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Left ventricular morphology and function in patients with rheumatoid arthritis

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Summary
Objectives Congestive heart failure (CHF) and inflammation are important contributors to the excess of overall morbidity and mortality in patients with rheumatoid arthritis (RA). CHF rather than ischaemic heart disease (IHD) appears to participate on the mortality in these patients. However, there are controversial results about significance of plasma N-terminal of pro-B type natriuretic peptide (NT-proBNP) and other inflammatory markers investigation for an early detection of heart dysfunction.

The *aim* of this study was to examine the cardiac morphology and function in patients with RA in relation to the plasma NT-proBNP and to inflammatory markers.

Subjects and methods Sixty patients with RA (52 women and 8 men) and 30 gender and age matched controls were included in the study. Blood samples were analyzed for NT-proBNP, tumor necrosis factor alpha (TNF-alpha), interleukin 6 (IL-6), and C-reactive protein (CRP). Transthoracic echocardiography was performed on the same day in all subjects.

Results RA patients had significantly higher plasma NT-pro BNP as compared with controls (99.39 ± 8.98 vs. 66.90 ± 7.93 pg/ml, $p < 0.05$) and significantly higher levels of TNF-alpha, IL-6 and CRP (for all $p < 0.01$). In RA group higher levels of NT-proBNP were detected in rheumatoid factor (RF) posivite patients. Patients with RA had significantly worse left ventriclular (LV) systolic function (LV ejection fraction (LVEF) 64.6 ± 0.8 vs. 70.1 ± 1.3 %, $p < 0.01$) and diastolic function (E/A 1.11 ± 0.05 vs. 1.32 ± 0.07, $p < 0.05$). There were no correlations of NT-proBNP with paramaters of systolic and diastolic function, however, a negative correlation of TNF-alpha with these parameters was detected (TNF-alpha vs. LV mass index (LVM-i): $r = -0.34$, $p < 0.05$), TNF-alpha vs. LVEF: $r = -0.30$, $p < 0.05$ and TNF-alpha vs. E/A: $r = -0.30$, $p < 0.05$).

Conclusions We conclude that TNF-alpha may be better marker of heart impairment caused by chronic inflammation in RA patients than NT-proBNP.

Keywords: Rheumatoid arthritis, NT-proBNP, TNF-alpha, Heart function, Echocardiography

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Linksventrikuläre Funktion und Morphologie bei Patienten mit rheumatoider Arthritis

Zusammenfassung
Ziel der Studie Kongestives Herzversagen und Entzündung tragen wesentlich zu der erhöhten Morbidität und Mortalität von Patienten mit rheumatoider Arthritis (RA) bei. Das kongestive Herzversagen scheint eher an der erhöhten Mortalität schuld zu sein als eine ischämische Herzerkrankung. Es existieren allerdings widersprüchliche Ergebnisse bezüglich der Bedeutung von Plasma N-terminal pro-B type natriuretic peptide (NT-proBNP) und anderen Entzündungsparametern bei der Erkennung der Verschlechterung der Herzfunktion.

Ziel dieser Studie war es, die Morphologie und Funktion des Herzens bei Patienten mit RA zu untersuchen und die Ergebnisse mit dem Plasma NT-proBNP und verschiedenen Entzündungsmarkern in Relation zu setzen.

Patienten und Methodik 60 Patienten mit RA (davon 52 Frauen) und 30 geschlechts- und altersmäßig gematchte Kontrollen wurden untersucht. Aus den Blutproben wur-

den NT-proBNP, TNF-alpha, IL-6 und CRP bestimmt. Bei allen Patienten und Kontrollen wurde am selben Tag eine transthorakale Echokardiographie durchgeführt.

