Original Article

Cardiac Involvement and Echocardiographic Characteristics in Rheumatoid Arthritis

Farahnaz Nikdoust[1], MD; Reza Zangeneh[1], MD; Seyed Abdolhussein Tabatabaei[1]*, MD

ABSTRACT

Background: As the cardiac function in patients with rheumatoid arthritis (RA) has not been well studied via echocardiography yet, we aimed to determine cardiac involvement and echocardiographic features in patients with RA of at least 5 years' duration who referred to our hospital between 2012 and 2014.

Methods: In this cross-sectional study, patients with RA were compared to healthy controls in terms of the cardiac function via Doppler echocardiography. After collecting the clinical and demographic data in both groups, we performed Doppler echocardiography for both groups to evaluate ventricular function and dimensions as well as valvular function.

Results: Forty-six patients with RA (mean age = 51.3 y) were compared to 48 healthy controls (mean age = 50.2 y). The body mass index was significantly higher in the patients with RA (P = 0.01). Left ventricular ejection fraction was significantly lower in the case group (P<0.001). The frequency of mitral and tricuspid regurgitation was higher in the patients with RA (P = 0.008 and P = 0.005, respectively). Also, chamber dimensions and tricuspid annular plane systolic excursion (TAPSE) were significantly abnormal in the case group. There was a reverse correlation between TAPSE and disease duration (r = -0.29; P = 0.04).

Conclusions: In this study, we observed disturbed echocardiographic characteristic features in the patients with RA as compared with the controls. ***(Iranian Heart Journal 2016; 17(2):18-24)***

Keywords: Echocardiography ■ Rheumatoid arthritis ■ Left ventricular ejection fraction

[1] Department of Cardiology, Shariati Hospital, Tehran University of Medical Sciences, Tehran, I.R. Iran.

Corresponding Author: Seyed Abdolhussein Tabatabaei, MD
E-mail: tabatabaeiseyedah@gmail.com **Tel:** 02188220000

Received: August 31, 2015 **Accepted:** April 25, 2016

Rheumatoid arthritis (RA) is a chronic autoimmune disease with inflammatory and multisystemic characteristics and is considered the most frequent autoimmune disease.[1] Articular damage is the most common organ involvement in this disease, while other organs such as the cardiovascular system can be involved.[2,3] Pericarditis,[1] cardiac conduction disorders,[4] coronary artery

disease,[5] valvular heart disease,[6] aortitis,[7] myocarditis,[8] and pulmonary hypertension[9] are the instances of cardiovascular involvement in RA. However, cardiac involvement in RA is not always symptomatic and sometimes has no apparent feature.[10,11] Therefore, data on cardiovascular involvement in RA are limited and many aspects of cardiovascular involvement have yet to be explored.

Postmortem studies have shown the presence of myocardial and endocardial involvement in patients with RA.[12] Meanwhile, heart failure in the context of RA results from systolic or diastolic dysfunction or a combination of both.[13] Diastolic left ventricular dysfunction can be related to structural heart abnormalities such as the hypertrophy of interstitial fibrosis and, therefore, abnormal myocyte relaxation due to ischemia.[14] Many noninvasive modalities like Doppler echocardiography, M-mode color Doppler echocardiography, tissue Doppler imaging, magnetic resonance imaging, and radionuclide ventriculography can be drawn upon to assess the systolic and diastolic functions of the heart.[15,16]

Although transthoracic Doppler echocardiography has been employed to discover cardiac involvement in many other autoimmune diseases, there is limited evidence regarding the echocardiographic features of patients with RA. It is obvious that the use of this modality can help to recognize RA cases with subclinical ventricular dysfunction. Accordingly, we aimed to investigate the echocardiographic characteristics of patients with RA of at least 5 years' duration who referred to our institution and to compare the results with those of healthy controls.

METHODS

In this study, we enrolled patients with RA of at least 5 years' duration who presented to the Rheumatology Clinic of Dr. Shariati Hospital, Tehran University of Medical Sciences, Tehran, Iran. We excluded patients with a history of cardiovascular disease. Age- and sex-matched healthy controls were selected from the hospital staff. All participants signed an informed consent before enrolment in the study, and the study protocol was approved by the Board of Research and Ethics Committee of Tehran University of Medical Sciences.

Following admission, a detailed history was obtained from the patients and clinical examinations were performed by the physician in charge. Demographic variables—comprising age, sex, height, and weight—were recorded. The patients and controls were also checked for the presence of classic cardiovascular risk factors such as hypertension, diabetes mellitus, dyslipidemia, smoking, and family history of premature coronary artery disease. Clinical parameters encompassed heart rate, systolic and diastolic blood pressures, presenting symptoms, history of myocardial infarction or stroke, and congestive cardiac failure.

