Journal of Arthritis
ISSN: 2167-7921

Benacka et al., J Arthritis 2016, 5:6
DOI: 10.4172/2167-7921.1000224

Research Article Open Access

Speckle-tracking Echocardiography is More Sensitive in Detecting Subclinical Myocardial Dysfunction in Patients with Rheumatoid Arthritis

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Received date: September 28, 2016; **Accepted date**: November 09, 2016; **Published date**: November 15, 2016

Abstract

Introduction: Patients with rheumatoid arthritis (RA) have shorter life expectancy and their risk of cardiovascular death is more than 50% higher than the rest of the population. Early myocardial dysfunction may be detectable more precisely and sooner using speckle tracking echocardiography.

Method: Cross-sectional study enrolled 55 patients with RA (mean age 44.1 years) without known cardiovascular disease and 31 healthy controls, matched for age, sex, blood pressure, BMI and smoking habit. All subjects underwent a standard echocardiographic and Doppler examination (isovolumic contraction and relaxation times (IVCT and IVRT), mitral valve inflow curve (E/A), septal mitral annular motion (e'), and E/e' ratio) as well as the speckle tracking assessment of left ventricle strains and strain rates.

Results: In standard echocardiographic examination RA patients exhibited higher indexed left ventricle mass (96.4 ± 20.9 g/m^2 vs. 95.8 ± 21.9 g/m^2; p=0.013), lower ejection fraction (64 ± 4% vs. 67 ± 4%; p=0.011) and prolonged IVCT (61.5 ± 9.3 ms vs. 53.7 ± 8.95 ms; p=0.001). Diastolic dysfunction was demonstrasted by prolonged IVRT (81.6 ± 9.6 ms vs. 74.6 ± 12.0 ms; p=0.007) as well as by higher E/e' ratio (8.2 ± 1.8 vs. 7.2 ± 1.5; p=0.009). Speckle tracking method detected decreased global longitudinal epicardial strain (-19.5% vs. -21.5%; p=0.049). Global longitudinal epicardial strain (GLES) correlated with IVCT and IVRT, disease duration and with marker of myocardial damage NTproBNP. RA pts exhibited higher prevalence of markers of myocardial damage (defined as presence NT-proBNP ≥ 125 ng/l or IVRT ≥ 74 ms or IVCT ≥ 57 ms or GLES ≥ -20.0%) 2.2 ± 1.0 vs. 1.3 ± 1.0 (p=0.001), RR 1.97 (95% CI: 1.24–3.15; p=0.004) in comparison with controls.

Conclusions: RA patients without known cardiovascular disease exhibited almost two times higher risk for detection of myocardial damage defined as impaired systolic or diastolic function or myocardial contraction deformity parameters or NT-pro-BNP as compared to matched controls. Speckle-tracking echocardiography significantly revealed incipient myocardial dysfunction, which correlates with clinical RA characteristics and other markers of cardiac damage.

Keywords: Rheumatoid arthritis; Speckle-tracking echocardiography; Left ventricle longitudinal strain; Early markers of myocardial damage

Introduction

Diastolic dysfunction is an early marker of myocardial damage in most commonly encountered cardiovascular diseases. Despite the contradictions about its clinical and prognostic value [1], there is a consensus about its increasing importance in non-cardiac diseases such as rheumatoid arthritis (RA) and other collagen diseases due to early occurance [2-4]. The early systolic dysfunction is unsatisfactorily studied in RA patients.

RA patients experience cardiovascular events earlier [5], have shorter life expectancy [6] and their risk of cardiovascular death is more than 50% higher [7] than the rest of the population. Moreover, these clinical events are only partially dependent on conventional cardiovascular risk factors [8,9] probably due to chronic inflammation [10] and inflammatory myocardial infiltration [11-15]. Until now, Doppler detected diastolic dysfunction by measuring the mitral annulus plane motion and transmitral flow is considered as typical early marker of myocardial dysfunction in RA patients [16-21].

Early systolic dysfunction can be detected by assessment of strain (percentage deformation of myocardium normalized to its original shape) and strain rate (how fast the deformation occurs) of global myocardium or predefined myocardial segments in standardized planes. Doppler is an angle-dependent method, therefore not suitable for measuring of strain (deformation) parameters. More informative could be the speckle-tracking echocardiography (STE) [22-25], which as an angle independent method allows evaluating local myocardial strain and strain rate in predefined segments on the basis of detection

and tracking the small natural reflection patterns in ultrasound B-mode picture.

The aim of this study was to detect subclinical pathologies in myocardial function in RA patients using standard and novel echocardiographic methods and to analyze their relationship to clinical characteristics and laboratory risk markers of RA.

Methods

Cross-sectional study comprised patients aged 25–55 years with at least 5 years history of seropositive RA without known cardiovascular disease. The study group was recruited from outpatient's registers at the 5th and 1st Departments of Internal Medicine in Bratislava and the Internal Department in Trnava, between 2012–2013.

Exclusion criteria eliminated patients with a history of congestive heart failure, coronary artery disease, atrial fibrillation, stroke, diabetes mellitus, cancer, chronic kidney disease, or venous thromboembolism. The control group was recruited from cohort of 50 employees of participating departments who were matched for age, sex, blood pressure, BMI and smoking habit roughly in ratio 1 control to 2 patients until the both groups had the same characteristics.

