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Rheumatoid Arthritis is Associated with Left Ventricular Concentric Remodeling: Results of a Population-based Cross-sectional Study

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Abstract

Objective—To study left ventricular (LV) geometry in patients with rheumatoid arthritis (RA) who have no heart failure (HF) versus subjects without either RA or HF, and to determine the impact of RA on LV remodeling.

Methods—A cross-sectional, community-based study was conducted among adult (>50 years) RA patients and age- and sex-matched non-RA subjects without a history of HF. All participants underwent a standard 2D/Doppler echocardiography. LV geometry was classified into four categories based on relative wall thickness and sex-specific cut-offs for LV mass index: concentric remodeling, concentric hypertrophy, eccentric hypertrophy, or normal geometry.

Results—The study included 200 RA patients and 600 matched non-RA subjects (mean age 65; 74% female in both cohorts). RA patients were significantly more likely to have abnormal LV geometry than non-RA subjects (odds ratio [OR] 1.44; 95% confidence interval [CI] 1.03, 2.00), adjusting for cardiovascular risk factors and comorbidities. Among those with abnormal LV geometry, RA patients had significantly increased odds of concentric LV remodeling (OR 4.73; 95% CI 2.85, 7.83). In linear regression analyses, LV mass index appeared to be lower in RA patients currently using corticosteroids (Beta $\pm$ standard error: -0.082 ± 0.027 ; $p=0.002$), adjusting for cardiovascular risk factors and comorbidities.

Conclusion—RA was strongly associated with abnormal LV remodeling, particularly, with concentric LV remodeling, among patients without HF. This association was significant beyond adjustment for cardiovascular risk factors and comorbidities. RA disease related factors may promote changes in LV geometry. The biological mechanisms underlying LV remodeling warrant further investigation.

Keywords

rheumatoid arthritis; left ventricular remodeling; risk factors

Patients with rheumatoid arthritis (RA) experience an excess risk of heart failure (HF) and associated mortality compared to the general population (1). Chronic inflammation plays a pivotal role in this increased risk. Despite the growing body of research on cardiovascular (CV) disease in RA, the key pathways underlying the development of abnormalities in myocardial structure and function associated with HF remain obscure. While the nature of impairments of left ventricular (LV) function appears to be complex, pathologic LV remodeling may contribute to impaired LV filling and/or relaxation, resulting in the subsequent progression of myocardial dysfunction and ultimate development of HF in RA (2).

The patterns of LV remodeling and their associations with inflammatory markers have been described in large studies of the general population (3). The implications of these findings for patients with chronic inflammatory diseases are unclear. We aimed to provide new insights into myocardial disease in RA by evaluating LV geometry in RA and non-RA subjects without HF.

Methods

This cross-sectional population-based study was conducted using the Rochester Epidemiology Project (REP), a unique centralized community-wide medical record linkage system (4).

From the previously assembled cohort of Olmsted County, Minnesota residents aged 18 years who fulfilled 1987 American College of Rheumatology criteria for RA we identified eligible patients who were 50 years old, currently residing in Olmsted County, and had no HF based on Framingham criteria. Each patient with RA was matched for age and sex to 3 non-RA subjects without HF from the same underlying population. As part of a population-based study of the burden of LV dysfunction in the community, the non-RA subjects underwent detailed echocardiographic evaluation according to predefined protocols (5). The study protocol was approved by Institutional Review Boards of Mayo Clinic and Olmsted Medical Center. Written informed consent was obtained from all participants.

All participants completed a questionnaire regarding HF symptoms, CV risk factors and medication use. The following CV risk factors were ascertained based on medical record review and questionnaire as previously described (6): smoking (current/former); diabetes mellitus; dyslipidemia; body mass index (BMI; kg/m²); and hypertension. Metabolic syndrome was defined according to the NCEP/ATPIII criteria. History of ischemic heart disease (IHD, i.e., angina pectoris, coronary artery disease, myocardial infarction [MI; including silent events], and coronary revascularization) was ascertained.

Medical records of RA patients were reviewed to determine RA duration and the presence of radiographic joint erosions. RA patients completed the health assessment questionnaire (HAQ), and questionnaire regarding the use of systemic corticosteroids (i.e., oral/parenteral forms of prednisone, methylprednisolone, hydrocortisone, and/or dexamethasone), disease-modifying antirheumatic drugs (DMARDs: methotrexate, hydroxychloroquine, sulfasalazine, leflunomide, and/or azathioprine), biologic response modifiers (BRM: tumor necrosis factor-alpha [TNF-alpha] blockers, anakinra, abatacept, and/or rituximab), non-steroidal anti-inflammatory drugs and coxibs. The medication use was verified with patients' pill bottles and medical records.