After collecting the baseline demographic and clinical data, we evaluated all participants via transthoracic echocardiography and tissue Doppler imaging, using GE Vivid 7 Dimensions ultrasound system (GE Healthcare, Milwaukee, WI). All echocardiographic evaluations were performed by a cardiologist, who was blinded to the study protocol. Valvular regurgitation severity was assessed via echocardiography and was scored 0 as none or trivial, 1 as mild, 2 as moderate, 3 as moderate to severe, and 4 as severe regurgitation. Left ventricular size was assessed by end-systolic and end-diastolic diameters in the parasternal long-axis view and end-systolic and end-diastolic volumes in the apical 4-chamber view. Left ventricular systolic function and ejection fraction were measured using the Simpson method, M-mode, and eyeball. Left ventricular size was evaluated by measuring left ventricular diameter in the apical 4-chamber view. End-systolic and end-diastolic volumes were measured both in the apical 4-chamber view. The reference limits of all

echocardiographic parameters were defined according to the guidelines of the American Society of Echocardiography.[9]

Statistical Analysis

The continuous variables are shown as means ± SDs, and the categorical variables are described as numbers (percentages). The Student *t*-test was drawn upon to compare the continuous variables between the study groups, and the χ^2 test was used to compare the categorical variables between the groups. A $P < 0.05$ was considered statistically significant. The statistical analyses were performed using PASW, version 18 (SPSS Inc., Chicago, Illinois, USA).

RESULTS

In the present study, we compared 48 patients with RA of at least 5 years' duration (mean age = 51.3 ± 11.9 y; male gender =11 [23.9%]) with 46 healthy individuals as the control group. The mean duration of disease in the patients with RA was 10.7 ± 5.7 years. Thirty-one (67.4%) patients of the case group were under treatment with prednisolone, 27 (58.6%) with methotrexate, 5 (10.4%) with hydroxychloroquine, and 4 (8.6%) were treated with either CellCept® or sulfasalazine. Except for the body mass index ($P = 0.012$) and systolic blood pressure ($P = 0.011$), both groups were more likely to be similar in the demographic and clinical variables. The baseline characteristics of the study groups are compared in Table 1.

In the echocardiography of the patients with RA, 2 patients were revealed to have rheumatoid nodules. (Both were female with a disease duration > 10 y.) None of the cases had pericarditis or any other specific finding in the echocardiographic evaluation. The only echocardiographic parameter that had a significant indirect correlation with RA duration was tricuspid annular plane systolic excursion (TAPSE) ($r = -0.29$; $P = 0.046$). No other echocardiographic characteristic was correlated with the duration of RA.

Table 1. Comparison of the baseline general characteristics between the patients with RA and the healthy controls

Parameters	Controls (n=48)	Patients with RA (n=46)	*P*
Age, y	50.2±9.2	51.3±11.9	0.68
Male gender, n (%)	16 (33.3)	11 (23.9)	0.4
Diabetes mellitus, n (%)	5 (10.4)	7 (15.2)	0.141
Hypertension, n (%)	6 (12.5)	7 (15.2)	0.77
Dyslipidemia, n (%)	0 (0)	2 (4.3)	0.135
Smoking, n (%)	6 (12.5)	7 (15.2)	0.341
BMI, kg/m^2	24.2±2.6	26.5±4.1	0.012
Abnormal ECG, n (%)	0 (0)	6 (13.0)	0.064
Systolic blood pressure	118.7±7.9	126.3±12.8	0.011
Diastolic blood pressure	80.5±3.5	80.2±4.0	0.795
Pulse rate, bpm	87.2+7.1	81.5±9.3	0.199
Respiratory rate /min	16.0±1.6	14.9±1.7	0.257

RA, Rheumatoid arthritis; BMI, Body mass index

In the comparison between the patients with RA and the control group for the echocardiographic parameters, the frequency of mitral regurgitation (MR) was significantly higher in the RA group than in the normal controls (52.1% vs. 29.1%; $P = 0.023$). Moreover, the degree of MR was significantly higher in the RA group ($P = 0.046$). Similarly, the number of patients with tricuspid regurgitation was significantly higher in the

RA group (P = 0.020), although the degree of regurgitation did not differ statistically between the 2 groups (P=0.353). The frequency of patients with aortic insufficiency was significantly higher in the RA group, while there was a trend toward worse aortic regurgitation severity in the RA group (P=0.002 and P=0.071, respectively). The other echocardiographic parameters were also significantly disturbed in the RA group, as is depicted in Table 2, particularly left ventricular ejection fraction and heart chamber dimensions. Nonetheless, pulmonary artery pressure was statistically similar between the groups.