Both groups underwent structuralized interview, basic anthropometric measurements and blood sampling for classic risk factors and safety parameters. N-terminal prohormone brain natriuretic peptide (NTproBNP) was analyzed as standard marker of myocardial damage. The Health Assessment Questionnaire (HAQ) was used to determine the mobility and functional capacity and the composite index Disease Activity Score (DAS28) was used to determine rheumatoid arthritis inflammatory activity.

An echocardiographic examination using an Esaote MyLab 60 ultrasonograph was performed by a single investigator in both groups. Left ventricle systolic function was assessed by calculated ejection fraction (EF - Teicholz), Doppler derived isovolumic contraction time (IVCT) and speckle tracking measured systolic strain and strain rate.

Diastolic function was assessed by isovolumic relaxation time (IVRT), pulsed-wave Doppler mitral valve inflow curve (E/A), and tissue Doppler imaging (TDI) was used to determine the septal mitral annular motion (e'/a'). The e' wave value (cut-off ≤ 8 cm/s) and the E/e' ratio (cut-off ≤ 9 cm/s) are considered as the most sensitive parameters for diastolic dysfunction detection [26]. Indexed left ventricular mass (LVM) and aortic root diameters were measured.

Using speckle-tracking echocardiography we estimated longitudinal epicardial, longitudinal endocardial, radial, transversal, circumferential strain (%) and strain rate (1/s). We measured it separately for six segments in every cross section.

Cross-sectioning was done in longitudinal (LAX) and transversal (SAX) planes at the mitral annulus level. In the LAX plane, longitudinal and transversal strain and strain rate were estimated, whereas in the SAX plane, radial and circumferential strain and strain rate were estimated [27-32] and then average in each plane.

A cut-off point for global longitudinal strain was set to -20.0% [33] and cut-off points for cardiac time intervals were given according to generally accepted values for IVRT 74 ms and for IVCT 57 ms [34,35].

Ethics

The study protocol was approved by an Ethics committee of University Hospital of Medical Faculty of Comenius University, Bratislava Slovakia and each participant signed an approved Informed consent.

Statistics

Statistical analyses were performed using SPSS 10.0 software (IBM SPSS Inc., Chicago, Illinois, USA).

Normal distribution of parametric data was tested using the one-way Kolmogorov-Smirnov test, followed by Student's t-test or ANOVA techniques for normally distributed data. Heterogeneously distributed data were either analyzed after log-transformation or they were compared using non-parametrical Mann-Whitney U test for two independent groups using Willcox test. Post hoc analysis by Dunnet or Duncan test was performed, when applicable. The impact of clinical characteristics was evaluated with non-parametric tests of qualitative data (χ^2 test with Yates's correction or Fisher's exact test as appropriate). To quantify the correlation between continuous parameters, Pearson's correlation coefficient was calculated, whereby a value of 1 represents an ideal correlation between two methods [36]. Power of the study was calculated for comparison of global longitudinal epicardial strain by method according to Machin et al. [36,37]. Risk ratio statistics and Bayes theorema (sensitivity, specificity, positive and negative predictive values) were calculated according to Altman [38]. Statistical significance was considered at the level of $p \leq 0.05$.

Results

The cross-sectional study included 55 patients with confirmed RA without known cardiovascular disease symptomatic for 13 ± 8 years and diagnosed for 11 ± 7 years, control group consisted of 31 healthy persons.

Parameter	RA (n=55)	Control (n=31)	pa
Age (years), mean (range)	44.1 (36–52)	43.6 (34–54)	0.824
Men/women (%)	80/20	74/26	0.777
BMI (kg/m^2)	25.6 (5.4)	23.7 (4.4)	0.108
Smoking (%)	20	26	0.593
Systolic BP (mmHg)	128 (17)	125 (13)	0.478
Diastolic BP (mmHg)	83 (11)	81 (10)	0.399
Total cholesterol (mmol/l)	5.3 (0.9)	5.6 (0,9)	0.195
LDL (mmol/l)	3.2 (0.8)	3.6 (0.9)	0.023
Triacylglycerol (mmol/l)	1.1 (0.6)	1.0 (0.5)	0.256
Heart rate (1/min)	68.2 (9.95)	66.5 (11.88)	0.483
WBC (×109/l)	6.9 (2.9)	5.7 (1.1)	0.006**
Haemoglobin (g/l)	134 (13)	142 (14)	0.026*
GFR-MDRD (ml/s)	1.67 (0.36)	1.55 (0.24)	0.091
NTproBNP (ng/l)	80.60 (61.88)	51.90 (35.50)	0.008**

VAS score	44 (21)	10 (12)	0.001**
HAQ mobility index	0.97	---	---
DAS28 composite index	3.4 (1.2)	1.0 (0.67)	0.001**

a Statistical testing done using Student's t-test, BMI: Body Mass Index; BP: Blood Pressure; LDL: Low Density Lipoproteins; WBC: White Blood Cells; ESR: Erythrocyte Sedimentation Rate; GFR-MDRD: Glomerular Filtration Rate By MDRD Equation; NTproBNP: N-terminal of the Prohormone Brain Natriuretic Peptide; VAS: Visual Analogue Scale; HAQ: Health Assessment Questionnaire; DAS: Disease Activity Score.