For RA patients, serum creatinine, C-reactive protein (CRP), rheumatoid factor (RF), anti-citrullinated protein antibodies (ACPA), TNF-alpha, interleukin-6 and brain natriuretic peptide (BNP) were measured in the provided blood sample. For non-RA subjects, the most

recent clinically obtained serum creatinine value within 6 months before/after the study visit was used. The serum creatinine assay was standardized (7) in October 2006, and we adjusted previous serum creatinine levels by subtracting 0.14 mg/dL, the mean change in donor serum creatinine levels after standardization. Glomerular filtration rate (GFR) was estimated using CKD-EPI formula. $GFR < 60 \text{ ml/min/1.73m}^2$ was considered abnormal.

Two-dimensional/Doppler echocardiography was performed in all subjects by registered diagnostic cardiac sonographers blinded to disease status following identical protocols for both cohorts (5). The findings were interpreted in the Mayo Clinic Echocardiographic Laboratory by expert cardiologists (BLK&DDB). The following parameters were assessed: septal (SWT) and posterior wall thickness (PWT) at end-diastole; LV internal diameter (LVID) at end-diastole and end-systole; relative wall thickness (RWT); LV mass; LV mass normalized to body surface area (BSA, g/m^2) and height ($\text{g/m}^{2.7}$) (2). RWT was calculated based on PWT and LVID at end-diastole. $RWT \leq 0.42 \text{ cm}$ was considered normal. The end-diastolic estimates of PWT, SWT and LVID normalized to BSA were used for LV mass index (LVMI) calculation by Devereux's formula. The LVMI cut-offs were: 95 g/m^2 for females and 115 g/m^2 for males (3). LV geometry was classified as: 1) Concentric remodeling: normal LVMI and $RWT > 0.42 \text{ cm}$; 2) Concentric hypertrophy: increased LVMI and $RWT > 0.42 \text{ cm}$; 3) Eccentric hypertrophy: increased LVMI and $RWT \leq 0.42 \text{ cm}$; 4) Normal geometry: normal LVMI and $RWT \leq 0.42 \text{ cm}$ (2). The following echocardiographic parameters including diastolic function measures were also assessed: pulmonary arterial pressure, left atrial volume index, tricuspid regurgitant jet velocity, pulsed-wave Doppler examination of mitral inflow peak early filling velocity (E) and velocity at atrial contraction (A) (before and during Valsalva maneuver) and of pulmonary venous inflow; Doppler-tissue imaging of the mitral annulus, E/A ratio, E/E' ratio and deceleration time.

Characteristics were compared between cohorts using chi-square and Wilcoxon rank-sum tests. Logistic regression models were used to examine the association between RA and abnormal LV geometry vs. normal geometry, and separately among patients with abnormal LV geometry, to identify association with concentric remodeling vs. concentric/eccentric hypertrophy. Linear regression models of log-transformed values were used to study the associations of LV measures with RA characteristics. These analyses were adjusted for CV risk factors and comorbidities: age, sex, smoking, diabetes mellitus, dyslipidemia, BMI, waist circumference, hypertension, IHD and GFR. To ensure full adjustment and reduce the bias of overfitting, a model including all adjustors was fit first, and its coefficients were held fixed when each RA characteristic was assessed. Multivariable models containing multiple RA characteristics were not examined.

Results

The study included 200 patients with RA and 600 age- and sex-matched non-RA subjects without HF (Table 1). The patients with RA had an unfavorable CV risk factor profile compared to the non-RA subjects. However, GFR values were higher in RA vs non-RA subjects, possibly due to glucocorticoid-induced increase in GFR (8). There were significant differences in echocardiographic measures between the cohorts (Table 2). LV mass normalized to BSA and LV mass normalized to height^{2.7} were lower in RA vs non-RA subjects, while RWT was higher in RA. Differences in LV diastolic function between the cohorts were consistent with our earlier studies (6). The differences persisted after adjustment for CV risk factors and comorbidities (Table 2).

