International Journal of Cardiology 240 (2017) 379–385

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Five-year changes in cardiac structure and function in patients with rheumatoid arthritis compared with the general population☆

John M. Davis III [a,*,1], Grace Lin [b,1], Jae K. Oh [b,1], Cynthia S. Crowson [c,1], Sara J. Achenbach [c,1], Terry M. Therneau [c,1], Eric L. Matteson [a,1], Richard J. Rodeheffer [b,1], Sherine E. Gabriel [d,e,1]

[a] Division of Rheumatology, Mayo Clinic, Rochester, MN, United States
[b] Division of Cardiovascular Diseases, Mayo Clinic, Rochester, MN, United States
[c] Division of Biomedical Statistics and Informatics, Mayo Clinic, Rochester, MN, United States
[d] Division of Epidemiology, Mayo Clinic, Rochester, MN, United States
[e] Rutgers Robert Wood Johnson Medical School, New Brunswick, NJ, United States

ARTICLE INFO

Article history:
Received 29 November 2016
Received in revised form 16 March 2017
Accepted 23 March 2017
Available online 31 March 2017

Keywords:
Echocardiography
Heart failure
Rheumatoid arthritis

ABSTRACT

Background: Patients with rheumatoid arthritis (RA) have increased risk of heart failure with preserved ejection fraction. The development and progression of left ventricular dysfunction before onset of clinical heart failure are unknown. The objective of this study was to evaluate longitudinal changes in cardiac structure and function of patients with RA compared with persons in the general population.

Methods: A prospective longitudinal study of a population-based cohort of 160 patients with RA and a population-based cohort of 1391 persons without RA (non-RA cohort) was performed. Each participant underwent 2-dimensional, pulsed-wave tissue Doppler echocardiography at baseline and after 4 to 5 years of follow-up. Age- and sex-adjusted linear regression models were used to test for differences between the RA and non-RA cohorts in annualized rates of change for echocardiographic parameters.

Results: Mitral A velocity increased more rapidly among the patients with RA than the non-RA cohort (age- and sex-adjusted parameter estimate, 0.030; $P < 0.001$). Correspondingly, the mean mitral inflow E/A ratio decreased faster in the RA cohort than the non-RA cohort (adjusted parameter estimate, −0.096; $P < 0.001$). The left atrial volume index increased at a higher rate in the RA cohort than the non-RA cohort (adjusted parameter estimate, 0.150; $P < 0.001$).

Conclusions: This pattern of echocardiographic findings confirms previous cross-sectional studies and indicates that subclinical changes in diastolic function occur more rapidly over 5 years in RA patients than in the general population. Further research into the mechanisms of myocardial disease in these patients and the relationship with disease activity and treatment is warranted.

1. Introduction

Heart failure (HF) is a cardiovascular comorbidity associated with rheumatoid arthritis (RA) [1]. The incidence of HF in population-based RA cohorts is approximately 2-fold greater than the general population [2–4]. This increased HF risk is explained by neither traditional risk factors nor typical coronary artery disease [5]. HF with preserved ejection fraction (HFpEF) is more common among patients with RA than patients with HF in the general population [6].

Even without clinical heart disease, patients with RA have a high prevalence of abnormalities in cardiac structure and function. Aslam et al. [7] published a systematic review and meta-analysis of 25 cross-sectional echocardiographic studies of left ventricular (LV) structure and function, comparing 1614 patients with 4222 control participants (controls). Using data from matched and unmatched studies, the authors found that RA patients had greater mitral inflow A wave velocities, lower E/A ratios, and longer isovolumetric relaxation times than non-RA

Abbreviations: HF, heart failure; HFpEF, heart failure with preserved ejection fraction; IRB, institutional review board; LA, left atrial; LV, left ventricular; non-RA, without rheumatoid arthritis; RA, rheumatoid arthritis; RAPID3, Routine Assessment of Patient Index Data 3.

☆ Presented in abstract form at the American College of Rheumatology Annual Scientific Meeting, Boston, Massachusetts, November 14–19, 2014, and at the European League Against Rheumatism Annual Congress, Rome, Italy, June 10–13, 2015.Conflict of interest: The authors have no relationships with industry to disclose.Funding Support: This work was supported by a grant from the National Institutes of Health (NIH), National Institute of Arthritis and Musculoskeletal and Skin Diseases (Award Number R01AR46849), and was made possible using the resources of the Rochester Epidemiology Project, which is supported by the National Institute on Aging of the NIH under Award Number R01AG034676. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH. The funding sources had no involvement in the study design or in the collection, analysis, or interpretation of the data.