Ergebnisse RA Patienten hatten signifikant höhere Plasma NT-proBNP Spiegel als die Kontrollen (99,39 ± 8,98 vs. 66,90 ± 7,93 pg/ml, $p < 0{,}05$) sowie signifikant höhere TNF-alpha, IL-6 und CRP Spiegel ($p < 0{,}01$ für alle). Innerhalb der Patienten mit RA wurden bei den Rheuma-Faktor positiven Patienten höhere NT-proBNP Konzentrationen gemessen. Patienten mit RA hatten eine signifikant schlechtere systolische Linksventrikelfunktion (LVEF 64,6 ± 0,8 vs. 70,1 ± 1,3 %, $p < 0{,}01$) und diastolische Funktion (E/A 1,11 ± 0,05 vs. 1,32 ± 0,07, $p < 0{,}05$). Es ergab sich keine Korrelation von NT-proBNP mit Parametern der systolischen und diastolischen Funktion. TNF-alpha allerdings war mit diesen Parametern negativ korreliert: TNF-alpha vs. LVM-i: $r = -0{,}34$, $p < 0{,}05$, TNF-alpha vs. LVEF: $r = -0{,}30$, $p < 0{,}05$ und TNF-alpha vs. E/A: $r = -0{,}30$, $p < 0{,}05$.

Schlussfolgerungen Wir schließen aus unseren Ergebnissen, dass TNF-alpha ein besserer Marker der bei RA Patienten durch chronische Entzündung ausgelösten Verschlechterung der Herzfunktion ist als hNT-proBNP.

Schlüsselwörter: Rheumatoide Arthritis, NT-proBNP, TNF-alpha, Herzfunktion, Echokardiographie

Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disease affecting approximately 1 % of the population [1]. Over the last decade, many studies demonstrated an increased mortality in patients with RA ranging from moderate to several fold higher risk. The strongest predictors of survival were extraarticular manifestations, comorbidities, and the presence of rheumatoid factor (RF) [2–4]. There is evidence that cardiovascular (CV) morbidity and mortality is the most prevalent among their other causes in RA [4–6]. Besides traditional risk factors for ischaemic heart disease (IHD) it was shown that congestive heart failure (CHF) as well as inflammation are important contributors to the excess of overall morbidity and mortality in RA patients independently in the presence of IHD. CHF rather than IHD appears to participate on the mortality of RA patients [6–8]. The influence of chronic inflammation on CV risk was supported by studies documenting a lower risk of CV diseases in RA patients using various antiinflammatory drugs including disease modifying antirheumatic drugs, nonsteroidal antiinflammatory drugs, glucocorticoids, or tumor necrosis factor alpha (TNF-alpha) inhibitors [9–11]. There are controversies regarding the etiology of CHF. Only a few studies documented a decreased left ventricular (LV) systolic function [12, 13], while many others found a high frequency of LV diastolic dysfunction, especially in those with long standing RA [14–17].

B type natriuretic peptide (BNP) is a humoral cardiovascular biomarker originated from cardiac atria and ventricles in response to their volume or pressure overload. BNP, particularly N-terminal fragment of pro-BNP (NT-proBNP) is widely used in clinical monitoring of patients with heart failure [18, 19]. It is considered to be a sensitive marker of symptomatic, and asymptomatic heart failure [20, 21].

There are also controversial results about significance of BNP evaluation in RA patients. Some authors found the association of BNP/NT-proBNP with echocardiographic parameters of diastolic function and relation to the LV or right ventricle dysfunction [22, 23]. On the other side, some confirmed only association of BNP/NT-proBNP with the disease activity and markers of chronic inflammation such as TNF-alpha [24, 25]. Majority of the studies were focused on either BNP/NT-proBNP assessment or echocardiographic measurement. There are only a few studies assessing both humoral and echocardiographic markers of cardiac morphology and function in relationship. Aim of this study was to examine the echocardiographic parameters of LV morphology and function in patients with RA in relation to NT-proBNP levels as well as to inflammatory markers.