Figure 1 shows the prevalence of LV geometry patterns. RA patients were less likely to have normal geometry (42.5%) than non-RA subjects (53.2%, $p=0.009$). Concentric remodeling was more prevalent in RA vs. non-RA cohort (44% vs. 19.2%, respectively, $p<0.001$) and

was the most common type of abnormal geometry in RA. In contrast, eccentric hypertrophy was less common in RA vs. non-RA cohort (6.5% vs. 17.3%, respectively, $p<0.001$). The prevalence of concentric hypertrophy was similar in both cohorts. Adjusting for CV risk factors and comorbidities, RA patients remained significantly more likely to have abnormal LV geometry than non-RA subjects (OR 1.44; 95%CI 1.03, 2.00). Among those with abnormal geometry, RA patients were significantly more likely to have concentric remodeling (OR 4.73; 95%CI: 2.85, 7.83) than non-RA subjects, even after adjusting for CV risk factors and comorbidities.

Table 3 shows RA characteristics and their associations with LV measures adjusting for CV risk factors and comorbidities. LVMI was lower among current corticosteroid users (Beta $\pm$ SE: -0.082 ± 0.027 ; $p=0.002$), but not in past corticosteroid users (-0.027 ± 0.025 ; $p=0.40$). The association of the cumulative corticosteroid dose with LVMI was not statistically significant ($p=0.73$). In the unadjusted model LVMI was higher for patients with higher CRP (0.026 ± 0.010 ; $p=0.015$) and RWT was positively associated with HAQ (0.044 ± 0.021 ; $p=0.031$). Both these associations were attenuated after adjusting for risk factors and comorbidities ($p=0.37$ and $p=0.25$, respectively, Table 3). Consistent with existing evidence, increased BNP tended to be associated with higher LVMI; however this association was of borderline statistical significance. The associations of RA characteristics with abnormal LV remodeling, in particular with concentric LV remodeling, did not reach statistical significance (data not shown).

Discussion

This large population-based cross-sectional study is among the first to report an association of RA with abnormal LV remodeling, especially concentric remodeling, even after adjusting for CV risk factors and comorbidities. Adverse LV remodeling and LV hypertrophy have been linked to the development of HF and CV-associated morbidity and mortality in the general population (9). Concentric remodeling has been shown to confer a detrimental impact on CV risk similar to that observed with LV hypertrophy (10). This suggests that adaptive changes of LV geometry, even in asymptomatic patients with normal LVMI, can be predictors of poor CV prognosis and may represent potential targets for intervention.

Despite its clinical importance, the literature regarding characteristics and prognostic implications of LV remodeling in RA is scarce. Of the few studies on LV structure in RA (11–13), only one study classified RA patients according to the types of LV geometry (13). In that study 15 of 16 patients with LV hypertrophy had eccentric hypertrophy; none of the patients had concentric remodeling. The small sample in this study and differences in patient characteristics, i.e., younger age, lower prevalence of CV risk factors and comorbidities, compared to our study preclude fair comparison of the results.

While RA itself clearly appears to be associated with abnormal LV remodeling, only few RA characteristics emerged as determinants for these changes. The use of corticosteroids, but not other antirheumatic medications, was associated with lower LVMI. Decreased LVMI following corticosteroid treatment was reported in experimental models of acute MI, and explained by the activation of endothelial nitric oxide synthase (14). However, the lack of association of past corticosteroid use and cumulative corticosteroid exposure suggests that this is not causal and possibly mediated by inflammation status.

CRP tended to be positively associated with LVMI, and HAQ tended to be associated with RWT in the RA cohort. A similar association of CRP with LV hypertrophy was reported in RA patients, as well as in elderly subjects from the general population (3, 13). Conversely, ACPA and biologics, but not corticosteroids, were associated with lower LV mass in RA in

cardiac MRI studies (12). Concordant with our study, the authors reported lower LV mass in RA vs. non-RA subjects. In contrast, some studies have reported increased LV mass in RA vs non-RA subjects (11, 13). Considering that myocardial structure can change over time, these seemingly contradictory findings may be explained by sequential changes in LV mass in the course of systemic disease. Indeed, RA duration has been suggested to be independently associated with LV mass (13). Taken together, these findings suggest that autoimmune inflammatory markers are likely to mediate myocardial remodeling, and this effect may be further modified by antirheumatic treatments.

