Evaluation of Ascending Aorta Wall in Rheumatoid Arthritis by Tissue and Strain Doppler Imaging During Anti-Tumor Necrosis Factor- α Therapy

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ABSTRACT

Background: Patients with rheumatoid arthritis (RA) are at increased risk of vascular events. Data on the effects of tumor necrosis factor- α (TNF- α) blocking agents on aortic vascular function are still debated.

Hypothesis: To evaluate the effects of anti-TNF- α treatment on elastic properties of the ascending aorta (distensibility, stiffness, and tissue Doppler imaging [TDI] strain) in RA patients.

Methods: We prospectively followed 13 patients affected by RA without cardiovascular risk factors for 1 year during anti-TNF- α treatment. Every subject received an echocardiographic examination before starting anti-TNF- α drugs and after 1 year. Aortic elastic properties were calculated from the echocardiographically derived thoracic aortic diameters, and TDI strain was measured on the wall of the ascending aorta 3 cm above the aortic valve.

Results: We found lower distensibility (12.9 ± 3.5 vs 21.5 ± 7.5 mm Hg $^{-1}$; $P < 0.001$) and a higher stiffness index (21.3 ± 3.6 vs 11.7 ± 1.4 ; $P < 0.001$) in RA cases at baseline compared with values after 1 year of treatment. Peak systolic (S') and diastolic (E' and A') waves of the aortic wall TDI were similar at baseline and at 1 year follow-up (S' wave: 5.6 ± 2.2 cm/s vs 6.5 ± 2.6 cm/s, E' wave: -4.6 ± 2.9 vs -5.0 ± 1.2 cm/s, A' wave: -5.6 ± 0.19 vs -5.9 ± 2.05 cm/s), whereas TDI strain of the aortic wall was improved after anti-TNF- α treatment ($-23.7 \pm 1.4\%$ vs $-31.6 \pm 2.8\%$, $P < 0.001$).

Conclusions: Anti-TNF- α treatment after 12 months significantly modifies the elastic properties of the aorta. This may reflect the favorable changes in its elastic tissue after anti-TNF- α treatment in RA patients without cardiovascular risk factors. This suggests a potential cardiovascular risk benefit.

Introduction

The increased risk of cardiovascular disease (CVD) in patients with rheumatoid arthritis (RA) cannot be explained fully by traditional risk factors.¹ Several disease-related mechanisms may be involved in the development of premature vascular damage in RA.

Arterial stiffness is considered a marker of subclinical vascular disease and increased cardiovascular (CV) risk, and it is markedly abnormal in patients with RA.^{2,3} In addition, small and large artery elasticity is inversely correlated with inflammatory markers, such as C-reactive protein (CRP) and vascular cell adhesion molecules levels.³

Anti-tumor necrosis factor- α (TNF- α) therapy was reported to decrease the cardiovascular risk in RA, with multiple reasons being attributed to this reduction:

decreased systemic inflammation, corticoid-sparing effects, and increased high-density lipoprotein cholesterol levels,^{4,5} but the exact underlying mechanism(s) have been widely debated.⁶

In the literature, there are some data about a reduced CV risk in RA as effect of anti-TNF- α therapy.⁷⁻⁹ A more recent study showed that anti-TNF- α therapy reduces aortic inflammation (evaluated by ^{18}F -fluorodeoxyglucose positron-emission tomography) in patients with RA, and this effect correlates with the decrease in aortic stiffness.¹⁰ This recent study adds diminution of localized vascular inflammation to the growing list of potential mechanisms by which anti-TNF- α biologics may reduce CVD risk.

The objective of this study was to investigate the effects of anti-TNF- α treatment in RA patients over a longer period—1 year—in terms of aortic properties evaluated by M-mode technique, tissue Doppler imaging (TDI), and strain Doppler echocardiography.

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Methods

After approval of the study by the local ethics committee (Spedali Civili and University of Study of Brescia, Brescia, Italy) we enrolled consecutive subjects with RA without CV risk factors.