Table 1: Clinical characteristics of 55 patients with rheumatoid arthritis and 31 healthy controls. Values are mean (SD) unless otherwise noted.

The RA patients were similar to controls in terms of classic risk factors for cardiovascular disease: blood pressure, smoking habit, glycaemia, and total cholesterol and triacylglycerol levels (Table 1).

No significant difference between groups was found in laboratory parameters, except of explainable higher leucocyte level and lower hemoglobin level in RA patients.

Most frequent therapy was DMARD (70.1%), followed by biologic agents (69.1%), NSAID (25.5%) and corticoids (21.8%) (Table 2).

Therapy	Overall	Mono-therapy	Dual-therapy	Triple-therapy	Quadru-therapy
Biologic	69.1	16.4	32.7	7.3	12.7
DMARDs	70.1	10.9	32.7	9.1	18.1
Corticoids	21.8	0	3.6	9.1	9.1
NSAID	25.5	0	10.9	12.7	1.8

Biologic: Biological Therapy; DMARDs: Disease Modifying Antirheumatic Drugs; NSAID: Non-steroid Anti-inflammatory Drugs

Table 2: Therapy in RA patients. Values are percentage.

The NTproBNP level was higher in RA patients than in the controls (80.6 ± 61.9 ng/l vs. 51.9 ± 35.5 ng/l; p=0.008), and it exhibited weak correlation with the HAQ mobility index (r=0.32; p=0.018) and with disease duration (r=0.26; p=0.054).

In echocardiographic examination, RA patients had more extended sinuses of Valsalva (33.2 ± 3.5 mm vs. 30.1 ± 3.8 mm; p=0.001) and a larger aortic annular base diameter (29.3 ± 3.4 mm vs. 25.8 ± 3.6 mm; p=0.001) as compared to controls.

As related to diastolic dysfunction, RA patients shown a higher E/e' ratio (8.2 ± 1.8 vs. 7.2 ± 1.5; p=0.009), but the mean values of e' did not differ between the groups. IVRT was prolonged in RA patients in comparison with controls (81.6 ± 9.6 ms vs. 74.6 ± 12.0 ms; p=0.007).

Regarding systolic function, RA patients had significantly prolonged IVCT (61.5 ± 9.3 ms vs. 53.7 ± 8.9 ms; p=0.001) and decreased EF (64.8 ± 3.9% vs. 67.1 ± 3.9%; p=0.011) than the controls (Table 3).

Speckle-tracking assessment of left ventricular function revealed decreased global longitudinal epicardial strain (-19.5% vs. -21.5%; p=0.049), and decreased local longitudinal epicardial strain in apicolateral segment (-12.9%vs.-15.5%; p=0.004) (Table 4). Radial, transversal and circumferential strain analysis did not reveal significant differences.

Parameter	RA (n=55)	Control (n=31)	pa
LVEDD (mm)	47.03 (4.65)	45.44 (3.74)	0.088
LVMI (g/m^2)	96.36 (20.90)	95,84 (21.86)	0.013*
Left atrium (mm)	30.02 (3.52)	29.10 (3.61)	0.252
Aortic annulus (mm)	29.31 (3.44)	25.84 (3.63)	0.001**
Sinuses of Valsalva (mm)	33.16 (3.53)	30.06 (3.75)	0.001**
EF Teicholz (%)	64.84 (3,87)	67.10 (3,87)	0.011*
IVCT (ms)	61.51 (9.30)	53.71 (8.95)	0.001**
IVRT (ms)	81.62 (9.56)	74.58 (12.02)	0.007**
E wave (cm/s)	74.02 (13.70)	71.94 (17.53)	0.543
A wave (cm/s)	61.78 (16.09)	55.26 (13.13)	0.058
E/A	1.27 (0.38)	1.37 (0.51)	0.287
e' wave (cm/s)	9.47 (1.83)	10.06 (2.06)	0.174
a' wave (cm/s)	7.62 (1.82)	7.55 (1.69)	0.861
e'/a'	1.30 (0.42)	1.45 (0.58)	0.226
E/e' mean	8.21 (1.76)	7.21 (1.52)	0.009**

[a]Statistical testing done using Student's t-test, LVEDD: Left Ventricle End-diastolic Diameter; LVMI: Left Ventricle Mass/Indexed; EF: Ejection Fraction Calculated With Teicholz Formula; IVCT: Isovolumic Contraction Time; IVRT: Isovolumic Relaxation Time.

Table 3: Echocardiographic results. Values are means (SD) unless otherwise noted.

Longitudinal endocardial strain rate directly correlated with IVRT (r=0.29; p=0.030) and E/e' ratio (r=0.30; p=0.026).

As related to clinical characteristics and markers, indirect correlations was found between longitudinal epicardial strain rate and the NTproBNP level (r=-0.28; p=0.041).

Global longitudinal epicardial strain (GLES) was indirectly correlated with RA disease duration (r=-0.28; p=0.044) (Table 5).

RA patients exhibited higher prevalence of markers of myocardial damage (defined as absence or presence -0/1) of NT-proBNP ≥ 125 ng/l or IVRT ≥ 74 ms or IVCT ≥ 57 ms or GLES ≥ -20.0%) 2.2 ± 1.0 vs. 1.3 ± 1.0 (p = 0.001) in comparison with controls (Figure 1).

