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ORIGINAL ARTICLE

Detection of Subclinical Left Ventricular Dysfunction in Active Rheumatoid Arthritis during Biological Treatment by Two-Dimensional Speckle Tracking Echocardiography

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Abstract

Background: ***One crucial element in the progression of rheumatoid arthritis (RA) is the cytokine tumor necrosis factor-α (TNF-α).***

Objectives: ***To compare the pre- and post-biological treatment left ventricular (LV) systolic performance in a group of patients with active RA by global longitudinal strain (GLS), a marker of myocardial deformation.***

Methods: ***This prospective trial involved 50 patients with active RA. Erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), Electrocardiogram (ECG), two-dimensional (2D)echocardiography, and 2D speckle tracking echocardiography were assessed.***

Results: ***There was a positive correlation between GLS average length and ejection fraction (EF), fractional shortening (FS), apical 2-chamber view (A2), apical 3-chamber view (A3), and apical 4-chamber view (A4)) post-treatment (P <0.001). There was no correlation between GLS average length and diastolic and systolic dimension, and das score CRP, ESR score, age, sex, biological treatment, and ECG post-treatment. There was a negative correlation between GLS average length and disease duration (P = 0.001). Das scores CRP and Das score ESR were significantly lower in patients post-treatment than in pretreatment (P <0.001). A2, A3, A4, and average were insignificantly different between pre and post-treatment. ECG, diastolic dimension, systolic dimension, EF, FS, and E/A were insignificantly different between post-treatment and pretreatment.***

Conclusion: ***Treatment with anti-TNF-α does not substantially impact global LV systolic function assessed by GLS in a cohort of active RA patients, indicating that these medications have a protective effect. There was no difference in GLS before or after therapy with anti-TNF-α.***

Keywords: LV Dysfunction; Active RA; Biological Treatment; Two-Dimensional Speckle Tracking Echocardiography; ECG

1. Introduction

Tumor necrosis factor-α (TNF-α) is a crucial cytokine in the development of rheumatoid arthritis (RA). The introduction of anti-TNF-α therapies, such as etanercept, infliximab, and adalimumab, has dramatically improved the outcomes of severe RA, exceeding the effectiveness of typical disease-modifying anti-rheumatic drugs (DMARDs) .[1,2]

Studies have shown that Anti-TNF-α medication reduces the risk of cardiovascular (CV) problems in patients with RA. Many factors contribute to this decrease: The benefits observed include a reduction in overall inflammation throughout the body, a decrease in the need for corticosteroid medications, and an increase in the levels of high-density lipoprotein (HDL) cholesterol .[3,4] However, the exact underlying processes have been extensively discussed and analyzed .[3] However, no trials have been condCV objectives in this context. CV risk in persons with RA may be complicatedly evaluated by looking at the impact of anti-TNF-α medicines. Moreover, the increased overall risk of mortality or hospitalization, especially for heart failure (HF), led to the discontinuation of clinical studies that were studying the use of anti-TNF-α medications (etanercept and infliximab) for HF in patients who did not have RA.[5,6]

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A greater risk of HF was identified in the group receiving a high dosage of infliximab (10 mg/kg body weight) compared to the placebo group .[5] These findings have caused worries over the possibility of HF in RA patients who are being treated with infliximab, etanercept, or adalimumab.

Additional evidence is necessary to further our understanding of the impact of anti-TNF-α treatments on cardiac function in individuals with RA who do not have HF. Individuals suffering from severe RA, particularly those with very active illness, have a heightened susceptibility to developing HF. Suppose therapy with anti-TNF-α drugs effectively reduces the inflammatory activity of the rheumatic condition. In that case, it is more likely to have a positive rather than a negative impact on the risk of HF .[7] Heart risk factor screenings and efficient treatment of rheumatic disorders and heart diseases are paramount. Hence, it is crucial to evaluate alterations in myocardial function associated with anti-TNF-α actions. However, there is a lack of information about how anti-TNF-α drugs impact cardiac contractility in the literature. Our comprehension of global ventricular function in RA patients using anti-TNF-α therapy might be improved with the availability of advanced non-invasive methods .[8] Speckle tracking is a novel Echocardiographic method that quantifies the extent of myocardial deformation, referred to as strain, over the whole cardiac cycle. This research investigated alterations in myocardial strain, assessed using speckle tracking echocardiography (STE), in individuals with (the mentioned condition) before and after three to six months of anti-TNF-α treatment .[9]

This study aimed to measure global longitudinal strain (GLS), which reveals the degree of ventricular deformation, to evaluate the left ventricular (LV) 's overall contractile performance. A group of individuals with RA who were actively receiving biological therapy for both the pre-and post-treatment periods was evaluated.