A total of 150 consecutive RA outpatients attending the rheumatology unit of Spedali Civili (Brescia, Italy) were included to participate to this study. At the time of the inclusion as well as at the end of this study, disease activity measured by means of the Disease Activity Score in 28 Joints (DAS-28)¹¹ and CRP value were recorded. The exclusion criteria of the study were: (1) arterial hypertension (blood pressure >140/90 mm Hg in more than 3 consecutive readings or use of any hypotensive drugs); (2) diabetes; (3) smoking; (4) symptomatic dyspnea or chest pain; (5) any previous myocardial infarction, or surgical or percutaneous revascularization, (6) a positive electrocardiography (ECG) result, perfusion, or echocardiographic exercise or pharmacological stress test; (7) more than mild aortic or mitral regurgitation and/or stenosis; (8) any previous surgical or interventional cardiac or vascular procedure; (9) familial hypercholesterolemia; and (10) any genetic cardiovascular disease, including cardiomyopathy or Marfan syndrome.

We selected 20 RA patients according to these criteria, but only 13 received a complete clinical examination, 12-lead ECG, and 2-dimensional and Doppler transthoracic echocardiography. Echocardiograms were done using Vivid 7 (General Electric Medical Systems, Milwaukee, WI) 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 The

individuals performing and interpreting echocardiograms were unaware of whether the subjects belonged to the RA or control group.

All conventional and TDI measurements were taken in 5 consecutive cycles, and respective means were used for statistical comparison. Systolic and diastolic arterial blood pressure, measured with a conventional sphygmomanometer, and heart rate were recorded during the echocardiographic study.

Aortic elasticity was assessed on the basis of a 2-dimensional guided M-mode recording of systolic (AoS) and diastolic (AoD) aortic diameters, 3 cm above the aortic valve. AoD was obtained at the peak of the R wave at the simultaneously recorded ECG, and AoS was measured at the maximal anterior motion of the aortic wall; 5 measurements were averaged for each diameter (Figure 1).

The following indexes of aortic elasticity were calculated: aortic distensibility = $(2[AoS - AoD]/AoD[PP])$ (mm Hg^{-1}); aortic stiffness index = $(\ln[SBP/DBP]/[AoS - AoD]/AoD)$ (pure number), where systolic blood pressure (SBP) and diastolic blood pressure (DBP) refer to brachial systolic and diastolic arterial blood pressure in millimeters of mercury, respectively; pulse pressure (PP) was calculated as $SBP - DBP$, and $\ln(SBP/DBP)$ refers to the natural logarithm of the relative pressures ratio.¹³

Parasternal long-axis recordings of the aortic anterior wall were done using Vivid-7 technology (General Electric Medical Systems) with activated TDI. Two-dimensional tissue velocity images of the aortic wall were obtained at 130 ± 15 frames per second, which implies a temporal resolution of approximately 16 ms. The velocity scale was

Figure 1. M-mode recording of aortic diameters. M-mode imaging of ascending aorta 3 cm above the aortic valve. AoD represents the aortic diameter at QRS time, whereas AoS represents the aortic diameter at maximal anterior wall motion.

Figure 2. Tissue Doppler imaging of ascending aorta. Tissue Doppler imaging wall velocities during systole (Sm), early relaxation (Em), and atrial systole (Am) were measured.

modified to avoid aliasing. A sample volume was placed in the region of interest on the anterior aortic wall (3 cm above the aortic valve at the same position as in M-mode measurements). TDI wall velocities during systole (Sm), early relaxation (Em), and atrial systole (Am) were measured in both groups (Figure 2). Velocity datasets were analyzed off-line using dedicated software (EchoPac; GE Healthcare, Waukesha, WI), and peak systolic strain was measured from the resulting deformation curves (Figure 3).

We carefully set the sample volume on the cited part of the ascending aorta and regulated its size. The software automatically set its position throughout the cardiac cycle.

Statistical Analysis

All data were expressed as mean $\pm$ standard deviation. Continuous variables were tested to confirm a normal distribution by using Kolmogorov-Smirnov test and

Figure 3. Tissue strain of the ascending aorta. Peak systolic strain in 4 cardiac cycles (arrows) is shown on the right. Echocardiographic image of ascending aorta is shown on the left: strain imaging mode (top) and traditional mode (bottom). The yellow circle represents the region of interest set on the anterior wall at about 3 cm above the aortic valve (the same as in Figures 1 and 2).

Shapiro-Wilk test. Differences between continuous variables were analyzed using the paired-samples Student *t* test, and the χ^2 test was used for categorical variables. A regression analysis was performed, and Spearman test was employed to analyze correlations between variables. Prior to initiating the study, 8 subjects (not in the experiment), participated in a test/retest assessment of measurement reliability; aortic elastic properties were assessed on 2 separate days, and interclass correlation coefficient (ICC) measured using a 2-factor mixed effects model and type consistency. Within a week, measures were repeated by 2 echocardiographers (E.V. and I.B.); interobserver and intraobserver reproducibilities were evaluated by means of Pearson correlation coefficient. Statistical significance was accepted at $P < 0.05$. Analyses were run using SPSS statistical package for Windows version 20.0 (SPSS, Inc., Chicago, IL).

