Left ventricular function in rheumatoid arthritis during anti-TNF-α treatment: a speckle tracking prospective echocardiographic study

Funzione ventricolare sinistra nell'artrite reumatoide durante trattamento anti-TNF-α:
uno studio prospettico ecocardiografico con speckle tracking

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Abstract

Aim. Rheumatoid arthritis (RA) shows a high risk for cardiovascular disease, including heart failure. Although TNF-α has been implicated in the pathogenesis of myocardial remodelling, TNF-α inhibition did not show any efficacy in patients with advanced heart failure and should be contraindicated in RA with cardiac complications. We aimed to assess global left ventricular (LV) systolic function using global longitudinal strain (GLS) as a measure of myocardial deformation, in a group of RA patients before and during anti-TNF-α treatment.

Methods. 13 patients (female:male 7:6) affected by RA were prospectively followed for one year during anti TNF-α treatment. Every subject underwent echocardiography before starting anti-TNF-α drugs and after one year of treatment, to evaluate LV ejection fraction (EF), telediastolic diameter, telediastolic volume and global longitudinal strain (GLS) that was calculated using 2D speckle tracking as the mean GLS from three standard apical views (2, 3 and 4 -chambers). The patients showed a mean age of 43 years at RA onset (SD: 13) and a mean follow-up of 7.3 years (SD: 4.8). Steroid and methotrexate were used in 84.6% and 100%, respectively, in association with etanercept (6 cases), adalimumab (4 cases) and infliximab (3 cases).

Results. Patients globally showed a normal EF before and after one year of treatment (mean: 65% and 65.7%, respectively). GLS did not differ before or after anti-TNF-α treatment (mean: -15.8% and -16.7%, respectively).

Conclusion. Anti-TNF-α treatment did not significantly modify myocardial contractility after 12 months.

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Riassunto

Scopo. L'artrite reumatoide (AR) si caratterizza per un elevato rischio di malattie cardiovascolari, tra cui lo scompenso cardiaco. Sebbene il TNF-α sia implicato nella patogenesi del remodelling miocardico, la sua inibizione non ha mostrato alcuna efficacia in pazienti con scompenso cardiaco avanzato e andrebbe evitato nell'AR con complicanze cardiache. Nostro scopo è stato valutare la funzione ventricolare sinistra globale, utilizzando il global longitudinal strain (GLS) come misura di deformazione miocardica, in un gruppo di pazienti affetti da AR prima e durante il trattamento anti-TNF-α.

Metodi. 13 pazienti (7 donne e 6 uomini) affetti da AR sono stati seguiti prospetticamente per un anno durante trattamento anti-TNF-α. Ognuno di essi ha eseguito un ecocardiogramma prima di iniziare tali farmaci e dopo un anno di trattamento, per valutare la frazione d'eiezione (FE) ventricolare sinistra, diametro e volume telediastolici del ventricolo sinistro e GLS, che è stato calcolato mediante il 2D speckle tracking come GLS medio tra le tre proiezioni apicali standard (2, 3 e 4-camere). I pazienti avevano un'età media di 43 anni all'esordio di AR (DS: 13) e hanno seguito un follow-up medio di 7.3 anni (DS: 4.8). Steroide e methotrexate erano assunti da 84.6% e 100% di essi, rispettivamente, in associazione con etanerecept (6 casi), adalimumab (4 casi) e infliximab (3 casi).

Risultati. I pazienti mostravano globalmente una normale FE prima e dopo un anno di trattamento (media: 65% e 65.7%, rispettivamente). Il GLS non differiva tra prima e dopo il trattamento anti-TNF-α (media: -15.8% e -16.7%, rispettivamente).

Conclusione. Il trattamento anti-TNF-α non ha modificato significativamente la contrattilità miocardica dopo 12 mesi.

Introduction

Cytokine tumor necrosis factor-α (TNF-α) plays a key role in the pathogenesis of rheumatoid arthritis (RA) [1]. The introduction of anti-TNF-α drugs infliximab, etanercept and adalimumab has dramatically improved the outcomes of severe RA beyond those achieved with traditional disease-modifying antirheumatic drugs (DMARDs) [2-4].

