Detection of Myocardial Dysfunction using Global longitudinal strain with Speckle-Tracking Echocardiography in Patients with vs without Rheumatoid Arthritis: A Systematic Review and Meta-analysis

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Abstract

Purpose Rheumatoid arthritis (RA) is a systemic autoimmune disorder primarily involving the peripheral joints. Systemic involvement can occur, including myocardial dysfunction. Speckle tracking echocardiography (STE) is a novel diagnostic study that is recently being used to detect subclinical cardiac dysfunction. Global longitudinal strain (GLS) by STE is more sensitive than standard echocardiographic parameters to detect occult cardiac dysfunction. Methods A systematic search of PUBMED, EMBASE, Cochrane, and Google Scholar databases was performed to identify studies comparing the STE parameters between RA and non-RA patients. Results Left ventricular (LV) GLS was significantly lower in patients with RA compared to non-RA patients with a standard mean difference (SMD) of -1.09 (-1.48 to -0.70, $P < 0.001$). LV Global Circumferential Strain (GCS) was reported in five studies and it was found to be lower in RA patients with an SMD of -1.25 (-2.59 to -0.10; $P < 0.0010$). Meta-regression analysis studies failed to show any significant impact of disease duration, activity, age, sex, and BMI on LV GLS and RV GLS. Conclusions RA patients have lower LV GLS and LV GCS compared to controls suggesting impaired myocardial dysfunction. Further studies need to be done to delineate the importance of lower GLS in asymptomatic rheumatoid patients to guide disease management and risk factor modification in this selected population.

Introduction

Rheumatoid arthritis (RA) is a chronic systemic inflammatory autoimmune disease of unknown etiology that affects about 0.5 to 1% of the global adult population [1,2]. Previously, there has been established evidence of accelerated atherosclerotic coronary artery disease associated with chronic inflammation and resultant significant cardiovascular morbidity in RA [3]. However, recently research focus has shifted towards exploring the proposed mechanism of inflammation leading to congestive heart failure (CHF) in the RA patient cohorts [4,5]. The Incidence of CHF in RA was estimated at 21%-34% from the recent population-based cohort studies, and the disease activity in RA is strongly correlated with progression of CHF [6,7]. Given the early onset and accelerated risk of cardiovascular events in RA, early detection of subclinical cardiovascular disease including CHF is important to improve the overall prognosis.

Speckle tracking echocardiography (STE) is a novel diagnostic tool that can provide insight into the functionality of individual myocardial fiber layers and can be clinically utilized to assess subclinical and overt myocardial dysfunction. Specifically, Global longitudinal strain (GLS) by STE is more sensitive than left ventricular ejection fraction (LVEF) by conventional 2D echocardiogram to assess myocardial dysfunction [8]. Recent studies have supported the superior prognostic role of GLS for predicting major adverse cardiac events compared to LVEF [9,10,11,12]. Furthermore, a noninvasive imaging biomarker like GLS that assesses inflammatory myocardial dysfunction allows for personalized risk assessment in RA patients, helps maximize risk reduction strategies and will be an invaluable tool for research and clinical use. However, the role of GLS in identifying the early cardiovascular disease in RA patients is limited. Therefore, we performed a systematic review and meta-analysis of all published studies comparing myocardial function by GLS in RA versus non-RA patients.

Materials And Methods

An application was initially submitted to Creighton University biomedical IRB and received an exempt status.

This systematic review and meta-analysis were conducted in accordance with Cochrane collaboration guidelines and reported according to the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA) [13,14].

A comprehensive search of major electronic databases including PubMed, EMBASE, Cochrane reviews, and Scopus was conducted from inception through September 2020, by two independent reviewers (VT and RB). The following keywords were used: "*speckle tracking echocardiography*", "*Rheumatoid arthritis*", "*global longitudinal strain*", and "*circumferential strain*". The search strategy was not limited by language and publication year.

The reference lists of selected articles were manually reviewed. We did not attempt to contact the authors of the articles for retrieving additional information or clarifications. Inclusion criteria: 1) Studies including 2 groups with and without RA and reported their data as mean with standard deviations. 2) Studies reported outcomes of left ventricular (LV) global longitudinal strain (GLS) and/or Global circumferential strain (GCS), and/or right ventricular (RV) strain in both groups. 3) Patients with underlying ischemic

heart disease and heart failure were excluded in the selected studies. Case reports, case series without a control group, reviews, and animal studies were excluded.