Results

We analyzed 13 patients affected by RA without CV risk factors, with a mean age at the moment of the clinical cardiac assessment of 60.4 ± 12.2 years and a mean RA duration of 10.6 ± 7 years. Eight out of the 13 patients were rheumatoid factor positive (61.5%), whereas only 7 (53.8%) had detectable anti-cyclic citrullinated peptides antibodies. Every patient was given methotrexate 10 to 15 mg weekly during anti-TNF- α treatment. TNF- α blocking agents used were: adalimumab (Humira) in 5 cases, etanercept (Enbrel), and infliximab (Remicade) in 4 patients each at the moment of the cardiac evaluation and throughout the study. High disease activity score as measured by DAS-28 was recorded at the entry of the study, whereas after 1 year a significantly 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 1 year of anti-TNF- α drugs ($P = 0.0287$). Demographic and clinical data are shown in Table 1.

The baseline CV data of the cohort are shown in Table 2. We found lower distensibility (12.9 ± 3.5 vs 21.5 ± 7.5 mm Hg $^{-1}$; $P < 0.001$) and a higher mean stiffness index

Table 2. Aortic Echocardiographic Parameters at Baseline and at Follow-up After Anti-TNF- α Therapy

	Baseline	After Anti-TNF- α	<i>P</i>
AoS, cm	3.3 ± 0.4	3.3 ± 0.4	0.5
AoD, cm	3.2 ± 0.4	3.1 ± 0.4	0.9
AoS – AoD, cm	0.10 ± 0.02	0.18 ± 0.07	0.006
Aortic distensibility, mm Hg $^{-1}$	12.9 ± 3.5	21.5 ± 7.5	0.007
Aortic stiffness index	21 ± 3.6	11.7 ± 1.4	0.004
Aortic wall TDI, cm/s			
S wave	5.6 ± 2.2	6.5 ± 2.6	0.4
E wave	-3.6 ± 2.9	-5.0 ± 1.2	0.1
A wave	-5.6 ± 0.19	-5.9 ± 2.05	0.7
Tissue strain of the aortic wall, %	-23.7 ± 1.4	-31.6 ± 2.8	0.002
Abbreviations: AoD, diastolic aortic diameter; AoS, systolic aortic diameter; TDI, tissue Doppler imaging; TNF, tumor necrosis factor.			

(21.3 ± 3.6 vs 11.7 ± 1.4 ; $P < 0.001$) in RA cases at baseline compared with values after 1 year of anti-TNF- α treatment. Sm, Em, and Am waves of the aortic wall TDI were similar at baseline and at 1 year follow-up (Sm wave: 5.6 ± 2.2 cm/s vs 6.5 ± 2.6 cm/s; Em wave: -4.6 ± 2.9 vs -5.0 ± 1.2 cm/s; Am wave: -5.6 ± 0.19 vs -5.9 ± 2.05 cm/s), whereas TDI strain of the aortic wall was improved after anti-TNF- α treatment ($-23.7 \pm 1.4\%$ vs $-31.6 \pm 2.8\%$, $P < 0.001$).

Increased aortic distensibility and decreased aortic stiffness were closely associated with anti-TNF- α therapy.

A high degree of reliability was found among aortic elastic properties measurements. The single measures ICC was 0.951 (95% confidence interval: 0.778–0.990) for TDI strain, with a mean between-day variation of $-0.8 \pm 0.4\%$; 0.946 (95% confidence interval: 0.758–0.989) for distensibility, with a mean between-day variation of 0.4 ± 1.1 mm Hg $^{-1}$; and 0.971 (95% confidence interval: 0.863–0.994) for stiffness index, with a mean between-day variation of -0.1 ± 0.4 . Moreover, distensibility showed an interobserver correlation coefficient of 0.981 ($P < 0.001$) and an intraobserver correlation coefficient of 0.991 ($P < 0.001$), stiffness index of 0.944 ($P = 0.001$) and 0.984 ($P < 0.001$), and tissue strain of 0.847 ($P = 0.016$) and 0.830 ($P = 0.021$).

Discussion

The main finding of this study was that patients with active RA without CV disease or any CV risk factors had an improvement of elastic aortic properties after 1 year of anti-TNF- α treatment evaluated by TDI and strain Doppler echocardiography.