Risk ratio for detection 2 up to 4 pathological markers of myocardial damage in RA patients was 1.97 (95% CI: 1.24–3.15; p=0.004) as compared to controls.

Number of patients needed to examine to reach given goal was 2.66 (5.58-1.74); p=0.04. Biological therapy was not associated with myocardial damage (data on file).

Parameter	RA	Control	pa	Parameter	RA	Control	pa
SLonEndoBS	-17.28	-18.96	0.28	SRLonEndoBS	-1.45	-1.46	0.953
SLonEndoMS	-20.62	-22.13	0.178	SRLonEndoMS	-1.3	-1.38	0.239
SLonEndoAS	-26.22	-27.76	0.317	SRLonEndoAS	-1.54	-1.73	0.195
SLonEndoAL	-21.15	-23.56	0.112	SRLonEndoAL	-1.37	-1.37	0.251
SLonEndoML	-19.95	-20.96	0.405	SRLonEndoML	-1.37	-1.52	0.07
SLonEndoBL	-21.1	-21.67	0.691	SRLonEndoBL	-1.61	-1.77	0.226
SLonEndoAve	-21.05	-22.51	0.119	SRLonEndoAve	-1.43	-1.55	0.072
SLonEpiBS	-24.54	-26.73	0.131	SRLonEpiBS	-1.72	-1.8	0.523
SLonEpiMS	-19.77	-21.3	0.135	SRLonEpiMS	-1.2	-1.31	0.17
SLonEpiAS	-12.15	-13.49	0.083	SRLonEpiAS	-0.74	-0.81	0.145
SLonEpiAL	-12.92	-15.49	0.004**	SRLonEpiAL	-0.84	-0.88	0.587
SLonEpiML	-21.73	-23.99	0.099	SRLonEpiML	-1.46	-1.62	0.145
SLonEpiBL	-25.92	-27.73	0.282	SRLonEpiBL	-1.88	-1.86	0.907
SLonEpiAve	-19.51	-21.46	0.049*	SRLonEpiAve	-1.3	-1.38	0.349

[a]Statistical testing done using Student's t-test, S: Strain; SR: Strain Rate; Lon: Longitudinal; Endo: Endocardial; Epi: Epicardial; Tran: Transversal; Cir: Circular; Rad: Radial; BS: Basal Septal; MS: Mid Septal; AS: Apical Septal; AL: Apical Lateral; ML: Mid Lateral; BL: Basal Lateral; Ave: Average.

Table 4: Strain and strain rate (segmental and overall), determined by the speckle-tracking method. Values are means.

	SLonEndo		SRLonEndo		SLongEpi		SRLongEpi	
RA patients	**r**	**p**	**r**	**p**	**r**	**p**	**r**	**p**
DAS28	0.232	0.089	0.176	0.198	0.066	0.635	0.071	0.605
HAQ	-0.085	0.539	-0.206	0.132	-0.032	0.817	-0.189	0.167
VAS	0.104	0.451	-0.032	0.817	0.083	0.546	-0.059	0.67
RA duration	- 0,055	0.691	-0.048	0.726	-0.272	0.044*	-0.146	0.287
NTproBNP	-0.103	0.456	-0.228	0.095	-0.176	0.199	- 0.277*	0.04*
EF	-0.111	0.419	0.094	0.496	-0.128	0.351	-0.15	0.274
IVRT	0.214	0.117	0.293*	0.030*	0.129	0.346	0.098	0.474
E/e'	0.217	0.112	0.299*	0.026*	0.19	0.165	0.35	0.084
Controls								
NTproBNP	-0.154	0.408	-0.081	0.665	-0.181	0.331	-0.099	0.597
EF	-0.285	0.12	-0.017	0.928	-0.177	0.342	-0.01	0.956
IVRT	0.092	0.622	0.103	0.582	0.146	0.432	0.057	0.76
E/e'	-0.306	0.094	-0.065	0.728	-0.131	0.482	-0.016	0.93

Statistical testing done using. "regular font" - Spearman's rank correlation coefficient
"italic font" - Pearson's correlation coefficient. BMI: Body Mass Index; BP: Blood Pressure; LDL: Low Density Lipoproteins; WBC: White Blood cells; ESR: Erythrocyte Sedimentation Rate; GFR-MDRD: Glomerular Filtration Rate By MDRD Equation; DAS: Disease Activity Score; HAQ: Health Assessment Questionnaire; VAS: Visual

Analogue Scale; RA: Rheumatoid Arthritis; NTproBNP: N-terminal of the Prohormone Brain Natriuretic Peptide; EF: Ejection Fraction; IVRT: Isovolumic Relaxation Time; E: Transmitral Doppler Flow E (early) wave; e': Tissue Doppler Septal Early Wave.

Table 5: Correlation (r, p values) between clinical variables and parameters of left ventricular functions.

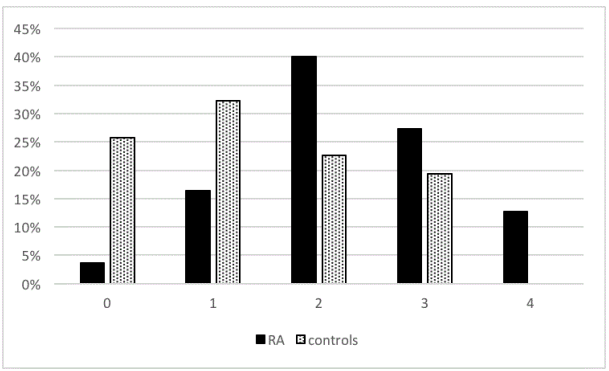

Figure 1: Prevalence of individual parameters of cardiac damage which are out of reference range. RA: rheumatoid arthritis; controls: control group.

