± 1.23 mm, p<0.05).

In agreement with our results, *Hanne et al.*, [23] compared the cardiac function in 85 adult patients with RA with that of healthy controls. They concluded that the interventricular septum was slightly thicker in the patients than in the control group (8±2 mm vs. 7±1 mm, p=0.036) [23]. In their systemic review and meta-analysis, *Carrao et al.*, [28] found a significant effect of RA on the interventricular septum thickness in RA patients which is correlated with our result [28]. **However,** *Vizzardi et al.*, [29] studied an Italian cohort of 93 RA patients compared to healthy controls; they did not show significant effect of RA on the interventricular septum.

We found a highly significant reduction of the average systolic mitral annular wave velocity (S′) in RA patients compared to healthy control (6.39 ±1.13 cm vs 7.17 ±0.64 cm, p< 0.05 respectively) as well as reduction in the average early mitral annular diastolic wave velocity (E′) in RA patients compared to control (8.72±1.91 cm vs. 11.04± 1. 35 cm, p<0.05). A higher E/E′ ratio was found in RA compared to healthy controls in our study.

In concordance with our results, *Cioffi et al.*, [22] found a significant reduction in LV systolic function of myocardial longitudinal fibers measured as S´ in RA patients compared to controls (9.3 ±1.7 cm vs. 10.5 ±2.1cm respectively, $p < 0.001$) and a higher E/E′ ratio in RA compared to control (7.3± 2.4 vs. 6.2 ±1.8, p<0.01).

Correlated with our results, ***Sitia et al.,*** [5] showed that RA patients had a significant reduction in (S′) and (E′) with higher E/E′ ratio compared to healthy controls by TDI parameters.

Also *Hanne et al.*, [23] concluded that diastolic function in patients with RA was altered compared to control group as characterized by high E/ E′ in RA (5.3 vs. 4.8, p<0.05).

We demonstrated a reduced velocity of the LV longitudinal shortening (S′), which might be a sign of minor LV dysfunction in patients with RA. Our results did not support those recently reported by several authors who found no difference in LV systolic function between patients with RA and controls [31, 32]. Using different diagnostic techniques (i.e., echocardiography or cardiac magnetic resonance), they revealed that LV systolic function was preserved in RA and that LV systolic dysfunction could not be considered an intrinsic feature of RA [30, 31].

In our study, we did not detect any significant difference regarding E wave, E/A ratio or deceleration time (DT) between RA patient and control group. This could be explained on the basis of diastolic function is mainly dependent on myocardial relaxation and LV load [32]. The similar findings of transmitral E and A velocities, and isovolumic relaxation time (IVRT) in the patients and controls, indicate that LV relaxation was not affected in the patients with RA. However, the higher (lateral) E/E′ ratio indicate that the patients with RA had higher LV-filling pressures than the controls [33, 34, 35]. An increased LV-filling pressure is usually associated with diastolic dysfunction and heart failure [32, 33].

In our results, we found the LV global longitudinal strain was (LV-GLS) significantly reduced in RA patients compared to control (17.22 ±1.46% vs. 21.98 ±2.48%, p <0.05) respectively.

Our findings are in line with these reported by *Fine at al.*,[6] studied 87 patients with RA, the mean age of matched RA and normal patients was 55.7±12.1 years and 54.5±12.2 years (p=0.42) respectively. LV-GLS was significantly reduced in RA patients compared to normal control (−15.7 ±3.2% versus −18.1 ±2.4%, p<0.001).

In agreements with our results, *Sitia et al.*, [5] evaluated the left ventricular function in 22 RA patients with short disease duration by echocardiography. They found a significant reduction in left ventricular longitudinal and radial strain mainly of basal and mid septal, basal and mid lateral and apical segments in RA patients without coronary artery disease compared to health control [5].

Ikonomidis et al.,[20] studied 46 RA patients without CVD and compared them with 23 healthy controls. Significant differences in LV systolic longitudinal, circumferential and radial strain between RA patients and controls were observed [20].

Meune et al.,[32] compared 27 RA patients without CVD with control subjects and found a significant difference in diastolic strain rate, but not systolic strain rate [32]. These findings contrast to ours and other studies in which systolic strain was significantly different between RA patients and controls. The reason for these discrepant findings may be the smaller number of patients included in the Meune study [32] limiting their statistical power to demonstrate differences, the measurement of strain rate (the rate of myocardial deformation change)

rather than strain, and that strain rate was measured using tissue-Doppler imaging rather than STE. Doppler-based strain measurement has more technical limitations than STE, including a higher imaging frame rate requirement and insonation angle dependency, whereas STE is more automated and is the preferred strain imaging modality for current research and clinical practice [35, 36, 37, 38, 39]. Whereas STE was able to analyze echocardiographic images providing objective and reproducible quantification of global and regional myocardial function. Being based on grey-scale image analysis, STE is not angle-dependent allowing the study of myocardial deformation in 3 spatial dimensions. Basically, longitudinal, circumferential and radial ε reflect regional deformation and end-systolic deformation could be considered a marker of myocardial function.

In our study, we found no significant correlation between LV systolic function measured by conventional M-mode (EF) with the antiCCP level. On the other hand by using more sensitive measure of LV systolic function (LV-GLS), we found a significant negative correlation between LV-GLS and antiCCP level ($r= -0.054$, $p<0.01$) in RA patients.

Our results were in agreement with Brian et al [40] who found highly significant negative correlation between LV function by GLS and antiCCP.

In our study, we did not found any significant correlation between LV- GLS and disease duration.

Heterogeneity of data about the effect of disease duration on cardiovascular risk in rheumatoid arthritis patients were found in literature. Sitia and his colleague [5] found significant negative correlation only between mid septal segment radial strain and disease duration ($p<0.01$, $r=- 0.53$). However, in our study we assess LV- GLS and not the radial or segmental strain. Also our studied patients had relatively shorter disease duration (38.04±16.82 months).

Limitation

This is a prospective, single –center study with small sample size. Thus, our findings require confirmation in larger studies before routine clinical utilization of strain imaging can be recommended in patients with RA.

We chose to measure longitudinal strain only because it has been demonstrated to be the most reproducible when measured using STE and the most sensitive for detecting early stages of myocardial disease, and therefore is the most frequently applied in clinical practice. Circumferential LV strain may in fact remain preserved in patients with HF with preserved LVEF, even at advanced stages so further research examining serial changes in all LV myocardial contractile vectors over time are needed to determine the impact of RA disease progression on ventricular mechanical performance.

Conclusion

RA patients without a history of CVD have impaired LV systolic longitudinal strain as measured using STE in comparison to matched subjects with normal cardiac function and without RA. These findings suggest subclinical myocardial disease may be present in RA patients prior to the development of symptomatic CVD. Strain imaging may represent an effective tool for detection of subclinical CVD, and identifying RA patients at increased risk for developing HF.

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