Stiffening of the aorta and other central arteries is a potential risk factor for increased CV morbidity and mortality.^{14,15} Assessment of aortic stiffness is considered the key determinant of LV systolic and diastolic function and an important way of determining the cardiovascular risk in nonhypertensive subjects.¹⁶ In particular, arterial stiffness was demonstrated as an important independent risk factor for adverse CV outcomes in population-based

Table 1. Demographic and Clinical Data in Rheumatoid Arthritis Patients

	Baseline	Follow-up	<i>P</i>
Age, y	51 ± 13	—	—
Female/male	6/7	—	—
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, kg/m 2	28.1 ± 2.7	27.1 ± 2.4	0.9
Systolic blood pressure, mm Hg	122.9 ± 10.6	122.5 ± 3.5	0.8
Diastolic blood pressure, mm Hg	68.7 ± 10.4	67.9 ± 10.6	0.7
Abbreviations: BMI, body mass index; CCP, cyclic citrullinated peptides; CRP, C-reactive protein; DAS, disease activity score.			

studies, beyond traditional CV risk factors and in apparently healthy subjects.^{17,18} Increased arterial stiffness has already been proven for RA patients,^{3,19–21} even in the absence of atherosclerosis,²¹ because it is associated with inflammatory markers¹⁹ and related to disease duration.²²

Arterial stiffness noninvasive assessment requires pressure and diameter changes of the artery of interest. This is typically done on the ascending aorta (such as what we did) or on carotid arteries. Moreover, the most widespread arterial stiffness measurement is the pulse wave velocity (PWV), which is related to the elastic modulus of the artery by Moens-Korteweg's formula.²³ It could be measured by different devices, such as tonometric, piezoelectronic, and oscillometric devices.^{24,25} They all measure carotid-femoral, aortic, and brachial-ankle PWV. Of note, recently, carotid-femoral PWV has been standardized as the gold standard, and its reference values have been published.²⁶

Previous results suggest that anti-TNF- α treatment may reduce CV risk in RA patients⁵ and improve aortic stiffness in those patients.²⁷

Mäki-Petäjä et al have recently published an interesting article demonstrating increased aortic inflammation, detected by ¹⁸F-fluorodeoxyglucose positron-emission tomography, in 17 patients affected by active RA compared with subjects with stable CV disease.¹⁰ They found that aortic inflammation was strictly related to aortic stiffness detected by the measurement of PWV. A 8-week treatment with anti-TNF- α drugs led to a significant reduction of vascular inflammation and concomitant improvement of endothelial function and wall stiffness.

We previously described an increased aortic stiffness in 44 RA patients without CV disease or risk factors, compared with 35 age- and sex-matched controls. Two-dimensional guided mode echocardiography of the aortic root combined with simultaneous sphygmomanometric measurements of the arterial pressure at the brachial artery has been used to assess aortic function indexes. Patients with longstanding RA (mean duration: 9.8 ± 7.6 years) had increased aortic diameters ($P < 0.001$), lower mean aortic strain ($P < 0.001$), and distensibility ($P < 0.001$), and higher mean stiffness index ($P < 0.001$) versus controls. Aortic stiffness and distensibility were strictly correlated with diastolic filling indexes ($P < 0.001$).²⁸ Although we could not demonstrate that abnormal elastic properties of aortic wall was due to local or systemic inflammation, we speculated that long-lasting inflammatory disease could lead to increased left ventricular (LV) mass, impaired LV diastolic function, and higher arterial stiffness. Similar results have been recently achieved by other authors in the context of systemic lupus erythematosus.²⁹

The present study suffers from some limitations. First, there was a small number of patients with RA and no CV risk factors. In our opinion, this is the cause of aortic TDI wall velocities not being statistically different before and after the treatment. Second, this was a nonrandomized design with nonblinding of the measurements. Third, anti-TNF- α treatment was different among cases. We can only hypothesize that the CV effects of the 3 cited drugs are similar, given their similar usefulness in the therapy of RA. Fourth, we approximated aortic pressure with that measured at the brachial artery level.

Conclusion

We found increased aortic stiffness in patients with RA without CV disease or risk factors. A 12-months treatment with anti-TNF- α drugs significantly reduced systemic inflammation, disease activity, and aortic wall stiffness. These findings support the hypothesis of a subclinical aortic inflammation in these patients and the positive action of these drugs against it.

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