2. Patients and methods

This research was conducted on a cohort of 50 male and female patients who were diagnosed with active RA. It was conducted under the consent of the Ethical Committee of Al Azhar University Hospitals in Cairo, Egypt, and the patients provided their informed written permission.

Exclusion Criteria were cardiac or vascular diseases, pulmonary disease, and hypercholesterolemia.

The patients underwent a series of procedures, including obtaining medical history, doing general and specific physical exams, performing laboratory tests [C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR)], conducting a 12-lead ECG, performing two-dimensional (2D) echocardiography, and 2D speckle tracking Echocardiography.

ECG:

All patients successfully completed the task. The ECGs were calibrated using a standard configuration of 25 mm/s for the paper speed and 10 mm/mV for the amplitude. They may display ST-segment depression, T-wave flattening, or T-wave inversion.

Two-dimensional (2D) speckle tracking Echocardiography:

The examination of speckle tracking was conducted utilizing the commercially accessible automated function imaging approach to assess GLS from apical long-axis slices, which included long-axis and 2- and 4-chamber views, following a previously established procedure.[10,11] The contours of the endocardial boundaries were delineated in the end-systolic frame of the Two-dimensional pictures obtained from the three apical views. Speckles were meticulously monitored in each frame of the left ventricle wall over the cardiac cycle, and distinct areas of interest were established in the basal, mid, and apical regions. The operator manually corrected segments that were only successfully tracked once the program authorized them. LPSS was quantified using apical 2-, 3-, and 4-chamber views. GLS was calculated by taking the average of the longitudinal strain measurements obtained from the segments visible in the 2-, 3-, and 4-chamber views. This resulted in the mean strain value of all 18 segments.

Statistical analysis:

The statistical analysis was conducted using IBM's SPSS v26 software, headquartered in Chicago, IL, USA. The data distribution's normality was evaluated using histograms and the Shapiro-Wilks test. A paired T-test was used to compare numerical data. The data was provided in the form of the mean together with the standard deviation (SD). The subject of mathematics. The Chi-square test was used to compare the categorical variables, represented as frequencies and percentages (%). The Spearman rank correlation equation assessed the correlation between variables that do not adhere to a normal distribution or exhibit non-linear monotonic correlations. The Pearson moment correlation equation was used to calculate linear correlations for variables that adhere to a normal distribution. The statistical significance was established using a two-tailed P value below 0.05.

3. Results

With a standard deviation of 11.78 years, the average age was 52.8/100. Sex was found to be male in 34 cases (68%) and female in 16 patients (32%). 15 patients (30%) had diabetes, thirteen (26%) had hypertension, three (6%) had asthma, 14 (28%) had no health problems, and 10 (20%) were smokers. The mean duration of disease was 6.3 ±5.25 years. 14 (28%) patients were treated by Humira (adalimumab) drug, 21 (42%) patients were treated by Simponi (golimumab) drug, and 15 (30%) patients were treated by Hyrimoz (adalimumab)drug. (Table 1)

Table 1. Demographic data, duration of disease and biological treatment of the studied patients

		N=50
AGE (YEARS)		52.8 ± 11.78
SEX	Male	34 (68%)
	Female	16 (32%)
MEDICAL HISTORY	DM	15 (30%)
	HTN	13 (26%)
	Asthmatic	3 (6%)
	IHD	2 (4%)
	Free	14 (28%)
	Smoker	10 (20%)
DURATION OF DISEASE (YEARS)		6.3 ± 5.25
BIOLOGICAL TREATMENT	Humira (adalimumab)	14 (28%)
	Simponi (golimumab)	21 (42%)
	Hyrimoz (adalimumab)	15 (30%)

Data presented as number or frequency (%), mean±SD, DM: Diabetes mellitus, HTN: hypertension, IHD: ischemic heart disease.

Das score CRP and das score ESR were significantly lower in patients post treatment than pre-treatment (P value <0.001). (Table 2)

Table 2. Das score CRP and ESR pre and post treatment of the studied patients

	PRETREATMENT	POST TREATMENT	P
DAS SCORE CRP	4.9 ± 0.97	4.6 ± 1.01	<0.001*
DAS SCORE ESR	5.3 ± 1.05	5 ± 1.11	<0.001*

Data presented as mean±SD, CRP: C- reactive protein, ESR: erythrocyte sedimentation rate, *: significant P<0.05.

ECG, diastolic dimension, systolic dimension, EF, FS and E/A were insignificantly different between post treatment and pretreatment. (Table 3)

Table 3. ECG and 2D echocardiogram pre and post treatment of the studied patients

		PRETREATMENT	POST TREATMENT	P
ECG	NSR	49 (98%)	49 (98%)	1.000
	NSR RBBB	1 (2%)	1 (2%)	
2D ECHOCARDIOGRAM	Diastolic dimension	5.1 ± 0.43	5.1 ± 0.4	0.079
	Systolic dimension	3.3 ± 0.32	3.3 ± 0.34	0.074
	EF	0.6 ± 0.06	0.6 ± 0.05	0.197
	FS	0.3 ± 0.04	0.3 ± 0.04	0.688
	E/A	0.9 ± 0.11	1 ± 0.1	0.054

Data presented as number or frequency (%), mean±SD, ECG: Electrocardiogram, NSR: normal sinus rhythm, EF: Ejection fraction, FS: Fahr's syndrome, E/A: early to atrial filling velocity ratio. 2D: two dimensional.