Patients, materials, and methods

Patients

The study participants were residents of East Slovakia region with the diagnosis of RA. Altogether 64 patients were included in the study. It was excluded for 4 patients and 60 patients (52 women, 8 men, average age 48.8 ± 11.9 years, median 51 years, range 23–64 years) were analyzed subsequently. 24 (40 %) patients had negative RF and 36 (60 %) were classified to be RF positive. According to the stage of the disease, 2 patients (3 %) belonged to stage I, 20 (33 %) to stage II, 18(30 %) to stage III and 13 (22 %) to stage IV, respectively. In seven (12 %) patients the disease was not clearly classified in stages. 48 (80 %) patients were treated by disease modifying antirheumatic drugs, 29 (48 %) patients by glucocorticoids and 30 (50 %) of all patients were treated by biologic therapy (infliximab, adalimumab, etanercept, certolizumab, and abatacept) when indication criteria were fulfilled. Mean duration of the disease was 11.8 ± 7.4 years (median 10, range 2–34 years). All patients fulfilled the classification criteria of The American Rheumatism Association 1987 [26].

Control group consisted of 30 gender and age matched subjects (25 women, 5 men). Average age of controls was 46.7 ± 11.0 years (median 51, range 24–62 years).

Exclusion criteria for RA patients and controls were as follows: age over 65 years (due to markedly increased cardiovascular morbidity in the age over 65 years) and history of heart disease especially coronary heart disease, cardiomyopathy, valvular disorders, and arrhythmias. Patients with heart failure (defined as present or previous clinical signs of heart failure) and severe renal failure (expressed as glomerulare filtration rate < 60/ml/min/1.73 m^2) were also excluded. All control subjects

had no history and no signs of systemic connective tissue diseases, inflammatory bowel diseases, or other chronic inflammatory diseases.

The information about comorbidities, especially common cardiovascular risk factors, of RA patients and controls was taken from history (including medication), documentation, and laboratory tests. Diagnosis of arterial hypertension was based on the criteria of The European Society of Hypertension and The European Society of Cardiology 2007 [27]. Diagnosis of dyslipidaemia was based on the criteria of The European Society of Cardiology and The European Atherosclerosis Society 2011 [28]. Diabetes mellitus or impaired glucose tolerance was defined in accordance with the criteria of The American Diabetes Association 1997 [29]. Overweight and obesity were stated in accordance with Body Mass Index (BMI) calculated as weight to square of height ratio (BMI 25.0–29.9 kg/m^2 for overweight and > 30.0 kg/m^2 for obesity).

The study protocol was approved by the Ethics Committee of University Hospital of Louis Pasteur, Košice, Slovakia. All patients gave their written informed consent prior to participation in accordance with the Declaration of Helsinki.

Study design

Blood samples were taken in all patients from antecubital vein in the morning of the day of echocardiographic evaluation after night fasting. Immediately after, blood sampling tubes were transferred to the laboratory for analysis. Investigations were performed in patiens with RA in remission (expressed as Disease Activity Score 28 < 2.6), without any active inflammatory disease.

Methods

Transthoracic echocardiography was performed with Esaote Technos MPX machine using 2.5–3.5 MHz transducer by registered cardiac sonographer. 2D and Doppler echocardiograms were used to measure the following parameters: interventricular septum thickness (IVST), LV posterior wall thickness (PWT), LV enddiastolic diameter index (LVEDD-i), and LV mass index (LVM-i). Indexes were calculated by adjustment for body surface area. LV ejection fraction (LVEF) was calculated by Simpson's rule. Systolic dysfunction was defined as LVEF < 55 %. Aditionally, deceleration time (DT), peak velocity of filling in early diastole (E) and in atrial systole (A), and their ratio (E/A) were evaluated as the expression of the diastolic function. There were three echocardiographic patterns of diastolic dysfunction: abnormal relaxation (E/A < 1.0 and DT > 200 ms), pseudonormal filling (E/A > 1.0, in Valsalva maneuver < 1.0 and DT 140–200 ms), and restrictive filling (E/A > 1.5 and DT < 140 ms). The prevalence of diastolic dysfunction was counted without differentiation of diastolic dysfunction patterns.