Data extraction:

The data extraction was performed using a pre-specified data collection form. The collected data included baseline characteristics of the included studies and participants, sample sizes, and outcomes values. The primary outcome of interest was left ventricular global longitudinal strain, and the secondary outcomes were LV circumferential strain and right ventricular GLS.

Statistical analysis:

For each study, all outcome data were abstracted as reported or figure-calculated means and standard deviations, which were utilized to conduct a random-effects meta-analysis. The standard deviations from both the RA and non-RA patient groups were pooled in order to calculate standardized mean differences (SMDs). We examined heterogeneity between studies with the I^2 statistic based on Cochran's Q (0% to 100%). Heterogeneity was defined as low (25% to 50%), moderate (50% to 75%), or high (>75%).

Regarding meta-regression, we evaluated heterogeneity across studies with a likelihood ratio test (LRT) for each outcome, which was estimated as the difference of -2 REML log-likelihoods generated from models with and without a random effect of study for each outcome. The resulting difference (LR) was assumed to follow a chi-square distribution with one degree of freedom. We added the study-specific factor of the mean duration of disease and DAS28 separately if there were at least three studies with available information. We examined age, BMI, gender, ESR, and CRP in a similar manner. For each predictor, we calculated the Pearson correlation coefficient and presented it as R^2 to examine the relationship with the predicted outcome. SAS v. 9.4 (SAS Institute, Inc, Cary, NC) and Stata 15.1 were used for all analyses; $P < 0.05$ indicates statistical significance.

Results

Overall, a total of 13 studies with 1516 patients were included in the meta-analysis that met predefined inclusion and exclusion criteria (Figure 1) [15-27]. The major characteristics of all the included studies and baseline characteristics are outlined in Table 1 and Table 2. The mean age was 52.7 years and about 68 % were females.

LV GLS and GCS:

All the 13 studies reported data on LV GLS, and the pooled analysis showed LV GLS was significantly lower in patients with RA compared to non-RA patients with a SMD of -1.09 (95% CI: -1.48 to -0.70, $P < 0.001$) with a high heterogeneity of $I^2 = 91.2\%$ (Figure 2).

The LV GCS was reported in five studies, and it was found to be lower in RA patients with an SMD of -1.25 (95% CI: -2.59 to -0.10; $P < 0.001$; $I^2=96.7\%$) (Figure 3).

Meta-regression model of the studies on LV GLS did not show any impact of disease duration (effect size change for every additional year of disease duration: 0.09, 95% CI: -0.02 to 0.20, $P = 0.088$) or DAS28 (effect size change for every additional unit of DAS28: -0.14, 95% CI: -0.80 to 0.51, $P = 0.623$) (Table 3). Disease duration and DAS28 explained 28.9% and 3.6% of the total variability, respectively. Similarly, no effect was found for age, BMI, gender, ESR and CRP.

RV GLS:

Four studies reported RV GLS and there was no statistical evidence of a difference between RA and non-RA patients with an SMD of -0.54 (95% CI: -1.47 to 0.39; $P = 0.254$); $I^2=94.0\%$ (Figure 4).

There was no statistical evidence of a change in effect size upon examination of disease duration (effect size change for every additional year of disease duration: 0.89, 95% CI: -2.09 to 3.87, $P = 0.164$), which explained 93.4% of the total variability (Table 4). There was no relationship between age, gender, and CRP to RVGLS.

Discussion

In our meta-analysis, we investigated the STE parameters including LV GLS, LV GCS, and RV GLS among patients with and without RA. The major findings were: 1) The RA patients had reduced LV GLS and GCS when compared to non-RA patients. 2) There is no statistically significant difference in RV GLS between RA patients and non-RA patients. 3) The disease duration, disease activity (DAS28), age, sex, ESR, and CRP levels did not have an impact on the overall LV and RV GLS.

Pathophysiology of LV dysfunction in RA:

Various pathophysiological mechanisms have been studied for a better understanding of HF in patients with chronic inflammation. It is proposed that cardiac myocytes react to chronic inflammation by producing cytokines and cell adhesion molecules, which increases the recruitment of leukocytes within the cardiac cell and reduces the myocardial contractility [28]. In addition, according to Lim et al, chronic inflammation leads to microvascular and endothelial dysfunction which causes myocardial remodeling and fibrosis, leading to LV dysfunction [29]. Similar evidence was demonstrated using evaluation with Cardiac magnetic resonance (CMR) which offers reliable information regarding myocardial inflammation and fibrosis. CMR findings on T2- weighted imaging and late gadolinium enhancement suggestive of inflammation and fibrosis respectively, were significantly associated with higher NT-proBNP among RA patients. This suggests that alterations in myocardial structure precede clinical HF [30].