Apical 2-chamber view (A2) was significantly higher post treatment than pretreatment (P value 0.04) while apical 3-chamber view (A3) and apical 4-chamber view (A4) were significantly lower post treatment than pretreatment (P value 0.029 and 0.039 respectively). Average was insignificantly different between pre and post treatment. (Table 4)

Table 4. Speckle GLS pre and post treatment of the studied patients

	PRETREATMENT	POST TREATMENT	P
A2	-18.7 ± 2.81	-16.3 ± 6.89	0.040*
A3	-18.8 ± 3	-20.3 ± 2.83	0.029*
A4	-17.7 ± 7.46	-20.2 ± 3.22	0.039*
AVERAGE	-18.2 ± 5.44	-17.8 ± 6.34	0.753

Data presented as mean±SD, GLS: global longitudinal strain. A2: apical 2-chamber view. A3: apical 3-chamber view. A4: apical 4-chamber view. *: Significant P<0.05.

There was positive correlation between GLS average length and (EF, FS, A2, A3 and A4) post treatment (P value<0.001). There was no correlation GLS average length and diastolic and systolic dimension, das score CRP, das score ESR, age, sex, biological treatment, and ECG post treatment. There was a negative correlation between GLS average length and duration of disease (P value = 0.001). (Table 5)

Table 5. Correlation between GLS average length and 2D echocardiogram, das score CRP, das score ESR, demographic data, duration of disease, biological treatment, ECG, and speckle GLS post-treatment of the studied patients

		EF	FS	DIASTOLIC DIMENSION	SYSTOLIC DIMENSION
GLS	r	0.826	0.834	0.126	0.178
	P	<0.001*	<0.001*	0.382	0.215
		Das score CRP		Das score ESR	
GLS	r	0.045		0.051	
	P	0.753		0.722	
		Age	Sex	Duration of disease	Biological treatment
GLS	r	0.041	0.127	-0.448	-0.058
	P	0.775	0.376	0.001*	0.687

r: person coefficient. EF: Ejection fraction, FS: Fahr's syndrome, *: significant, P<0.05, GLS: global longitudinal strain. CRP: C-reactive protein. ESR: erythrocyte sedimentation rate.

4. Discussion

Congestive heart failure (CHF) ranks second among the leading causes of death for people with RA following myocardial infarction. The increased risk of HF may be due to the damage resulting from myocardial infarction and the subsequent creation of scar tissue .[12,13]

In this study, the disease activity score decreased after treatment. Das scores CRP and Das score ESR were significantly lower in patients' post-treatment than in pretreatment (P<0.001). Disease activity has been regarded as a distinct CV risk factor in people with RA. Disease activity ratings can forecast the presence of hidden left and right ventricular dysfunction. This conclusion is congruent with the study conducted by Atzeni et al.[14] which demonstrated a reduction in disease activity after therapy with anti-TNF. Initially, these patients' average Disease Activity Score 28 (DAS28) was 3.9 ± 2.4. Following a thorough assessment of their curriculum vitae, the individuals were administered anti-TNF medications in conjunction with methotrexate at a dosage of 7.5–10 mg per week. Additionally, five patients were prescribed corticosteroids at a daily dose of 5 mg. The Left ventricular ejection fraction (LVEF) and E/A ratio (which indicates the function of the left ventricle) showed no significant differences compared to the control group. After therapy, the DAS28 score showed significant improvement in patients (4.80; IQR: 4.65–5.22 vs 2.78; IQR: 2.52–2.99; p < 0.01). Also, Naseem et al.[15] evaluated Using STE; this research investigates how RA disease activity affects LV and residual volume (RV) functioning. One hundred twenty RA patients were free of cardiovascular disease (CVD)symptoms, and forty healthy people for comparison were part of the research. The values of LV GLS were significantly correlated with RA disease activity ratings. The Simple Disease Activity Index (SDAI) and DAS28 scores demonstrated a correlation between increased disease activity and worse LV GLS. Furthermore, there were notable associations between the level of disease activity scores in RA and the value of RV GLS. Specifically, as the disease activity level rises, the RV GLS value deteriorates for both SDAI and DAS28 scores.