Table 2. Comparison of the echocardiographic characteristics of the patients with RA and the healthy controls

Parameters	Controls (n=48)	Patients with RA (n=46)	*P*
MR, n (%)	14 (29.1)	24 (52.1)	0.023
MR severity, n (%)			0.046
Trivial	8 (16.7)	4 (8.7)	
Mild	6 (12.5)	15 (32.6)	
Mild to moderate	0 (0)	3 (6.5)	
Moderate	0 (0)	2 (4.3)	
TR, n (%)	14 (29.1)	28 (60.8)	0.02
TR severity, n (%)			0.353
Trivial	6 (12.5)	6 (13.0)	
Mild	8 (16.7)	20 (43.5)	
Moderate	0 (0)	2 (4.3)	
AI, n (%)	8 (16.6)	21 (45.6)	0.002
AI severity, n (%)			0.071
Trivial	6 (12.5)	5 (10.9)	
Mild	2 (4.2)	10 (21.7)	
Mild to moderate	0 (0)	1 (2.2)	
Moderate	0 (0)	5 (10.9)	
LVEF, %	57.9±4.8	53.0±4.5	<0.001
LVEDD	44.1±4.8	50.8±4.1	<0.001
LVESD	28.0±3.8	38.5±5.8	<0.001
LAD	32.0±4.2	28.5±4.5	0.002
RVD	27.6±3.1	26.3±3.1	0.097
SWT	8.4±1.3	9.3±1.1	0.011
PWT	8.5±1.3	9.3±1.1	0.003
TAPSE	23.4±3.5	21.4±1.3	0.001
RWMA	0 (0)	2 (4.3)	0.3
Pulmonary artery pressure	20.7±5.5	21.9±11.0	0.613

RA, Rheumatoid arthritis; AR, Aortic regurgitation; AS, Aortic stenosis; LA, Left atrium; LVEDD, Left ventricular end diastolic diameter; LVEF, Left ventricular ejection fraction; LVH, Left ventricular hypertrophy; LVESD, Left ventricular end systolic diameter; PAP, Pulmonary artery pressure; MR, Mitral regurgitation; MVP, Mitral valve prolapse; PI, Pulmonary insufficiency; PS, Pulmonary stenosis; TR, Tricuspid regurgitation; TS, Tricuspid stenosis

DISCUSSION

In the present study, we observed disturbed echocardiographic parameters in our patients with RA in comparison with the healthy controls, despite similarity in the baseline characteristics. Additionally, valvular insufficiency was more prevalent and more severe in the patients with RA.

Due to the incognito nature of cardiac symptoms in RA, providing thorough information on cardiovascular conditions in patients with RA has always been an issue. The patients with RA in our study had a reduction in systolic and diastolic ventricular functions as compared to the control group. These findings are in line with previous studies.[17-20] Nonetheless, we did not find an

association between the echocardiographic parameters and the duration of the disease, which is similar to the results of a single study.[20]

Several mechanisms have been proposed for diastolic dysfunction in patients with RA; these mechanisms include myocardial fibrosis, myocarditis, granulomatous lesions, infarction, vasculitis, and focal inflammation.[21-24] Chronic immune activation and inflammatory processes play a significant role in the cardiac involvement of patients with RA. Cytokine overactivity—particularly TNF-α—contributes in the cardiomyocyte apoptosis, ventricular dysfunction/ remodeling, and finally heart failure.[25-27] Moreover, high inflammatory markers are associated with significantly high plasma NT-proBNP levels in patients with RA as compared to controls.[20] All these processes can result in increased cardiovascular mortality. This increased risk is so high that a study showed that the prevalence and extent of myocardial ischemia in asymptomatic patients with RA was as much as that in patients with type 2 diabetes mellitus.[28] A recent meta-analysis has shown an increase in absolute and indexed left ventricular mass in otherwise healthy patients with RA. This increase was associated with an increased risk of cardiovascular events and thereby mortality.[29] The disturbances in the echocardiographic parameters in our study also suggest the burden of RA on the cardiovascular system of the patients. Overall, cardiovascular assessment in patients with RA, even in the absence of the related symptoms, seems to be crucial.