Speckle-tracking Echocardiography:

The LV myocardium has a spiral architecture with myocardial fibers in two orientations, longitudinal in the endocardial region and epicardial region, and circumferential in the mid-wall. This contributes to longitudinal, circumferential, and radial strain during LV contraction. In addition, the helical orientation of the myocardial fibers results in LV torsional strain from a twisting motion. Assessment of LV function using ejection fraction (EF) alone has intrinsic limitations of inter and intraobserver variability [31]. Speckle-tracking is a sophisticated semi-automated method to evaluate the complicated myocardial mechanics and LV strain [32]. It addresses the limitations of EF and is currently considered the most accurate and sensitive parameter for the assessment of early left ventricular dysfunction. GLS was noted to be more reproducible and clinically useful compared to circumferential and radial strains [33,34].

Significance of Measuring Strain using STE in RA:

In 2009, Ikonomidis et al first studied association of RA with reduced LV GLS in a small cohort of 46 patients and later several investigators reported similar results. The findings of our meta-analysis are consistent with prior reports and by including about 1516 patients (861 with RA and 665 without RA) we increased the power to estimate the association between RA and early myocardial dysfunction. Recently, a large cohort study by Mantel et al including about 12,943 newly diagnosed and 45k established RA patients showed the increased risk of nonischemic cardiomyopathy in RA patients with Hazard's ratio of 2.06 (95% CI: 1.37 to 3.20) and 1.71 (95% CI: 1.57 to 1.87) respectively [35].

In our cohort, the prevalence of traditional risk factors for cardiovascular disease including hypertension (21.3%), diabetes (5.5%), obesity and cigarette smoking was low when compared to the population within this age group (In age group 40-59 yrs, prevalence of hypertension and diabetes was 33% and 10% respectively). Even with this low burden of comorbidities, RA patients had lower LV

GLS, suggesting this finding may be used as a better risk predictor for cardiovascular disease compared to the traditional risk factors.

Naseem et al in 2018 established that there is a positive correlation between disease activity (DAS28 score) and reduction in RV and LV GLS [25]. A significant improvement in GLS with better disease control while undergoing treatment with TNF and Interleukin inhibitors has also been shown [15-18, 36]. In contradiction, the meta-regression model of our analysis did not find any association between GLS and disease duration or activity or inflammatory markers. This can possibly be explained by the loss of individual patient characteristics in the pooled analysis.

Right ventricular GLS by STE is a better indicator of RV function when compared to conventional echocardiographic parameters like RV fractional area change (FAC) and tricuspid annular plane systolic excursion (TAPSE) [37-39]. This can be used as a prognostic tool in assessing the mortality risk among patients with heart failure [40,41]. However, the clinical relevance of detecting RV dysfunction in patients without any cardiovascular disease is not well established.

Limitations:

Potential limitations for our study include differences in inclusion and exclusion criteria of the studies included and the differences in the patient characteristics in terms of cardiovascular risk factors and comorbidities. Meta regression analysis done failed to reveal any correlation to age, sex, BMI and disease activity. This was surprising as we suspected patients with more severe RA, characterized by high disease activity or inflammatory markers would have worsened cardiac dysfunction in our pooled analysis. Loss of individual patient characteristics in the pooled analysis might possibly be responsible for this.

There is significant heterogeneity documented among studies on LVGLS, LV GCS and RV GLS. Although GLS is more reproducible and reliable compared to other strain parameters, there is a concern for heterogeneity among comparison of data extracted by different echocardiography machines and different software used. We accounted for the heterogeneity among the studies by using a random effects approach in the meta-analysis.

Future Directions:

Overall, there is an increased incidence of HF in RA patients, and with STE we can detect early cardiac dysfunction. Among patients undergoing anthracycline-based chemotherapy, LV surveillance using GLS had increased the use of cardioprotective therapy (beta-blocker or Angiotensin converting enzyme inhibitor/Angiotensin receptor blocker) thereby reducing the incidence of cardiac dysfunction [42]. While there is no supportive evidence of starting cardioprotective medications in RA patients with low GLS at this time, we believe there is a necessity for further research in this area.