Regarding Speckle GLS, A2, A3, and A4 were insignificantly different between pre-and post-treatment, suggesting a protective role of these drugs. This might be attributed to the inhibitory effect of cytokines on the development of atherosclerotic plaques in the coronary arteries, hence reducing cardiac distress and the risk of HF. Similar findings were obtained by Vizzardi et al.[16] which demonstrated a typical EF both before and after one year of therapy. No significant differences were seen in GLS before or after anti-TNF-α therapy. After 12 months, the administration of anti-TNF-α medication did not substantially impact cardiac contractility. In the same context, Kotyla.[17] this study focused on the epidemiological data about the safety of anti-TNF therapy in patients with RA. The study examined the underlying pathophysiological pathways via which TNF may have varying effects in RA and other disorders. Evidence indicates that inhibiting inflammation may have a cardioprotective impact on people with RA. However, it remains uncertain if TNF functions similarly in people with CHF and RA.

The present investigation found a significant positive association between the average duration of GLS and the post-treatment values of EF and FS (P value<0.001). There was no correlation between GLS average length (diastolic dimension, and systolic dimension).

Also, in this study, there was no correlation between GLS average length and das score CRP and ESR score post-treatment. However, a strong association exists between heightened disease activity and cardiac function in individuals with treatment-naive early RA. Løgstrup et al.[18] found a significant correlation: patient global assessment by VAS, patient fatigue assessment by VAS, and DAS28-CRP; corrected for pertinent confounding variables, including age, gender, pulse, and blood pressure. Moreover, the univariate analysis showed a strong and statistically significant correlation between anti-CCP and GLS. After adjusting for age, gender, pulse, and blood pressure, the correlation remained significant in multivariate analysis. Through strain study of LV function, we observed a notable disparity in GLS between individuals exhibiting elevated levels of anti-cyclic citrullinated peptide (anti-CCP) and those without anti-CCP.

The current study found no correlation between GLS average length and (age, sex, and biological treatment) post-treatment. There was a negative correlation between GLS average length and disease duration (P value = 0.001). Disease duration affected heart function negatively, as proposed by Cioffi et al.[19] A total of 140 outpatients diagnosed with RA and without any apparent cardiac conditions received a comprehensive assessment, including clinical examination, laboratory tests, and echocardiography, both at the beginning of the study and after a follow-up period of 35 months. A CDAI score over 10 indicated the existence of

moderate to high disease activity in RA; information about ACPA positive was documented at the beginning of the study.

This study had no correlation between GLS average length and ECG post-treatment. In contrast, there was a positive correlation between (A2, A3, and A4) post-treatment. There are suggestions to refrain from using antiTNF-α medicines in patients with HF, not only in those with more severe functional classes as described by Danila et al.[20] but also in those with mild symptoms. It is recommended to discontinue medication if symptoms deteriorate. Evaluating the global LV systolic function in individuals with RA is crucial to establish their suitability for anti-TNF-α treatment. Nevertheless, the assessment of LV EF encounters many difficulties associated with picture clarity, the presuppositions of LV structure, and the proficiency of the echocardiographer. 2D strain is a computerized and precise method to quantify the overall long-axis function from gray-scale photographs. The evaluation of longitudinal tissue deformation involves monitoring individual speckles throughout the cardiac cycle on a frame-by-frame basis. The GLS is then determined by taking the mean of 18 cardiac segments, using the method provided by Belghiti et al. [21].

Prior studies have shown a correlation between GLS and measurements of LV function obtained using both echocardiography and magnetic resonance imaging.[10] The GLS assessment was dependable and expeditious across observers of varying levels of expertise [21].

Consistent with the study findings, Karlsen et al.[22] demonstrated that GLS is more reproducible than LVEF, irrespective of echocardiographic training and image quality. The level of training has a greater impact on LVEF calculation. The results of this study endorse the clinical utility of GLS as a valuable adjunct for assessing LV function, with minimal variability observed among observers, including those with limited echocardiographic experience.

Also, Similar findings were obtained by Elbeialy et al.[23] except for a notably lower value of LA GLS in patients with active RA compared to those in remission; there were no significant differences seen between the two groups in any of the measurements. The LA-GLS exhibited a substantial correlation with the RA disease activity score. The functioning of the left atrium is compromised in RA, and this compromise is directly related to the level of disease activity. LAGLS outperforms other methods in identifying subclinical left atrial dysfunction.

Limitations: The sample size was small, and there was probably a short follow-up time. We did not include a control group of healthy individuals of the same gender. The research was conducted in a solitary facility. The study only included female participants, and the research design did not allow for testing the generalizability of these results to the total community of individuals with RA.

4. Conclusion

Treatment with anti-TNF-α does not appear to substantially impact global LV systolic function assessed by GLS in a cohort of active RA patients, indicating that these medications may have a protective effect. There was no difference in GLS before or after therapy with anti-TNF-α.

Disclosure

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Authorship

All authors have a substantial contribution to the article

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