Anti-TNF-α therapy has been reported to decrease cardiovascular risk in RA, with multiple reasons being attributed to this reduction: decreased systemic inflammation, corticoid-sparing effects, and increased high density lipoprotein (HDL) levels [5,6] but the exact underlying mechanism(s) have been widely debated [7].

However there has not been yet any trial with cardiovascular endpoints in this setting and the interpretation of the effects of anti-TNF-α therapies on cardiovascular risk in RA patients is very complex. Furthermore, trials with anti-TNF-α therapies (etanercept and infliximab) against heart failure (HF) in non-RA patients were halted due to higher combined risk of death from any cause or hospitalization for HF [8,9].

An even higher HF risk than that observed with placebo was found in a high-dose infliximab group (10 mg/kg body weight) [8]. This raised concerns about HF risk in RA patients treated with infliximab, etanercept, or adalimumab.

Further data are required to extend our knowledge of the effects of anti-TNF-α therapies on cardiac function in patients with RA without HF.

Patients with severe RA, especially those with highly active disease, are at increased risk of developing HF. If treatment with anti-TNF-α inhibitors is effective in reducing the inflammatory activity of the rheumatic disorder, it is more likely to be beneficial than harmful with regard to the risk of HF. Screening for cardiac risk factors and effective treatment of both the rheumatic disorder and cardiac disease are essential. Therefore the assessment of anti-TNF-α related changes in myocardial function is very important. Nonetheless there has not been any literature data about the effects of anti-TNF-α inhibitors on cardiac contractility.

The availability of sophisticated noninvasive techniques may enhance our understanding of global ventricular function in RA submitted to anti-TNF-α therapies. Speckle tracking is a recently developed echocardiographic technique that analyzes the degree of myocardial deformation, known as strain, throughout the cardiac cycle.

In this study we examined changes in myocardial strain as measured by speckle tracking echocardiography in RA patients before and after one year of anti-TNF-α treatment.

Materials and methods

A total of 13 consecutive patients with RA who met the revised American College of Rheumatology classification criteria for RA [10] were prospectively enrolled. Inclusion criteria were: (i) no clinical history of cardiac or vascular diseases, diabetes mellitus, renal failure, pulmonary disease, hypercholesterolemia, and smoking; (ii) normal rest electrocardiogram and sinus rhythm; (iii) blood pressure taken on two different days (systolic pressure <140 mmHg and diastolic pressure <90 mmHg); (iv) no significant valvular heart disease; (v)

normal values for serum electrolytes, fasting and postprandial glycaemic levels, and thyroid function test; (vi) normal wall motion and systolic function documented by two-dimensional (2D) echocardiography; (vii) good quality echocardiographic imaging; and (viii) written informed consent.

Swollen joint count, tender joint count, erythrocyte sedimentation rate (ESR), and visual analogue pain score (0-100 mm) were recorded for the disease-activity score-28 (DAS-28) [11]. C-reactive protein (CRP) and rheumatoid factor (latex agglutination test) were also determined at the time of enrollment and at the end of the study.

Echocardiograms were done using Vivid 7 (General Electric Medical Systems, Milwaukee, WI, USA) equipment with a 3.5 MHz transducer, with the patients in the left lateral decubitus position, in accordance with the standardization of the American Society of Echocardiography [12]. Digital loops were stored on the hard disk of the echocardiograph for on-line and off-line analyses and transferred to a workstation (EchoPac, Vingmed, General Electric) for off-line analysis. Left ventricular (LV) volumes and ejection fraction (EF) were obtained by the modified biplane Simpson's method. Speckle tracking analysis using the commercially available automated function image technique was applied for assessment of global longitudinal strain (GLS) from apical long-axis slices (long-axis and 2- and 4-chamber views) using a previously reported method [13,14].

The endocardial borders were traced in the end-systolic frame of the 2D images from the three apical views. Speckles were tracked frame by frame throughout the LV wall during the cardiac cycle and basal, mid, and apical regions of interest were created. Segments that failed to track were manually adjusted by the operator until the software approved them.

Longitudinal peak systolic strain (LPSS) was acquired in the apical 2-,3-, and 4-chamber views. GLS was calculated as the average longitudinal strain of the segments of 2-,3- and 4 chamber views (as the mean strain of all 18 segments). All measurements were made blinded to other results and clinical details.