Discussion

Comparing the standard echocardiographic and Doppler parameters for systolic and diastolic left ventricle function in age, gender, BMI and smoking habits matched RA patients without known cardiovascular disease with controls did not reveal dramatic differences, confirming difficulties in identification of early myocardial abnormality markers in RA patients. Majority of the differences between the groups were within the reference values and out-off reference range parameters were found also in control group. Moreover, none of analyzed parameters were specific for rheumatic arthritis myocardial damage. On other hand with power of our study reaching 0.82 due to homogeneity of both groups (see standard deviations), we were able to discriminate and validate even small differences between RA diseased and controls.

Analysis of four independent myocardial damage parameters (IVRT, IVCT, GLES, NTproBNP) out of generally accepted reference ranges shown more frequent prevalence in RA group (Figure 1). On other side 42% of the controls had two or three out of range parameters; therefore it is possible to attribute the myocardial damage to rheumatic etiology only with some statistical certainty. Considering ≥2 abnormal parameters as cut-off point caused increase of RR for detection of myocardial damage in RA patients two times (RR=1.97). Sensitivity for given association is 76%, with positive predictive value 78% and negative predictive value 56%. Considering ≥3 abnormal parameters do improve the value of RR only negligible (RR=0.01) (data not shown). Bayes analysis confirms that even early stages of the RA are associated with early detectable myocardial damage with acceptable clinical certainty; however the finding is not specific.

Strain and strain rate

The dominant speckle-tracking parameter is considered longitudinal strain and strain rate [29,32,39]. Presented study demonstrated lower trend for the average values of longitudinal strain and strain rate in RA patients than in healthy controls in both global and defined segments of the left ventricle, predominantly affecting apicolateral epicardial segment. Recent study by Midtbo [40] showed that speckle tracking can be sensitive method for finding of subclinical left ventricle dysfunction.

Also study by Fine et al. [23] confirmed decreased global left ventricle longitudinal strain in RA patients and it´s correlations with a reduced HAQ mobility index, and contrary to our patients, lacking correlation with disease duration. Longitudinal strain in Fine's study might have been influenced by more prevalent classic cardiovascular risk factors (hypertension 85%; smoking habit 44%; and dyslipidemia 71%, diabetes mellitus 14%) as well as higher blood pressure in RA patients, which may confuse the results. More reduced HAQ mobility index and lacking correlation with disease duration in Fine et al. study could be explained by higher age (55.7 vs 44.1 years). However, our study with the same risk factors, but strictly balanced, has provided the same results suggesting the causal effect of RA on longitudinal strain.

Strain parameters in our study correlated with NTproBNP and disease duration and similar association was found also by other authors: in a small study of Sitia et al. (22 patients and 20 controls) using analogous inclusion and exclusion criteria as in our study, RA patients exhibited same abnormalities in longitudinal strain correlating with disease duration [22]. Baktir et al. compared 37 RA patients divided in two age-matched groups (45 years) according to disease duration (2.8 vs. 14.6 years) (no healthy control group) and found significantly lower longitudinal strain in patients with advanced disease [24].

NTproBNP

NTproBNP is cardiac neurohormone responding to ventricular overload, hypoxia, hypertension and increased ventricular wall tension or hypertrophy and in RA patients it correlates with systolic and diastolic volumes and left ventricular mass as measured by Doppler echocardiography [41-44]. In our study with participants balanced for blood pressure and other traditional risk factors, we did not detect a correlation between the NTproBNP level and standard echocardiography parameters for systolic (EF, IVCT) and diastolic function (IVRT, E/e') similarly to previous studies in patients with chronic inflammatory disease [45,46]. Both LV mass or volume overload parameters did not explain differences in NTproBNP between RA patients and controls. Identification of causal relationship between echocardiographical parameters with soluble biomarkers and clinical characteristics could be therefore dependent on modulating factors as age, duration of the disease, functional capacity, therapy, concomitant disease and other difficult-to-balance factors.

Cardiac time intervals

Cardiac time intervals (IVRT a IVCT) are powerful and independent predictors of future ischemic heart disease, heart failure or cardiac death in cardiovascular patients [47]. RA patients in our study had a significantly prolonged IVRT, which may indicate some

active relaxation disturbance of the left ventricle in early diastole, as already suggested by Lascano et al. [48] and other authors [49,50] and it may tempt to explain its association with increased NTproBNP, however, the correlation is only borderline (r=0.35; p=0.054). Any of mentioned studies, including our one, did not find correlation between IVRT with other clinical characteristics as disease duration or HAQ.

In patients with diastolic dysfunction is frequently diagnosed arterial hypertension with the prevalence of 60–88% [51,52]. Majority of cited RA studies including our [8,10,11,13] investigated groups with comparable blood pressure and therefore, the slightly impaired diastolic parameters and LV mass in RA patients cannot be explained by an effect of hypertension on diastolic function [53].