* Corrresponding author at: Division of Rheumatology, Mayo Clinic, 200 First St SW, Rochester, MN 55905, United States.
E-mail address: davis.john4@mayo.edu (J.M. Davis).

[1] This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

http://dx.doi.org/10.1016/j.ijcard.2017.03.108
0167-5273/

controls, essentially confirming that RA is associated with alterations in diastolic function. In addition, they observed that RA patients had increases in left atrial (LA) dimension, LV mass index, and estimated pulmonary artery pressure.

However, little is known about the importance and progression of abnormalities in myocardial structure and function in patients with RA. Whether these alterations regress, remain stable, or progress over time and whether they differ for persons with RA compared with the general population is unknown. These knowledge gaps represent barriers to development of screening approaches that identify persons with asymptomatic LV dysfunction who might benefit from early cardiovascular intervention [8].

A population-based cohort study is underway at our institution to understand the pathophysiologic factors of myocardial dysfunction in patients with RA. Previously, we have reported the baseline echocardiographic findings [9]. Herein, we report the 5-year prospective longitudinal follow-up of cardiac structure and function assessed with echocardiography of RA patients compared with persons from the general population.

2. Materials and methods

A prospective, longitudinal, population-based cohort study was conducted using the resources of the Rochester Epidemiology Project, a distinctive centralized, communitywide medical records linkage system [10]. The sampling frame for patients with RA was a previously assembled population of adult (age ≥ 18 years) residents of Olmsted County, Minnesota, who fulfill the American College of Rheumatology 1987 criteria for the classification of RA [11]. The study used a previously identified, randomized sample of persons from the general population of this community, assembled to evaluate the burden of LV systolic and diastolic dysfunction as a comparison (non-RA) cohort [12–14]. All members of both cohorts were included; there were no exclusion criteria. The institutional review boards (IRBs) of Mayo Clinic (IRB number 06-005445) and Olmsted Medical Center (IRB number 039-omc-06) in Rochester, Minnesota approved this study. All participants provided written informed consent.

Both cohorts were evaluated longitudinally at 2 prespecified time points, hereafter called *examination 1* and *examination 2*. In the non-RA cohort, examination 1 occurred from 1997 through 2000; examination 2 occurred from 2001 through 2004. In the RA cohort, examination 1 occurred from 2007 through 2009 and examination 2 from 2012 through 2014. The interval between examinations was approximately 4 years for the non-RA cohort and 5 years for the RA cohort. At each research appointment, participants completed questionnaires regarding HF symptoms, cardiovascular risk factors, and medications. Patients completed the global assessment (range, 0–100), Health Assessment Questionnaire disability index, and Routine Assessment of Patient Index Data 3 (RAPID3) [15,16]. Data were collected from participants' questionnaires and health records. Cardiovascular risk factors (i.e., coronary or ischemic heart disease, diabetes mellitus, hypertension, and obesity) were defined as described previously [9,13]. Clinical HF was defined by the Framingham criteria [17].

Comprehensive standardized echocardiography was performed for all participants by registered diagnostic cardiac sonographers and according to the recommendations of the American Society of Echocardiography [9,12,13,18,19]. The echocardiographic methods of the more contemporary (RA) cohort were designed to be as similar as possible to the historical (non-RA) cohort, with minor changes in measurements (e.g., LA volume index) in accordance with current guidelines. The methods were also similar for each cohort at the baseline and follow-up time-points. Interpretation of the echocardiographic images for the non-RA cohort was performed by a single echocardiologist as previously described [12]. All echocardiographic images for the RA cohort were interpreted in the core laboratory.

Linear measurements of LV dimensions and wall thicknesses were obtained from the parasternal long-axis view to calculate LV mass. LV chamber volumes were derived from apical 4- and 2-chamber views and calculated with the modified Simpson biplane method [18]. LV diastolic function was assessed with pulsed-wave Doppler examination of mitral inflow (E and A velocities and E/A ratio) and tissue Doppler examination of septal and lateral mitral annular velocities (e′ velocity) [19]. LA volume index was determined in the non-RA cohort with the formula $\pi/6\,(SA_1 \cdot SA_2 \cdot LA)$, where SA_1 is the M-mode LA dimension and SA_2 and LA are measurements of short and long axis in the apical 4-chamber view at ventricular end systole, indexed to body surface area (m^2) [20]. For the RA cohort, LA volume index was calculated using the area-length method, according to current recommendations [19]. (For further background on the echocardiographic methods, please see references [12] and [19].)

