# Chronic inhibition of tumor necrosis factor-α with infliximab improves myocardial deformation in parallel with aortic elasticity in rheumatoid arthritis

## Romatoid artritli hastalarda tümör nekroz faktör-α'nın infliksimab ile uzun süreli inhibisyonu miyokart deformasyonunu ve buna paralel olarak aort esnekliğini düzeltir

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## ABSTRACT

***Objectives:*** This study investigated the effects of infliximab, a monoclonal antibody against TNFα, on myocardial deformation and aortic elasticity in patients with rheumatoid arthritis (RA), and the association of aortic elasticity with myocardial deformation.

***Study design:*** 38 female rheumatoid arthritis (RA) patients and 30 healthy controls were included in the study. Twenty patients received infliximab and 18 patients received prednisolone. Left ventricular (LV) longitudinal, circumferential and radial strain, systolic strain rate and early diastolic strain rate using speckle-tracking echocardiography, and aortic elasticity using M-mode echocardiography were assessed at baseline and post-treatment.

***Results:*** LV systolic longitudinal basal-, mid-, and apical strain, systolic mid- and apical strain rate, basal-, mid- and apical early strain rate, circumferential systolic apical strain and systolic strain rate were reduced in RA patients compared to controls. Compared to baseline, infliximab treatment increased aortic strain, aortic distensibility and decreased aortic β index. No significant aortic elastic changes were observed with prednisolone treatment. Longitudinal basal- and apical strain, basal-, mid- and apical systolic and diastolic strain rates, circumferential basal systolic strain, radial mid- and apical strain and apical strain rate were increased following infliximab treatment. Infliximab treatment improves aortic elasticity in parallel to myocardial deformation, but no significant association was observed following prednisolone treatment.

***Conclusion:*** Myocardial deformation is impaired in RA patients and is related to aortic stiffness. Chronic inhibition of TNFα improves LV deformation in association with aortic elasticity.

## ÖZET

***Amaç:*** Bu çalışmada, infliksimab'ın (TNFα'ya karşı monoklonal antikor) romatoid artritli (RA) hastalarda miyokart deformasyonu ve aort esnekliğine olan etkisini ve miyokart deformasyonu ile aort esnekliği arasındaki ilişkiyi araştırdık.

***Çalışma planı:*** Çalışmaya romatoid artritli 38 kadın ve sağlıklı 30 kontrol olgusu alındı. RA'lı hastaların 20'sine infliksimab 18'ine prednizolon tedavisi uygulandı. Tedavi öncesi ve sonrasında speckle tracking ekokardiyografi ile sol ventrikül (SV) uzunlamasına, çevresel ve ışınsal strain, sistolik strain hızı ve erken diyastolik strain hızı; M-mod ekokardiyografi ile de aort esnekliği ölçüldü.

***Bulgular:*** Romatoid artritli hastalarda kontrol grubuna göre SV sistolik uzunlamasına bazal-, mid-, ve apikal strain; sistolik mid- ve apikal strain hızı; bazal-, mid- ve apikal erken strain hızı; çevresel sistolik apikal strain ve sistolik strain hızı azalmış olarak bulundu. Bazale göre karşılaştırıldığında infliksimab tedavisi aortik strain ve aort gerginliğini artırırken, aortik β indeksini azalttı. Prednizolon tedavisi ile aort esnekliği parametrelerinde değişiklik olmadı. İnfliksimab tedavisi ile uzunlamasına bazal- ve apikal strain, bazal-, mid- ve apikal sistolik ve diyastolik strain hızları, çevresel bazal sistolik strain, ışınsal mid- ve apikal strain ve apikal strain hızı arttı. İnfliksimab tedavisi ile aort esnekliği miyokart deformasyonuna paralel olarak iyileşirken, prednizolon tedavisi ile böyle bir düzelme görülmedi.

***Sonuç:*** Romatoid artritli hastalarda miyokart deformasyonu mevcut olup bu durum aort sertliği ile ilişkilidir. Uzun süreli TNFα inhibisyonu SV deformasyonu ile birlikte aort esnekliğini de düzeltir.