Systolic IVCT in RA patients was studied only in several studies - Levendoglu et al. found in RA patients in similar age and duration of disease identical IVCT in controls as our study (54 ms) but substantially shorter duration in RA patients (40 ms) which could be caused by high inflammatory activity or lacking biological therapy in their gropus. Alpaslan et al. in RA patients in age 52 years also found shorter IVCT (38 ms vs. 41 ms) in group also without biological therapy [18,49]. Difference in IVCT duration can be also caused by different method of assessment (flow Doppler vs. tissue Doppler). Until now, there are no established reference values and recommended measurement method of IVCT in the guidelines [54-57].

Study limitations

Major limitation of presented study could be lacking interobserver comparison of speckle tracking measurement which can cause “virtual dyskinesia” due to intraindividual error [58,59]. When the endocardial borders are manually traced even with experienced specialist, subjective evaluation may overestimate the myocardial thickness and may lead to impaired epicardial strain assessment. The measurement of total and segmental strain could be improved by the measurement of isovolumic times, maximum mitral inflow velocities, and mitral annulus motion, which decrease the chance of false positive strain assessment.

On other side, even when reproducibility of the strain measurements is conditioned by inter-individual variability, studies with one investigator [22,25] as well as studies with more operators [23,24] obtained relatively consistent findings.

Conclusion

Standard echocardiographic assessment of myocardial functions in patients with RA without signs of

Cardiovascular disease suggested minimal changes in left ventricular systolic function (by IVCT and LVEF by Teicholz) and diastolic function (by E/e’ and IVRT). The speckle-tracking method for myocardial strain analysis showed unambiguously systolic impairment of longitudinal strain parameters, which correlates with biomarkers and clinical characteristics of RA.

Clustering of minor impairments of systolic, diastolic and myocardial contraction deformity parameters together with increased NT-pro-BNP is almost two fold higher in rheumatic arthritis patients serving for identification of increased cardiovascular risk in RA patient and giving impetus for further consideration on cardiovascular therapy.

Conflict of Interest Statement

Neither the first author nor any of the co-authors have any conflict of interest with respect to the presented study.

Funding

This work was supported by the Grant of Comenius University (UK/488/2011).

References

1. Abhayaratna WP, Marwick TH, Smith WT, Becker NG (2006) Characteristics of left ventricular diastolic dysfunction in the community: an echocardiographic survey. Heart 92: 1259-1264.
2. Vizzardi E, Cavazzana I, Bazzani C, Pezzali N, Ceribelli A, et al. (2012) Echocardiographic evaluation of asymptomatic patients affected by rheumatoid arthritis. J Investig Med 60: 1204-1208.
3. Bayram NA, Cicek OF, Erten S, Keles T, Durmaz T, et al. (2013) Assessment of left ventricular functions in patients with Sjögren's syndrome using tissue Doppler echocardiography. Int J Rheum Dis 16: 425-429.
4. Sharma A, Kaushik R, Kaushik RM, Kakkar R (2015) Echocardiographic evaluation of diastolic dysfunction in rheumatoid arthritis–a case–control study. Mod Rheumatol 25: 552-557.
5. Peters M, Symmons DP, McCarey D, Dijkmans BA, Nicola P, et al. (2010) EULAR evidence-based recommendations for cardiovascular risk management in patients with rheumatoid arthritis and other forms of inflammatory arthritis. Ann Rheum Dis 69: 325-331.
6. Wong JB, Ramey DR, Singh G (2001) Long-term morbidity, mortality, and economics of rheumatoid arthritis. Arthritis Rheum 44: 2746-2749.
7. Aviña-Zubieta JA, Choi HK, Sadatsafavi M, Etminan M, Esdaile JM, et al. (2008) Risk of cardiovascular mortality in patients with rheumatoid arthritis: A meta-analysis of observational studies. Arthritis Rheum 59: 1690-1697.
8. deL Rincon I, Williams K, Stern MP, Freeman GL, Escalante A (2001) High incidence of cardiovascular events in a rheumatoid arthritis cohort not explained by traditional cardiac risk factors. Arthritis Rheum 44: 2737-2745.
9. Roman MJ, Moeller E, Davis A, Paget SA, Crow MK, et al. (2006) Preclinical carotid atherosclerosis in patients with rheumatoid arthritis. Ann Intern Med 144: 249-256.
10. Solomon DH, Kremer J, Curtis JR, Hochberg MC, Reed G, et al. (2010) Explaining the cardiovascular risk associated with rheumatoid arthritis: traditional risk factors versus markers of rheumatoid arthritis severity. Ann Rheum Dis 69: 1920-1925.
11. Radovits BJ, Popa-Diaconu DA, Popa C, Eijsbouts A, Laan RF, et al. (2009) Disease activity as a risk factor for myocardial infarction in rheumatoid arthritis. Ann Rheum Dis 68: 1271-1276.
12. Rovenský J, Vlcek M, Imrich R (2010) Cardiovascular diseases in rheumatoid arthritis. Vnitr Lek 56: 721-723.
13. Innala L, Möller B, Ljung L, Magnusson S, Smedby T, et al. (2011) Cardiovascular events in early RA are a result of inflammatory burden and traditional risk factors: a five year prospective study. Arthritis Res Ther 13: R131.
14. Karpouzas GA, Malpeso J, Choi TY, Li D, Munoz S, et al. (2014) Prevalence, extent and composition of coronary plaque in patients with rheumatoid arthritis without symptoms or prior diagnosis of coronary artery disease. Ann Rheum Dis 73: 1797-1804.
15. Myasoedova E, Davis JM 3rd, Crowson CS, Roger VL, Karon BL, et al. (2013) Brief Report: Rheumatoid Arthritis Is Associated With Left Ventricular Concentric Remodeling: Results of a Population-Based Cross-Sectional Study. Arthritis Rheum 65: 1713-1718.
16. Corrao S, Sallì L, Arnone S, Scaglione R, Pinto A, et al. (1996) Echo-Doppler left ventricular filling abnormalities in patients with rheumatoid