Blood samples were analyzed for NT-proBNP, TNF-alpha, interleukin 6 (IL-6), and C-reactive protein (CRP).

NT-proBNP was examined by the electrochemiluminiscent immunoassay (ECLIA) using kits Roche Germany on ELECSYS analyzer. The cut-off level was defined by method and analyzer producer (Roche Germany) and analyzing laboratory on the basis of general population. It was set 125 pg/ml without gender difference. TNF-alpha and IL-6 were measured by enzyme-linked immunosorbent assay (ELISA) using kits Thermo Scientific USA. CRP was measured by routine method.

Statistical analysis

Values are expressed as means ± standard error of mean (means ± SEM). Differences between measured parameters in patients and controls were assessed by unpaired T test. If the data were not normally distributed, it was udes Mann–Whitney test. The assesment of qualitative parameters was performed by χ^2 test. Linear regression analysis with determination of Pearsons correlation coefficients (r) was used for evaluation of correlations. A level of $p < 0.05$ was considered to be statistically significant.

Results

The prevalence of common cardiovascular risk factors in RA and control groups is shown in the Table 1. Patients with RA had significantly higher prevalence of arterial hypertension ($p < 0.05$) and significantly higher prevalence of diabetes mellitus/impaired glucose tolerance ($p < 0.05$) as compared with controls. There were no significant differences in the prevalence of overweight

Table 1. Prevalence of common cardiovascular risk factors in patients with RA and controls

Risk factor	RA patients		Controls		Significance
	Number	Percentage	Number	Percentage	
Arterial hypertension	25	42	6	20	$p < 0.05$
Impaired glucose tolerance/diabetes mellitus	8	13	0	0	$p < 0.05$
Dyslipidaemia	32	53	21	70	NS
Overweight/obesity	29	48	15	50	NS
Smoking	9	15	6	20	NS

RA rheumatoid arthritis, *NS* no significance

Table 2. Mean values of demographic and laboratory parameters in RA patients and controls

Parameter	RA patients	Controls	Significance
Age (years)	48.8 ± 1.5	46.7 ± 2.0	NS
Gender (*number* (%))			
Women	58 (86.7)	25 (83.3)	NS
Men	8 (13.3)	5 (16.7)	NS
BMI (kg/m^2)	24.6 ± 0.5	26.3 ± 0.8	$p<0.05$
NT-proBNP (pg/ml)	99.39 ± 8.98	66.90 ± 7.93	$p<0.05$
TNF-alpha (pg/ml)	26.01 ± 5.28	6.94 ± 2.29	$p<0.01$
IL-6 (pg/ml)	2.55 ± 0.68	2.22 ± 1.37	$p<0.01$
CRP (mg/l)	6.23 ± 1.08	1.94 ± 0.27	$p<0.01$

BMI body mass index, *NT-proBNP* N-terminal fragment of pro-B type natriuretic peptide, *TNF-alpha* tumor necrosis factor alpha, *IL-6* interleukin 6, *CRP* C-reactive protein, *RA* rheumatoid arthritis, *NS* no significance

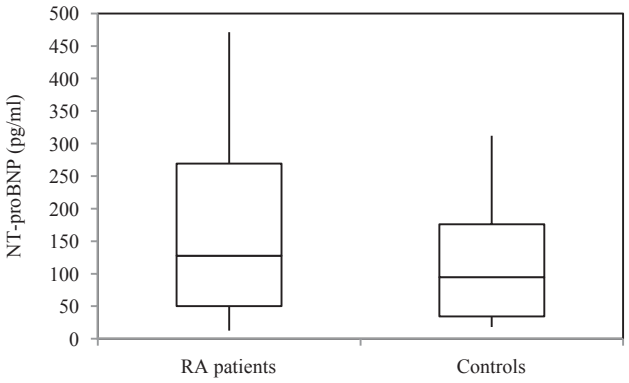

Fig. 1 Plasma levels of NT-proBNP in RA patients and controls

or obesity, dyslipidaemia, and smoking between both groups.