Statistical analysis

Data are presented as mean ± standard deviation (SD). A p value of <0.05 was used to indicate differences between the groups that were statistically significant. Differences between groups were compared with the paired Student's t-test for continuous variables, after assessing their gaussianity with the Kolmogorov-Smirnov test. Data analysis was performed with a commercially available statistical analysis software package (SPSS for Windows 12.0, SPSS, Chicago, IL, USA).

Results

Thirteen patients (female:male: 7:6) were enrolled in the study and showed a mean age of 43 years at RA onset (SD: 13) and a mean follow-up of 7.3 years (SD: 4.8). Mean disease duration was 11.4 years (SD: 4.9).

Eight out of the thirteen patients were rheumatoid factor positive (61.5%) while 7 (53.8%) had detectable anti-cyclic cytrullinated peptide (anti-CCP). Every patient was given methotrexate (10-15 mg weekly) and all the patients but one were taking 5 mg prednisone daily at the time anti-TNF-α treatment started. The TNF-α blocking agents used were adalimumab (Humira, 40 mg every two weeks) in 5 cases, etanercept (Enbrel, 25 mg twice a week) and infliximab (Remicade, 3 mg/kg every 8 week) in 4 patients, each at the time of the cardiac evaluation and throughout the study. High disease activity score as measured by DAS28 was recorded at the entry on the study while after one year a sig-

Table 1. Demographic and clinical data of the study population.

	Baseline	Follow-up	*P*
Age (years)	51±13		-
Women/Men	6/7		-
BMI (kg/m^2)	28.1± 2.7	27.1±2.4	0.9
Systolic blood pressure (mmHg)	122.9±10.6	122.5±3.5	0.8
Diastolic blood pressure (mmHg)	68.7±10.4	67.9±10.6	0.7
Rheumatoid factor positiveness	8 (61.5%)		-
Anti-CCP positiveness	7 (53.8%)		-
DAS 28	4.44±0.91	2.35±1.32	0.0002
CRP (mg/dL)	11.45±13.70	1.55±2.83	0.0287

BMI, body mass index; CCP, cyclic cytrullinated peptides; DAS, disease activity score; CRP, C-reactive protein.

nificantly lower score was recorded (*p*=0.0002). The same was observed with CRP values that significantly decreased from a mean of 11.45 to 1.55 mg/dL after one year of anti-TNF-α drugs. Clinical and demographic characteristics of the study population are shown in Table 1.

Patients globally showed a normal left ventricle EF before and after one year of treatment (mean:65% and 65.7%, respectively; p>0.05).

2D strain was obtainable in all patients. Results of 2D segmental and LPSS strain analysis are shown in Table 2. GLS did not differ before or after anti-TNF-α treatment (mean: -16.3% and -17.16%, respectively; p>0.05). In particular there was no significant difference in every segmental strain. Left ventricular EF and GLS in RA were neither related to disease activity nor to the use of TNF-α blockers.

Table 2. Peak systolic regional strain values of population by segment.

2D strain (%)	Baseline	After anti-TNF-α therapy	P
Longitudinal 4-chamber view			
Basale septal	-10.3	-12.3	ns
Mid septal	-15.3	-17.59	ns
Apical septal	-17.27	-18.95	ns
Apical lateral	-17.27	-18.45	ns
Mid-lateral	-15.40	-17.48	ns
Basal lateral	-15.20	-16.72	ns
Global longitudinal strain	-15.3	-16.9	ns
Longitudinal 3-chamber view			
Basal posterior	-14.64	-14.73	ns
Mid posterior	-15.32	-15.89	ns
Apical posterior	-16.76	-16.62	ns
Apical anteroseptal	-17.45	-17.92	ns
Mid anteroseptal	-18.33	-17.86	ns
Basal anteroseptal	-18.15	-18.42	ns
Global longitudinal strain	-16.8	-16.8	ns
Longitudinal 2-chamber view			
Basal inferior	-17.12	-18.21	ns
Mid posterior	-15.92	-16.05	ns
Apical posterior	-16.34	-17.34	ns
Apical anteroseptal	-18.5	-19.5	ns
Mid anteroseptal	-17.07	-17.36	ns
Basal anteroseptal	-17.51	-18.52	ns
Global longitudinal strain	-17.08	-17.8	ns

Discussion

Despite animal and human studies highlighting the importance of TNF-α in the pathogenesis of HF, randomized controlled trials have shown a lack of efficacy of anti-TNF-α agents in patients with advanced HF [8,9]. RA patients have a higher risk of HF than the general population [15-17]. There are recommendations to avoid the use of anti-TNF-α agents in patients with HF, not only in those with worse functional classes [18] but even in those with moderate symptoms, suggesting discontinuation if symptoms worsen on treatment.