Of the 244 patients with RA in our original study [9], 160 returned for examination 2, yielding a return participation rate of 66%. Of the 1402 participants in the non-RA population [14], 9 were excluded because of enrollment in the RA cohort and 2 were excluded because of missing echocardiographic measurements at both time points. Therefore, 1391 participants comprised the non-RA cohort.

Descriptive statistics were used to summarize participant characteristics at baseline and follow-up. Age- and sex-adjusted linear or logistic regression models were used to compare the RA and non-RA cohorts for baseline characteristics and annualized rates of change in echocardiographic parameters. Changes in these parameters between baseline and follow-up were tested using paired *t* tests. Standardized regression coefficients—computed by dividing a parameter estimate by the ratio of the sample standard deviation of the echocardiographic variable to the sample standard deviation of cohort variable—were used to facilitate comparison of annualized rates of change across the parameters. Interactions between age and sex were used to determine whether rates of change differed between women and men with RA. Smoothing splines displayed trends in these figures. Analyses were performed with SAS statistical software version 9.4 (SAS Institute, Inc.) and R software version 3.0.2 (R Foundation for Statistical Computing).

3. Results

The RA cohort consisted of 160 patients; the non-RA cohort had 1391 participants (Table 1). At examination 1, mean age was slightly less in the RA cohort than the non-RA cohort (58.5 vs 61.1 years, $P = 0.001$). As expected, the proportion of female participants was greater in the RA cohort (76.3% vs 50.6%, $P < 0.001$). Patients with RA had greater prevalence of hypertension, obesity, and HF than non-RA participants. With regard to CV medications, baseline use of angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and β-blockers was significantly greater in the RA cohort.

The interval between echocardiographic examinations 1 and 2 was a median (range) of 4.0 (2.1–5.7) years for the non-RA cohort and 5.0 (4.8–5.5) years for the RA cohort ($P < 0.001$). The trends in differences between the cohorts for these characteristics at examination 1 appeared to persist at examination 2; however, these trends were not tested formally because of the different follow-up intervals between the 2 cohorts. Age- and sex-adjusted annualized rates of change in echocardiographic parameters differed between the cohorts (Supplementary Table, Table 2, and Fig. 1).

In cardiac structure, both LV septal thickness and posterior wall thickness decreased in both cohorts (Supplementary Table). After adjustment for age and sex, the LV septal thickness (parameter estimate, −0.015; $P < 0.001$) and the posterior wall thickness (parameter estimate, −0.010; $P = 0.006$) declined at a faster rate among patients with RA. These dimensional changes persisted after further adjustment for hypertension, obesity, diabetes, coronary artery disease, and smoking status (Table 2). In contrast, the LV end-diastolic dimension increased more rapidly in the RA cohort than the non-RA cohort (parameter estimate, 0.029; $P = 0.002$).

The mean LV mass index declined between examinations from 94.3 g/m^2 to 90.9 g/m^2 in the non-RA cohort ($P < 0.001$) and from 80.9 g/m^2 to 77.3 g/m^2 in the RA cohort ($P = 0.03$). Annualized rates of decline in the LV mass index were similar between cohorts (Table 2).

The LA volume index increased from 24.4 mL/m^2 to 24.7 mL/m^2 ($P = 0.06$) in the non-RA cohort and from 26.9 mL/m^2 to 34.4 mL/m^2 ($P < 0.001$) in the RA cohort (Supplementary Table). During follow-up, the LA volume index increased significantly faster in the RA than the non-RA cohort (parameter estimate, 0.150; $P < 0.001$), after adjusting for age, sex, and cardiovascular risk factors (Table 2). Notwithstanding the differences between cohorts in the calculation of this parameter, the changes in LA volume index were substantial and significant.

With respect to systolic function, a statistically significant increase occurred in the ejection fraction over time among non-RA participants. No change was seen in ejection fraction among RA patients, resulting in a significant difference in the rates of change between the groups, albeit not clinically meaningful (Table 2 and Fig. 1A).

With respect to diastolic function through assessment of mitral inflow velocities, the mean E velocity increased between examinations among the non-RA participants (from 0.67 to 0.73, $P < 0.001$) but did not change significantly among the RA patients (from 0.70 to 0.70, $P = 0.80$) (Supplementary Table). Although the adjusted rates differed between the groups (Table 2), the plots of the E velocities over time appeared similar (Fig. 1B).

The principal findings concern longitudinal changes in the mitral inflow A wave velocity and E/A ratio. The mean A velocity increased significantly in both groups (Supplementary Table), but the increase was larger in the RA cohort than the non-RA cohort (from 0.42 to 0.70 vs