Study limitations

The cross-sectional nature of this analysis does not permit us to infer the mechanisms of myocardial alterations. Longitudinal studies are needed to better understand the progression of myocardial remodeling in RA and its impact on HF. Definitive conclusions should not be made regarding the cause-and-effect relationships of the reported associations. Due to the voluntary nature of the study, the possibility of participation bias could not be fully excluded. However, a previous study of these cohorts found that the differences between RA participants and non-participants were similar to those in non-RA subjects (15). Thus, participation bias is unlikely to significantly influence the comparisons.

Study strengths

This is the first large population-based study of subjects without HF, comparing LV remodeling in RA and age- and sex-matched non-RA subjects. The study included subjects from two large population-based NIH-funded cohorts assembled through the REP, who were representative of subjects with and without RA in the community. A standardized echocardiography protocol with detailed review and interpretation by expert cardiologists was used for all subjects which we believe increased the validity of the results. The use of comprehensive inpatient and outpatient medical records, including RA characteristics and CV risk factors, further strengthens the results.

In conclusion, RA is associated with abnormal LV remodeling, especially with concentric remodeling among patients without HF, and this association is significant beyond adjustment for traditional CV risk factors. Some RA-related factors may promote changes in LV geometry in RA. Further research is necessary to determine the underlying mechanisms for these changes and to understand prognostic and therapeutic implications of LV remodeling on CV outcomes in RA.

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Figure 1.
Prevalence of LV geometry patterns in RA patients compared to non-RA subjects

Table 1

Cardiovascular risk factors and comorbidities in RA and non-RA cohorts

Variable	RA (n=200)	Non-RA (n=600)	p-value
Age, mean $\pm$ SD (years)	64.7 $\pm$ 9.7	64.8 $\pm$ 9.5	0.89
Female, n (%)	148 (74)	444 (74)	1.00
Smoking, n (%)			
- Ever	95 (47.7)	233 (41.4)	0.12
- Current	11 (5.5)	31 (5.2)	0.84
Diabetes mellitus or use of insulin/oral hypoglycemics, n (%)	30 (12)	128 (7)	0.014
Dyslipidemia or use of lipid-lowering medications, n (%)	87 (43.5)	154 (25.7)	<0.001
BMI, mean $\pm$ SD (kg/m ²)	28.7 $\pm$ 5.8	27.7 $\pm$ 5.3	0.04
Waist circumference, mean $\pm$ SD (cm)	93.3 $\pm$ 15.3	87.2 $\pm$ 13.8	<0.001
SBP, mean $\pm$ SD (mm Hg)	130.8 $\pm$ 18.7	124.9 $\pm$ 19.5	< 0.001
DBP, mean $\pm$ SD (mm Hg)	71.5 $\pm$ 9.2	67.7 $\pm$ 9.9	<0.001
Hypertension or use of antihypertensive medications, n (%)	138 (69)	284 (47.3)	<0.001
Metabolic syndrome, n (%)	101 (50.5)	150 (25)	<0.001
History of ischemic heart disease, n (%)	27 (13.5)	66 (11)	0.34
GFR, mean $\pm$ SD (mL/min/1.73 m ²)	78.8 $\pm$ 15.7	73.5 $\pm$ 13.8	<0.001
abnormal GFR, n (%)	27 (13.5)	54 (19.1)	0.102

RA = rheumatoid arthritis; BMI = body mass index; SD = standard deviation; SBP = systolic blood pressure; DBP = diastolic blood pressure; GFR = glomerular filtration rate