Conclusion

STE can detect and measure subclinical myocardial dysfunction in rheumatoid arthritis patients facilitating better risk prediction for cardiovascular disease and personalized treatment in this high-risk group. Further studies are necessary to establish the role of early screening for myocardial dysfunction and starting cardioprotective therapy among this patient population.

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Authors contribution:

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by [Raahat Bansal] [Sonia Gupta] [Venkat s. Pajjuru] [Dixitha Anugula] and [sarah Aurit]. The first draft of the manuscript was written by [Vinay K. Thallapally] [Abhishek Thandra] [Ahmed Aboeata] [Joseph Nahas] and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Ethics:

This is a meta-analysis, and no ethical approval is required.

Abbreviations

LVEF: Left ventricular Ejection Fraction

STE: Speckle Tracking Echocardiography

GLS: Global Longitudinal Strain

GCS: Global Circumferential strain

SMD: Standard mean difference

Tables

Table 1. Studies included in the meta-analysis and individual characteristics.

Study	Type of study	Countries	Strain software	Comments
Ikonomidis et al, 2009 n=69 RA=46 Non-RA=23	Observational study	Greece	Echopac (GE Medical systems, Horten, Norway)	The LV GLS strain was lower in RA patients (-18.5% vs -22.5%, P=0.002). LV dysfunction improved in patients after treatment with IL-1 inhibitors.
Fine et al, 2014 n=118 RA=59 Non-RA=59 males=90	Observational study, retrospective	Minnesota, USA	Syngo Velocity Vector Imaging (VVI) software (version 3.5) (Siemens Medical Solutions, Malvern, Pennsylvania)	Global LV strain reduced in RA patients compared to control group (-15.7±3.2% vs -18.1±2.4%, P<0.001). RA patients had reduced RV GLS. The reduced strain values are associated with RA disease severity and treatment.
Ikonomidis et al, 2014 n=50 RA=20 Non-RA=30	Double blind randomized control trial	Greece	Echopac (GE Medical systems, Horten, Norway)	After anakinra, there was a greater improvement in longitudinal strain values (33±5% vs 18±2%).
Ayyilidiz et al, 2015 n=68 RA= Non-RA=	Observational study, Prospective	Turkey	QLAB 6.0 (Philips Medical Systems, Bothell, Washington, USA)	The LV GLS was lower in RA patients (16.5% vs 20%, P<0.01). Patients treated with infliximab experienced a significant increase in GLS. No significant changes were observed among patients treated with prednisolone.
Magda et al, 2016 n=46 RA=29 Non-RA=17	Cross sectional study	Romania	Not reported	Correctly treated RA with normal inflammatory markers have reduced RV GLS suggesting subclinical RV dysfunction.
Midtbo et al, 2016 n=124 (active RA vs control) RA= 78 Non-RA= 46	Observational study, retrospective	Norway	EchoPAC BT12 software (GE Vingmed Ultrasound)	Active RA patients had lower LV GLS compared to RA patients in remission and control group. No significant difference in GLS among RA patients in remission vs controls.
Mohammed et al, 2016 n=83 RA=50 Non-RA=33	Observational study, single center	Egypt	EchoPAC version 110.1.2	LV GLS is reduced in RA compared to controls (-17.2% vs -21.9%, P<0.05).
Hamdy et al, 2017 n=90 RA=50 Non-RA=40	Cross sectional study	Egypt	EchoPAC version 110.1.2	LV GLS is low in RA patients (-17.7% vs 20%, P=0.0001). LV GLS significant negative correlation with disease activity (DAS 28 score) and inflammatory markers (ESR and CRP).
Cioffi et al, 2018 n=388 RA= Non-RA=	Observational study, prospective	Italy	XStrain 2D speckle-tracking technology software (Esaote Biomedica)	In normotensive cohort, RA patients had lower GLS compared to controls (-18.6% vs 20%, P=0.02) LV GLS is an independent predictor of all-cause and cardiovascular hospitalizations among normotensive RA patients.
Gullo et al, 2018 n=99 RA=41 Non-RA=48	Observational study, prospective	Italy	EchoPAC, version 8.0.0	RA patients exhibited impaired GLS (-18% vs -23%, P<0.001%) and GCS (-20% vs -24.5%, P<0.001) compared to healthy controls with negative correlation to disease activity (DAS 28 score).
Naseem et al, 2018 n=121 RA=81 Non-RA=40 Remission=39	Observational study, prospective	Egypt	Echo Pac, GE Vivid E9 echocardiography system version 113	RA patients had reduced LV GLS and RV GLS with negative correlation with RA disease activity (DAS28 and SDAI score).
Hanvivadhanakul et al, 2019 n=120	Cross sectional study	Thailand	Excelera workstation (QLAB11, Philips)	LV GLS significantly lower in RA patient's vs controls (-17.6% vs 20.4%, P=0.03).