arthritis without clinically evident cardiovascular disease. Eur J Clin Invest 26: 293-297.

17. Di Franco M, Paradisoa M, Mammarellaa A, Paolettia V, Labbadia G, et al. (2000) Diastolic function abnormalities in rheumatoid arthritis. Evaluation by echo Doppler transmitral flow and pulmonary venous flow: relation with duration of disease. Ann Rheum Dis 59: 227-229.
18. Alpaslan M, Onrat E, Evcik D (2003) Doppler echocardiographic evaluation of ventricular function in patients with rheumatoid arthritis. Clin Rheumatol 22: 84-88.
19. Rexhepaj N, Bajraktari G, Berisha I, Beqiri A, Shatri F, et al. (2006) Left and right ventricular diastolic functions in patients with rheumatoid arthritis without clinically evident cardiovascular disease. Int J Clin Pract 60: 683-688.
20. Meune C, Wahbi K, Assous N, Weber S, Kahan A, et al. (2007) Myocardial dysfunction in rheumatoid arthritis: a controlled tissue-Doppler echocardiography study. J Rheumatol 34: 2005-2009.
21. Yazici D, Tokay S, Aydin S, Toprak A, Inanc N, et al. (2008) Echocardiographic evaluation of cardiac diastolic function in patients with rheumatoid arthritis: 5 years of follow-up. Clin Rheumatol 27: 647-650.
22. Sitia S, Tomasoni L, Cicala S, Atzeni F, Ricci C, et al. (2012) Detection of preclinical impairment of myocardial function in rheumatoid arthritis patients with short disease duration by speckle tracking echocardiography. Int J Cardiol 160: 8-14.
23. Fine NM, Crowson CS, Lin G, Oh JK, Villarraga HR, et al. (2014) Evaluation of myocardial function in patients with rheumatoid arthritis using strain imaging by speckle-tracking echocardiography. Ann Rheum Dis 73: 1833-1839.
24. Baktir AO, Sarli B, Cebicci MA, Saglam H, Dogan Y, et al. (2015) Preclinical impairment of myocardial function in rheumatoid arthritis patients. Detection of myocardial strain by speckle tracking echocardiography. Herz 40: 669-674.
25. Løgstrup BB, Deibjerg LK, Hedemann-Andersen A, Ellingsen T (2014) Left ventricular function in treatment-naive early rheumatoid arthritis. Am J Cardiovasc Dis 4: 79-86.
26. Nagueh SF, Appleton CP, Gillebert TC, Marino PN, Oh JK, et al. (2009) Recommendations for the evaluation of left ventricular diastolic function by echocardiography. J Am Soc Echocardiogr 22: 107-133.
27. Geyer H, Caracciolo G, Abe H, Wilansky S, Carerj S, et al. (2010) Assessment of myocardial mechanics using speckle tracking echocardiography: fundamentals and clinical applications. J Am Soc Echocardiogr 23: 351-369.
28. Mor-Avi V, Lang RM, Badano LP, Belohlavek M, Cardim NM, et al. (2011) Current and evolving echocardiographic techniques for the quantitative evaluation of cardiac mechanics: ASE/EAE consensus statement on methodology and indications: endorsed by the Japanese Society of Echocardiography. J Am Soc Echocardiogr 24: 277-313.
29. Buccheri S, Monte I, Mangiafico S, Bottari V, Leggio S, et al. (2013) Feasibility, reproducibility, and agreement between different speckle tracking echocardiographic techniques for the assessment of longitudinal deformation. Biomed Res Int 2013: 297895.
30. Chapman CB, Ewer SM, Kelly AF, Jacobson KM, Leal MA, et al. (2013) Classification of left ventricular diastolic function using American Society of Echocardiography Guidelines: agreement among echocardiographers. Echocardiography 30: 1022-1031.
31. Abduch MCD, Alencar AM, Mathias Jr M, de Campos Vieira ML (2014) Cardiac mechanics evaluated by speckle tracking echocardiography. Arq Bras Cardiol 102: 403-412.
32. Mada RO, Duchenne J, Voigt JU, Doppler T (2014) Strain and Strain Rate in ischemic heart disease "How I do it". Cardiovascular ultrasound 12: 38.
33. Yingchoncharoen T, Agarwal S, Popović ZB, Marwick TH (2013) Normal ranges of left ventricular strain: a meta-analysis. J Am Soc Echocardiogr 26: 185-191.
34. Hirschfeld S, Meyer R, Korfhagen J, Kaplan S, Liebman J (1976) The isovolumic contraction time of the left ventricle. An echographic study. Circulation 54: 751-756.
35. Lind B, Nowak J, Cain P, Quintana M, Brodin LA (2004) Left ventricular isovolumic velocity and duration variables calculated from colour-coded myocardial velocity images in normal individuals. Eur J Echocardiogr 5: 284-293.
36. Peacock JL, Kerry S (2007) Presenting medical statistics from proposal to publication: a step-by-step guide. Oxford University Press, UK.
37. Machin D (2011) Sample size tables for clinical studies. John Wiley & Sons, USA.