It should also be noted that some of the drugs used for the treatment of RA have cardiotoxic effects. These adverse effects include heart failure, myocarditis, and vasculitis—which are mostly caused by chloroquine, hydroxychloroquine, and gold salts.[30,31] Therefore, distinction between the exact etiologies of cardiac abnormalities in patients with RA seems difficult.

We also noticed that left ventricular end-diastolic and systolic diameters were significantly higher in the patients with RA, which may be a sign of diastolic dysfunction. This is in line with another study that showed that left ventricular diastolic function was impaired in patients with prolonged RA.[31]

Study Limitations

First and foremost among the limitations of the current study is its limited number of participants. RA is not a very common disease and, thus, case selection for clinical studies on RA is challenging. Moreover, this was a single-center study in a university hospital, where patients receive standard care and treatment. It is, therefore, probable that the patients in this study were well-controlled and, consequently, had an acceptable clinical condition with minimal complications as opposed to patients with RA who live in smaller cities and may, as such, not receive ideal care and may develop more complications such as cardiovascular involvement. We would recommend a multicenter study including a larger number of patients with RA in different stages of the disease. Long follow-up of patients and regular echocardiographic evaluations may help us understand the exact changes in the cardiac function and structure in patients with RA.

CONCLUSIONS

Transthoracic and Doppler echocardiography is a useful method for assessing cardiovascular involvement in RA. Our study showed valvular involvement as well as ventricular dysfunction in patients with RA with significantly different echocardiographic parameters as compared to those in the healthy controls. The findings of the present study highlight the necessity of the assessment of the cardiac function in patients with RA. Further research is needed on the

various aspects of the cardiac involvement in RA.

REFERENCES

1. Hara KS, Ballard DJ, Ilstrup DM, Connolly DC, Vollertsen RS. Rheumatoid pericarditis: clinical features and survival. Medicine. 1990;69(2):81-91.

2. Mulherin D, Fitzgerald O, Bresnihan B. Synovial tissue macrophage populations and articular damage in rheumatoid arthritis. Arthritis Rheum. 1996;39(1):115-24.

3. Goodson NJ. Cardiac involvement in rheumatoid arthritis. Handbook of systemic autoimmune diseases. 2003;1:121-43.

4. Seferović P, Ristić A, Maksimović R, Simeunović D, Ristić G, Radovanović G, et al. Cardiac arrhythmias and conduction disturbances in autoimmune rheumatic diseases. Rheumatology (Oxford). 2006;45(suppl 4):iv39-iv42.

5. Maradit-Kremers H, Crowson CS, Nicola PJ, Ballman KV, Roger VL, Jacobsen SJ, et al. Increased unrecognized coronary heart disease and sudden deaths in rheumatoid arthritis: a population-based cohort study. Arthritis Rheum. 2005;52(2):402-11.

6. Roberts WC, Kehoe JA, Carpenter DF, Golden A. Cardiac valvular lesions in rheumatoid arthritis. Arch Intern Med. 1968;122(2):141-6.

7. Kaneko S, Yamashita H, Sugimori Y, Takahashi Y, Kaneko H, Kano T, et al. Rheumatoid arthritis-associated aortitis: a case report and literature review. SpringerPlus. 2014;3(1):509.

8. Miller JJ, French JW. Myocarditis in juvenile rheumatoid arthritis. Am J Dis Child. 1977;131(2):205-9.

9. Sadeghi S, Granton JT, Akhavan P, Pasarikovski CR, Roos AM, Thenganatt J, et al. Survival in rheumatoid arthritis-associated pulmonary arterial hypertension compared with idiopathic pulmonary arterial hypertension. Respirology. 2015;20(3):481-7. Epub 2015/01/15.

10. Gravállese EM, Corson JM, Coblyn JS, Pinkus GS, Weinblatt ME. Rheumatoid aortitis: a rarely recognized but clinically significant entity. Medicine. 1989;68(2):95-106.

11. Mavrogeni S, Dimitroulas T, Gabriel S, Sfikakis PP, Pohost GM, Kitas GD. Why currently used diagnostic techniques for heart failure in rheumatoid arthritis are not enough: the challenge of cardiovascular magnetic resonance imaging. Rev Cardiovasc Med. 2014;15(4):320-31. Epub 2015/02/11.

12. Liebowitz W. The heart in rheumatoid arthritis: a clinical and pathological study of 62 cases. Ann Int Med. 1963;58:102-10.