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Rheumatoid arthritis (RA) is a systemic autoimmune disease, characterized by chronic inflammation and excess risk of cardiovascular disease and mortality.[1] Tumor necrosis factor alpha (TNF-α) plays a key role in the RA process, and may cause development of left ventricular (LV) dysfunction, left ventricular remodelling, increased cardiac myocyte apoptosis, endothelial dysfunction, insulin resistance and activation of the inducible form of nitric oxide synthase.[2]

Infliximab, a monoclonal antibody against TNFα, is one choice of RA treatment.[3] It has been shown that treatment with infliximab reduces TNFα-mediated arterial stiffness in RA patients.[4] This condition could help to explain improvement of cardiovascular survival in patients with RA who receive TNFα-blocking therapy. Furthermore, treatment with infliximab contributed significantly to an increase in left ventricular ejection fraction, as shown by conventional echocardiography, accompanied by a reduction in biochemical markers of heart failure.[5] The usual indices of global LV function, such as ejection fraction and volumes, are load-dependent. The echocardiographic measurement of myocardial deformations offers a series of regional and global angles and load independent-parameters that may be useful in the assessment of systolic and diastolic function.[6] Strain (ε) and strain rate (SR) are measures of tissue deformation. Speckle-tracking echocardiography (STE) is a reliable method for the assessment of longitudinal, radial and cicumferential LV myocardial deformation during the cardiac cycle.[7,8] Recently, two studies using STE demonstrated that LV deformation parameters were impaired in RA patients without coronary artery disease despite normal conventional echocardiography results.[9,10] Furthermore Ikonomidis et al. showed that chronic inhibition of interleukin-1 improves LV deformation, as well as endothelial function and nitro-oxidative stress.[10]

We investigated the effects on LV myocardial deformation of chronic treatment with infliximab when compared with prednisolone, and the association between aortic elasticity and LV myocardial deformation.

## PATIENTS AND METHODS

### Study population and protocol

From the rheumatology unit, we included 38 RA patients, according to the revised American Rheumatism Association criteria,[14] who had an inadequate response to disease-modifying antirheumatic drugs (DMARDs) and corticosteroids, and 30 age- and sex-matched, healthy subjects from the cardiology unit between January 2012 and January 2013.[11] The control group consisted of 30 healthy subjects of similar age and sex. All patients were on methotrexate 15 mg once per week, leflunamide 20 mg once daily and prednisolone 5-7.5 mg once daily. The patients had occasionally been treated with non-steroidal anti-inflammatory drugs within the previous 6 months. Six of the 38 patients (15%) were on stable treatment with statins and 11 patients (29%) were stable with cardioactive medications over the previous year. Composite inflammatory disease activity score (DAS), which utilises C-reactive protein (CRP), the visual analogue score of wellbeing and the number of tender and swollen joints, was used in order to evaluate the activity of RA.[12] We used the Duke Activity Status Index (DASI), a brief self-administered questionnaire designed to estimate patients' exercise capacity measured in metabolic equivalents.[13] Twenty patients received infliximab treatment (initially, 3 mg/kg, 2 and 6 weeks after the first infusion of 3 mg/kg, and thereafter the same dose applied every 8 weeks) for 6 months, and 18 patients recieved prednisolone treatment. These were selected on a 1:1 basis to have similar baseline age, sex and inflammatory disease activity as assessed by DAS with the infliximab-treated group. Patients were examined in the outpatient clinic every month to assess clinical status and compliance with therapy. None of the patients had cardiovascular and renal disease or ischemic and arrhythmic events during the previous year. Patients with known or suspected epicardial coronary artery disease were excluded to ensure measurement of aortic stiffness. Measurements were taken of the RA patients' biochemical, aortic and LV function parameters at baseline and after 180 days of infliximab and prednisolone treatment. The healthy control subjects had a single baseline measurement of the examined parameters.