Mean values of demographic and laboratory parameters in RA patients and controls are shown in the Table 2. Despite no significant difference in the prevalence of overweight/obesity, RA patients had significantly lower BMI ($p<0.05$). As expected they had a higher levels of proinflammatory cytokines, i.e., TNF-alpha ($p<0.01$), IL-6 ($p<0.01$), and CRP ($p<0.01$), respectively. As shown in the Fig. 1, although plasma levels of NT-proBNP overlaped in RA patients and controls, plasma NT-proBNP was significantly higher (99.39 ± 8.98 vs. 66.90 ± 7.93 pg/ml, $p<0.05$) in RA patients. RF positive RA patients had significantly higher levels of NT-proBNP than RF negative patients (119.39 ± 12.60 vs. 69.40 ± 9.48 pg/ml, respectively, $p<0.01$).

Mean values of echocardiographic parameters of the LV structure and function are demonstrated in the Table 3. In general, LVEF was found to be significantly decreased in RA patients as compared to control group ($p<0.01$). There were significant differences in LVEDD-i which was higher ($p<0.05$) and diastolic function expressed as E/A which was significantly lower in RA patients ($p<0.05$). No significant differences were detected in IVST, PWT, LVM-i, and DT between both groups. The prevalence of LV systolic dysfunction was

Table 3. Mean values of selected echocardiographic parameters of the left ventricle structure and function in RA patients and controls

Parameter	RA patients	Controls	Significance
LVEF (%)	64.6 ± 0.8	70.1 ± 1.3	$p<0.01$
LVEDD-i. (cm/m^2)	2.70 ± 0.04	2.55 ± 0.06	$p<0.05$
IVST (cm)	0.94 ± 0.02	0.95 ± 0.02	NS
PWT (cm)	0.94 ± 0.02	0.93 ± 0.03	NS
LWM-i. (g/m^2)	102.2 ± 3.8	100.9 ± 4.7	NS
E/A	1.11 ± 0.05	1.32 ± 0.07	$p<0.05$
DT (ms)	184.4 ± 7.5	164.2 ± 7.9	NS

LVEF left ventricle ejection fraction, *LVEDD-i* left ventricle enddiastolic diameter index, *IVST* interventricular septum thickness, *PWT* left ventricle posterior wall thickness, *LVM-i* left ventricle mass index, *E* peak velocity of filling in early diastole, *A* peak velocity of filling in atrial systole, *DT* deceleration time, *RA* rheumatoid arthritis, *NS* no significance

detected in only two (3 %) RA patients, what was not significant ($p=1,0$) in comparison with controls. The exclusion of these two patients (LVEF 53 and 51 %, NT-proBNP 170.50 and 17.42 pg/ml, respectively) did not influence significant difference of NT-proBNP levels between RA patients and controls. We were not able to detect the difference in the prevalence of diastolic dysfunction which was slightly, but not significantly more frequent (42 vs. 27 % in RA and control group respectively). No significant differences were demonstrated in the prevalence of the LV dilation and hypertrophy. Nevertheless, the prevalence of any echocardiographic signs of the LV impairment including morphological and functional changes was significantly higher in RA patients ($p<0.05$).

Using linear regression analysis in RA group a significant positive corerelation was demonstrated between age and NT-proBNP ($r=0.38$, $p<0.01$), BMI vs. NT-proBNP ($r=0.35$, $p<0.01$) and LVM-i. vs. NT-proBNP ($r=0.28$, $p<0.05$) as well. Moreover, a negative correlation was found between TNF-alpha and LVM-i ($r=-0.34$, $p<0.05$). TNF-alpha also negatively correlated with LVEF ($r=-0.30$, $p<0.05$) and E/A ($r=-0.30$, $p<0.05$). There were no correlations between other inflammatory markers (IL-6 and CRP) and echocardiographic parameters. The correlations between the duration of RA vs. BMI, NT-proBNP, and echocardiographic parameters of LV (data not shown) were also not detected . The sensitivity of NT-proBNP for any heart pathology detection in RA patients by cut-off value 125 pg/ml without gender difference was 69 %, specificity was 51 %, positive predictive value was 34 % and negative predictive value was 19 %.