RA=60 Non-RA=60				Multivariate regression analysis demonstrated significant correlations between subclinical LV dysfunction with disease duration and activity.
Nikdoust et al, 2020 n=70 RA=35 Non-RA=35	Observational study, retrospective	Iran	Not reported	LV and RV GLS was significantly reduced in RA patient compared to healthy subjects (-19.5% vs -20.4% and -18.7% vs -21.7%).

RA=Rheumatoid arthritis; GLS=Global Longitudinal strain; GCS=Global circumferential strain; LV=Left ventricle; RV=Right ventricle

Table 2. Demographic and clinical data of subjects enrolled in included studies

study	RA* patients (n)	Non-RA controls (n)	Age (years)	Females(n)	BMI (kg/m2)	Hypertension (%)	Smokers (%)	Hyperlipidemia (%)	Diabetes (%)
ikonomidis et al	46	23	56	31	28.6	20	13	13	9
Fine et al	59	59	55.7	45	29.1	50	26	42	8
Ikonomidis et al	20	30	58	14	29.3	9	8	N/A	N/A
Ayyildiz et al	38	30	52.1	38	30.5	10	5	2	8
Magda et al	29	17	55.5	28	27	16	0	13	1
Midtbø et al	78 41	46	60.7 62.1	60 31	25.5 25.6	0	19 6	0	0
Mohamed	50	33	45.8	44	N/A	0	N/A	N/A	N/A
Hamdy et al	50	40	35.4	46	N/A	N/A	N/A	N/A	N/A
Cioffi et al	194	194	54	63	24.4	0	40	52	3
Gullo et al	41	58	46.5	32	25.15	0	0	0	0
Naseem et al	120	40	54.52 55.08	55 27	N/A	0	12 7	N/A	0
Hanvivadhanakul et al	60	60	50	55	22	0	3	17	0
Nikdoust et al	35	35	43.33		N/A	N/A	N/A	N/A	N/A

*RA=Rheumatoid arthritis

Table 3: Meta-regression analysis - Impact of various variables on change in effect size of Left Ventricular Global Longitudinal strain in Rheumatoid Arthritis.

	Estimate (95% CI)	P	R ²
Disease Duration (per additional year)	0.09 (-0.02 to 0.20)	0.088	0.289
DAS28 (per 1 unit increase)	-0.14 (-0.80 to 0.51)	0.623	0.036
Age (per additional year)	0.03 (-0.05 to 0.10)	0.411	0.062
BMI (per 1 kg/m ² increase)	-0.01 (-0.30 to 0.28)	0.932	0.001
Gender (per 1% increase)	-0.01 (-0.04 to 0.03)	0.791	0.007
ESR (per 1 unit increase)	-0.02 (-0.08 to 0.04)	0.393	0.124
CRP (per 1 unit increase)	0.01 (-0.07 to 0.08)	0.872	0.003

BMI=Body mass index; DAS=Disease activity score; ESR=Erythrocyte sedimentation rate; CRP= C=reactive protein

Table. 4. Meta-regression analysis - Impact of various variables on change in effect size of Right Ventricular Global Longitudinal strain in Rheumatoid Arthritis.

	Estimate (95% CI)	<i>P</i>	<i>R</i> ²
Disease Duration (per additional year)	0.89 (-2.09 to 3.87)	0.164	0.934
Age (per additional year)	-0.01 (-0.40 to 0.38)	0.906	0.009
Gender (per 1% increase)	0.09 (-0.01 to 0.19)	0.058	0.992
CRP (per 1 unit increase)	0.07 (-0.59 to 0.73)	0.397	0.659

CRP=C-reactive protein

Figures

Flow chart showing identification and selection of studies included in the meta- analysis (according to PRISMA guidelines)

Figure 1

Flow chart showing identification and selection of studies included in the meta-analysis (according to PRISMA guidelines)

Figure 2

Left ventricular Global Longitudinal Strain in patients with Rheumatoid Arthritis (RA) and controls.

Figure 3

Left ventricular Global Circumferential Strain in patients with Rheumatoid Arthritis (RA) and controls.

Figure 4

Right ventricular Global Longitudinal Strain in patients with Rheumatoid Arthritis (RA) and controls.