Table 2

Echocardiographic measures in RA and non-RA cohorts

Measurement, mean $\pm$ SD	RA (n=200)	Non-RA (n=600)	p-value unadjusted	p-value adjusted**
Septal wall thickness *, mm	9.8 $\pm$ 1.6	10.2 $\pm$ 1.8	0.15	<0.001
Posterior wall thickness *, mm	9.9 $\pm$ 1.4	9.3 $\pm$ 1.3	<0.001	<0.001
LV internal diameter *, mm	46.3 $\pm$ 4.6	48.2 $\pm$ 4.9	<0.001	<0.001
Relative wall thickness, mm	0.43 $\pm$ 0.07	0.39 $\pm$ 0.07	<0.001	<0.001
LV mass, g	158.8 $\pm$ 39.4	162.3 $\pm$ 43.7	0.56	<0.001
LV mass normalized to height ^{2.7} , g/m ^{2.7}	40.4 $\pm$ 8.7	43.1 $\pm$ 11.3	0.02	<0.001
LV mass normalized to BSA, g/m ²	84.6 $\pm$ 15.9	91.7 $\pm$ 22.2	0.001	<0.001
EF (%)	61.9 $\pm$ 6.9	65.0 $\pm$ 6.1	<0.001	<0.001
<50%	3 (1.5)	7 (1.2)	0.72	0.90
Left atrial volume index, cc/m ²	27.4 $\pm$ 7.4	24.3 $\pm$ 7.4	<0.001	<0.001
> 28 cc/m ²	69 (41)	143 (25)	<0.001	<0.001
E/A ratio	1.8 $\pm$ 0.6	1.1 $\pm$ 0.4	<0.001	<0.001
E/E' ratio	10.0 $\pm$ 4.4	10.8 $\pm$ 4.8	<0.001	0.004
Pulmonary artery pressure, mm Hg	30.5 $\pm$ 6.7	23.0 $\pm$ 5.5	<0.001	<0.001
Tricuspidal regurgitant jet velocity, m/sec	2.5 $\pm$ 0.3	2.4 $\pm$ 0.3	0.001	0.019
Deceleration time, msec	226 $\pm$ 50	225 $\pm$ 40	0.64	0.98
Heart rate, beats per min	67.1 $\pm$ 11.8	66.9 $\pm$ 11.7	0.78	0.23
Valvular heart disease	3 (2)	13 (2)	0.56	0.81

* measures at end-diastole;

** adjusted for CV risk factors and comorbidities.

RA = rheumatoid arthritis; LV = left ventricular; EF = ejection fraction; SD = standard deviation; BSA = body surface area

Table 3Disease characteristics of RA patients (n=200) and their association with LV measures ^{*X}

Variable	Value	LVMI (Beta ± SE)	RWT
RA duration, mean ± SD (years)	10.0 ± 7.0	0.001 ± 0.002 P=0.47	0.0001 ± 0.002 P=0.95
RF and/or ACPA positive, n (%)	138 (69)	-0.029 ± 0.027 P=0.28	0.005 ± 0.025 P=0.84
Erosions / destructive changes, n (%)	106 (53)	-0.007 ± 0.025 P=0.78	0.005 ± 0.023 P=0.82
HAQ score, mean ± SD	0.5 ± 0.6	-0.033 ± 0.022 P=0.13	0.023 ± 0.020 P=0.25
VAS pain, mean ± SD (mm)	28.7 ± 23.1	-0.003 ± 0.018 P=0.86	0.013 ± 0.016 P=0.42
C-reactive protein, mean ± SD (mg/L) ^{††}	4.34 ± 6.8	0.009 ± 0.010 P=0.37	-0.001 ± 0.009 P=0.88
Interleukin 6, mean ± SD (pg/mL) ^{††}	5.3 ± 10.1	-0.011 ± 0.013 P=0.42	-0.007 ± 0.012 P=0.54
TNF-alpha, mean ± SD (pg/mL) ^{††}	20 ± 64	0.004 ± 0.008 P=0.64	0.002 ± 0.008 P=0.74
BNP, mean ± SD (pg/mL) ^{††}	70 ± 75	0.024 ± 0.013 P=0.07	-0.012 ± 0.012 P=0.33
<i>Antirheumatic medications</i>			
Methotrexate, n (%)	112 (56)	0.007 ± 0.025 P=0.79	0.027 ± 0.023 P=0.24
Other DMARDs, n (%)	76 (38)	-0.026 ± 0.026 P=0.31	0.028 ± 0.023 P=0.23
Corticosteroids, n (%)	55 (28)	-0.082 ± 0.027 P=0.002	0.006 ± 0.025 P=0.81
Biologic response modifiers, n (%)	27 (14)	0.052 ± 0.036 P=0.15	-0.008 ± 0.033 P=0.82
Coxibs, n (%)	8 (4)	0.013 ± 0.067 P=0.85	-0.001 ± 0.061 P=0.98
NSAIDs, n (%)	124 (62)	-0.020 ± 0.026 P=0.45	0.002 ± 0.023 P=0.93

* Statistically significant association (p<0.05) is shown in bold;

^X associations are adjusted for CV risk factors and comorbidities;^{††} Log-transformed values

RA = rheumatoid arthritis; RF = rheumatoid factor; ACPA = anti-citrullinated protein antibodies; HAQ = Health Assessment Questionnaire; VAS = Visual Analogue Scale; TNF-alpha = tumor necrosis factor alpha; BNP = brain natriuretic peptide; DMARDs = disease modifying antirheumatic drugs; NSAIDs = non-steroidal anti-inflammatory drugs