Discussion

In the present study, we found markedly higher plasma levels of proinflammatory markers, i.e., TNF-alpha ($p<0.01$), IL-6 ($p<0.01$), and CRP ($p<0.01$) and significantly higher plasma NT-proBNP levels in RA patients as compared to controls ($p<0.05$). The similar findings were demonstrated by other studies [22, 24]. We also con-

firmed a positive correlation between NT-proBNP vs. age and BMI. However, no correlation was observed between NT-proBNP and inflammatory markers including TNF-alpha, IL-6, and CRP. There was a discrepancy with the results of studies in RA patients and common patients with CHF, where positive correlation of plasma BNP or NT-proBNP with inflammatory markers (TNF-alpha, CRP, and IL-6), was observed [24, 25, 31]. We found low sensitivity (69 %) and very low specificity (51 %) of NT-proBNP for detection of any heart pathology. Solus et al. [24] also showed that specificity of BNP measurement was significantly lower in RA patients than in non-RA patients. In accordance with these studies, we can conclude that increased NT-proBNP may overestimate the severity of heart failure in RA patients and the presence of inflammation should be considered a noncardiac source of NT-proBNP elevation. Therefore, a BNP assessment may be less effective for screening in RA subjects compared to the general population.

We confirmed slightly but significantly decreased systolic function in RA patients as compared with control group despite the fact that two patients exerted systolic dysfunction of LV. Our results are in agreement with the finding of others confirming a slightly reduced systolic function in RA patients [12, 13, 32]. Thus, we suppose that slight reduction of LVEF may be present in RA patients, however, the prevalence of systolic dysfunction may be similar to general population. We did not confirm the results of Rudominer et al. [33] who demonstrated preserved systolic function in RA . They also found increased LVM, higher prevalence of LV hypertrophy, and higher LVEDD in RA. We only confirmed the significantly higher LVEDD, but no other significant differences in the LV structural parameters including IVST, PWT, and LVM-i.

RA patients in our study had significantly lower diastolic function expressed as E/A ratio, however, the prevalence of diastolic dysfunction was similar to controls. There was no association between RA duration and echocardiographic parameters as well as NT-proBNP levels and echocardiographic parameters except of slight association with LVM-i. ($r = 0.28$, $p < 0.05$). In the study of Crowson et al. [23], altough RA patients had more likely elevated levels of BNP only few of them with elevated BNP had actually LV diastolic dysfunction. Our findings are also in contrast with other studies with impaired diastolic function correlating with RA duration [14, 16, 17]. This discrepance could be explained probably by the wide range of RA duration in the group of patients, which can also explain only a slight decrease in diastolic function.

We found significant negative correlation of TNF-alpha with LVM-i., LVEF, and E/A ($p < 0.05$ for all). There was no correlation of IL-6 and CRP with echocardiographic parameters. Several studies showed the association of inflammatory markers as TNF-apha, IL-6, and IL-10 with systolic and diastolic dysfunction in general population [34, 35]. In RA patients, there is only one study of Liang et al. [17] presenting the significant association of IL-6 with left ventricle diastolic dysfunction but without the association of TNF-alpha with echocardiographic parameters in RA patients . These results indicate that TNF-alpha rather than BNP or NT-proBNP levels is related to the cardiac structure and function in RA.

According to our best klnowledge, this is the study confirming that TNF-alpha may be the better marker of heart impairment caused by chronic inflammation in RA patients. NT-proBNP seems to be less considerable. Therefore, it is less convenient for screening of early stages of heart impairment in RA patients and the interpretation of NT-proBNP levels as cardiac marker should be in relation to inflammatory activity in RA patients. It needs to be confirmed by other studies on larger cohort of patients.

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Conflict of interest
The authors declare that there is no conflict of interest.

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