13. Apstein CS, Eberli FR. Diastolic function and dysfunction with exercise, hypertrophy, ischemia, and heart failure. Cardiologia. 1998;43(12):1269-79. Epub 1999/02/16.

14. Aurigemma GP, Gaasch WH. Diastolic heart failure. N Engl J Med. 2004;351(11):1097-105.

15. Lester SJ, Tajik AJ, Nishimura RA, Oh JK, Khandheria BK, Seward JB. Unlocking the mysteries of diastolic function: deciphering the Rosetta Stone 10 years later. J Am Coll Cardiol. 2008;51(7):679-89. Epub 2008/02/19.

16. Nishimura RA, Tajik AJ. Evaluation of diastolic filling of left ventricle in health and disease: Doppler echocardiography is the clinician's Rosetta Stone. J Am Coll Cardiol. 1997;30(1):8-18. Epub 1997/07/01.

17. Di Franco M, Paradiso M, Mammarella A, Paoletti V, Labbadia G, Coppotelli L, et al. Diastolic function abnormalities in rheumatoid arthritis. Evaluation by echo Doppler transmitral flow and pulmonary venous flow: relation with duration of disease. Ann Rheum Dis. 2000;59(3):227-9.

18. Liang KP, Myasoedova E, Crowson CS, Davis JM, Roger VL, Karon BL, et al. Increased prevalence of diastolic dysfunction in rheumatoid arthritis. Ann Rheum Dis. 2010;69(9):1665-70.

19. Rexhepaj N, Bajraktari G, Berisha I, Beqiri A, Shatri F, Hima F, et al. Left and right ventricular diastolic functions in patients with rheumatoid arthritis without clinically evident

cardiovascular disease. Int J Clin Pract. 2006;60(6):683-8.

20. Lazúrová I, Oetterová M, Pundová L, Petrášová D, Studenčan M. Left ventricular morphology and function in patients with rheumatoid arthritis. Wiener klinische Wochenschrift. 2013;125(9-10):233-8.

21. LEBOWITZ WB. The heart in rheumatoid arthritis (rheumatoid disease): a clinical and pathological study of sixty-two cases. Ann Intern Med. 1963;58(1):102-23.

22. Okada T, Shiokawa Y. Cardiac lesions in collagen disease. Jpn Circ J. 1975;39(4):479-84.

23. Ferrans VJ, Rodríguez ER. Cardiovascular lesions in collagen-vascular diseases. Heart Vessels. 1985;1(1):256-61.

24. Goldenberg J, Ferraz MB, Pessoa AP, Fonseca AS, Carvalho AC, Hilario MO, et al. Symptomatic cardiac involvement in juvenile rheumatoid arthritis. Int J Cardiol. 1992;34(1):57-62.

25. Sun M, Chen M, Dawood F, Zurawska U, Li JY, Parker T, et al. Tumor necrosis factor-α mediates cardiac remodeling and ventricular dysfunction after pressure overload state. Circulation. 2007;115(11):1398-407.

26. Krown KA, Page MT, Nguyen C, Zechner D, Gutierrez V, Comstock KL, et al. Tumor necrosis factor alpha-induced apoptosis in cardiac myocytes. Involvement of the sphingolipid signaling cascade in cardiac cell death. J Clin Invest. 1996;98(12):2854.

27. Pearson TA. Heightened risk of cardiovascular disease in patients with rheumatoid arthritis, heightened risk of cardiovascular disease in patients with rheumatoid arthritis. Introduction. The American journal of medicine. 2008;121(10 Suppl 1):S1-2.

28. Toutouzas K, Sfikakis PP, Karanasos A, Aggeli C, Felekos I, Kitas G, et al. Myocardial ischaemia without obstructive coronary artery disease in rheumatoid arthritis: hypothesis-generating insights from a cross-sectional study. Rheumatology (Oxford). 2013;52(1):76-80.

29. Corrao S, Argano C, Pistone G, Messina S, Calvo L, Perticone F. Rheumatoid arthritis affects left ventricular mass: Systematic review and meta-analysis. Eur J Intern Med. 2015;26(4):259-67.

30. Nicola PJ, Maradit-Kremers H, Roger VL, Jacobsen SJ, Crowson CS, Ballman KV, et al. The risk of congestive heart failure in rheumatoid arthritis: a population-based study over 46 years. Arthritis Rheum. 2005;52(2):412-20.

31. Alpaslan M, Onrat E, Evcik D. Doppler echocardiographic evaluation of ventricular function in patients with rheumatoid arthritis. Clin Rheumatol. 2003;22(2):84-8.