38. Altman DG, Andersen PK (1999) Calculating the number needed to treat for trials where the outcome is time to an event. BMJ 319: 1492-1495.
39. Ernande L, Rietzschel ER, Bergerot C, De Buyzere ML, Schnell F, et al. (2010) Impaired myocardial radial function in asymptomatic patients with type 2 diabetes mellitus: a speckle-tracking imaging study. J Am Soc Echocardiogr 23: 1266-1272.
40. Midtbø H, Semb AG, Matre K, Kvien TK, Gerdts E, et al. (2016) Disease activity is associated with reduced left ventricular systolic myocardial function in patients with rheumatoid arthritis. Ann Rheum Dis.
41. Kozera L, Andrews J, Morgan AW (2011) Cardiovascular risk and rheumatoid arthritis—the next step: differentiating true soluble biomarkers of cardiovascular risk from surrogate measures of inflammation. Rheumatology (Oxford) 50: 1944-1954.
42. Harney SMJ, Timperley J, Daly C, Harin A, James T, et al. (2006) Brain natriuretic peptide is a potentially useful screening tool for the detection of cardiovascular disease in patients with rheumatoid arthritis. Annals of the rheumatic diseases 65: 136.
43. Provan SA, Angel K, Ødegård S, Mowinckel P, Atar D, et al. (2008) The association between disease activity and NT-proBNP in 238 patients with rheumatoid arthritis: a 10-year longitudinal study. Arthritis research & therapy 10: R70.
44. Provan S, Angel K, Semb AG, Atar D, Kvien TK (2010) NT-proBNP predicts mortality in patients with rheumatoid arthritis: results from 10-year follow-up of the EURIDISS study. Ann Rheum Dis 69: 1946-1950.
45. George J, Khan F, Struthers AD (2014) The source of BNP in rheumatoid arthritis. Int J Cardiol 174: 740.
46. Tomáš L, Lazúrová I, Pundová L, Oetterová M, Zakuciová M, et al. (2013) Acute and long-term effect of infliximab on humoral and echocardiographic parameters in patients with chronic inflammatory diseases. Clin Rheumatol 32: 61-66.
47. Biering-Sørensen T, Mogelvang R, Jensen JS (2014) Prognostic Value of Cardiac Time Intervals Measured by Tissue Doppler Imaging M-Mode in the General Population. Circulation 130: A12199.
48. Lascano C, Alba P, Gobbi C, Videla F, Campos F, et al. (2009) Ventricular diastolic dysfunction in rheumatoid arthritis. Rev Fac Cien Med Univ Nac Cordoba 66: 58-65.
49. Levendoglu F, Temizhan A, Ugurlu H, Ozdemir A, Yazici M (2004) Ventricular function abnormalities in active rheumatoid arthritis: a Doppler echocardiographic study. Rheumatol Int 24: 141-146.
50. Udayakumar N, Venkatesan S, Rajendiran C (2007) Diastolic function abnormalities in rheumatoid arthritis: relation with duration of disease. Singapore Med J 48: 537.
51. McMurray JJ, Carson PE, Komajda M, McKelvie R, Zile MR, et al. (2008) Heart failure with preserved ejection fraction: Clinical characteristics of 4133 patients enrolled in the I-PRESERVE trial. Eur J Heart Fail 10: 149-156.
52. Yusuf S, Pfeffer MA, Swedberg K, Granger CB, Held P, et al. (2003) Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved Trial. Lancet 362: 777-781.
53. Corrao S, Argano C, Pistone G, Messina S, Calvo L, et al. (2015) Rheumatoid arthritis affects left ventricular mass: Systematic review and meta-analysis. Eur J Intern Med 26: 259-267.
54. Thomas JD, Popovi ZB (2006) Assessment of left ventricular function by cardiac ultrasound. J Am Coll Cardiol 48: 2012-2025.
55. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, et al. (2005) Recommendations for chamber quantification: a report from the

American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. J Am Soc Echocardiogr 18: 1440-1463.

56. Quiñones MA, Otto CM, Stoddard M, Waggoner A, Zoghbi WA, et al. (2002) Recommendations for quantification of Doppler echocardiography: a report from the Doppler Quantification Task Force of the Nomenclature and Standards Committee of the American Society of Echocardiography. J Am Soc Echocardiogr 15: 167-184.

57. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, et al. (2015) Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr 28: 1-39.

58. Kumar V, Kishan AJ, Daga LC, Shrivastava S (2014) Strain Rate Imaging: Real World Scenario? J Cardiovasc Dis Diagn 2: 145.

59. Arias-Godínez JA, Guadalajara-Boo JF, Patel AR, Pandian NG (2011) Function and mechanics of the left ventricle: from tissue Doppler imaging to three dimensional speckle tracking. Arch Cardiol Mex 81: 114-125.