It is very important to evaluate global LV systolic function in RA patients to determine the eligibility for anti-TNF-α therapy. However, the measurement of LV EF presents a number of challenges related to image quality, the assumptions of LV geometry, and expertise of the echocardiographist. 2D strain is an automated and quantitative technique for the measurement of global long-axis function from gray-scale images. Longitudinal tissue deformation is evaluated by frame-by-frame tracking of individual speckles throughout the cardiac cycle, and GLS is calculated from the mean of 18 cardiac segments [14].

Previous investigations have correlated GLS with measures of LV function, derived both by echocardiography and by magnetic resonance imaging [19], in populations with normal EF, [14] chronic HF, and acute ST-elevation myocardial infarction [13]. The calculation of GLS was proven to be both reliable and quick across both experienced and inexperienced observers [14], being angle-independent (differently from tissue Doppler imaging [TDI]). In particular, Birdane *et al*. showed that biventricular TDI is impaired in 60 RA patients, revealing diastolic dysfunction and an important key to comprehend heart involvement in RA. In fact, myocardium perfusion by coronary arteries occurs during diastole, and diastolic dysfunction may contribute to reduce blood supply. Moreover, [20] Sitia *et al*. recently demonstrated that both tissue Doppler imaging and 2D speckle tracking strain analysis are altered in 22 RA patients without coronary artery disease despite normal standard echocardiography, as compared with age- and gender-matched healthy controls [21]. They concluded that 2D strain is a feasible and promising tool in the follow-up of these subjects.

The early detection of ventricular dysfunction may be very important in RA patients especially when starting treatment with anti-TNF-α. Speckle tracking is a noninvasive imaging technique that allows the detection of early subclinical dysfunction not possible with conventional echocardiography and in an insonation angle-independent way.

Our study suggests that anti-TNF-α treatment does not seem to significantly modify myocardial contractility after 12 months. However, GLS was lower in RA patients than what has been reported in normal subjects in previously published studies [22]. These data are in accord

to those by Sitia *et al.* [21]. A subclinical alteration in GLS than healthy subjects is a demonstrated sign of heart involvement in RA. However, Sitia *et al.* included only 10 patients out of 22 treated by anti-TNF-α drugs and did not provide any argumentation about the difference between the two groups [21]. In addition, no RA patients enrolled by Birdane *et al.* was treated with such drugs [20]. To the best of our knowledge, this study is the first to analyze the effect of ant-TNF-α treatment on myocardial contractility. We found that 2D strain subclinical alterations remain stable during one-year follow-up in every LV segment, suggesting a protective role of these drugs. In fact, we can hypothesize that a blocking that cytokine may prevent the evolution of atherosclerotic plaques in coronary arteries, thus limiting myocardial suffering and HF incoming.

Our study suffers from some limitations. First, the small number of patients involved and a probably short follow-up time. However, we calculated that our study have a statistical power between 50 and 60% in detecting a 2D strain difference between paired samples of 2-3% according to its values in Sitia *et al.* [21] and accepted formulae [23]. Second, anti-TNF-α treatment is different among cases. According to our best knowledge, we can only hypothesize that the cardiovascular effects of the three cited drugs are similar, being the same their usefulness in the therapy of RA. Third, we lack informations about B-type natriuretic peptide and exercise capacity, which may allow us to better comprehend the anti-TNF-α effects on myocardium. Forth, we did not considered a sex- and gender-matched healthy control group.

Conclusions

The present study is the first of its kind to thoroughly investigate LV systolic function by the use of speckle tracking techniques in addition to conventional echocardiography in RA patients before and after anti TNF-α therapy. It seem to conclude that these drugs do not modify LV systolic function after one year of treatment, preventing the evolution of atherosclerotic plaques in coronary arteries, thus limiting myocardial suffering and HF incoming.

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