**Abbreviations:**

| | |
|---|---|
| *AoD* | *Aortic distensibility* |
| *AoS* | *Aortic stiffness* |
| *Aoε* | *Aortic strain* |
| *CRP* | *C-reactive protein* |
| *DAS* | *Disease activity score* |
| *DASI* | *Duke Activity Status Index* |
| *IL-1* | *Interleukin-1* |
| *LV* | *Left ventricular* |
| *RA* | *Rheumatoid arthritis* |
| *RF* | *Rheumatoid factor* |
| *SR* | *Strain rate* |
| *STE* | *Speckle-tracking echocardiography* |
| *TNF-α* | *Tumor necrosis factor alpha* |
| *ε* | *Strain* |

The protocol study was approved by the local Ethics Committee and all participants gave written informed constent.

### Echocardiography

All echocardiographic examinations were performed in the left lateral decubitus position (2.5-3.5 MHz transducer, ie33, Philips Medical System, Bothell, Washington, USA) by one experienced observer blinded to clinical and laboratory data. Apical four-chamber and parasternal views of the LV were obtained at end-expiratory apnea. Three cardiac cycles were stored from each view in cineloop format for subsequent offline analysis by an investigator blinded to patient data. Speckle-tracking analysis was performed off-line by commercially available software QLAB 6.0 (Philips Medical System, Bothell, Washington, USA).

### 2D Echocardiography and tissue Doppler imaging

We measured the following parameters from cross-sectional echocardiographic images of the cardiac chambers: *(i)* end-diastolic interventricular septum thickness (IVS), end-diastolic posterior wall thickness (PW) (mm) of LV, and *(ii)* end-diastolic (EDV), end-systolic (ESV) volume (ml) and ejection fraction (%) of LV, and end-systolic volume (ml) of left atrium (LAV) with the Simpson's method.[14,15] Mitral inflow and systolic mitral annular velocity (S'), peak early diastolic mitral annular velocity (E'), and late peak diastolic annular velocity (A') were measured using conventional Doppler and tissue Doppler imagings.[16]

### Speckle-tracking echocardiography

The methods of image acquisition and post-processing of strain measurement with speckle-tracking have been described previously.[17] All images were obtained at a frame rate of 50 to 80 frames/s. Briefly, the observer traced the endocardial and epicardial borders on end-diastolic frame and the software automatically tracked the border on the subsequent frames. Adequate tracking can be verified in real-time and corrected by adjusting the region of interest, or by correcting the border to ensure optimal tracking manually. The aortic valve closure measured by Doppler has been identified as end-systole. The software is able to represent deformation in time-strain graphs, where it is possible to identify the different phases of the cardiac cycle.

### Measurement of aortic strain and distensibility by echocardiography

Aortic strain (Aoε) is deformation (percentage change in diameter) of the aorta due to pulse pressure as a stress force. It is dimensionless and is defined as:

Aoε (%) = systolic diameter-diastolic diameter/diastolic diameter.

Aortic stiffness (AoS) is the resistance to deformation, and is dependent on the complex interaction between vascular smooth muscle cells and the extracellular matrix containing elastin, collagen, and fibrillin. By contrast, aortic distensibility (AoD) is defined as the relative compliance or relative change in diameter as pressure step increases.[18] Aoε and AoD were measured using M-mode echocardiography, by calculating the systolic and diastolic diameter of the ascending aorta approximately 3 cm above the aortic valve in the parasternal long-axis view. The systolic diameter of the aorta was measured at the point of highest forward motion of the aorta, while the diastolic diameter was measured at the area equivalent to the peak of the QRS complex on electrocardiography.[19]

AoD ($cm^2$ $dyne^{-1}$ $10^{-6}$)= 2 x Aoε/brachial pulse pressure[20]

The following formula is applied as the AoS index (Aoβ)[21]

Aoβ (pure number) = ln (brachial systolic blood pressure/brachial diastolic blood pressure)/Aoε.

### Laboratory assays

C-reactive protein (CRP) was measured using routine methods. IgM rheumatoid factor (RF) was measured by means of immunonephelometry using the quantitative N Latex RF System (Dade Behring, Marburg, Germany), with RF titres of >15 IU/ml being considered positive. Serum levels of total cholesterol, triglycerides, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol and creatinine were determined using an autoanalyzer under fasting conditions on the same day as the other evaluations.

### Statistical analysis

Propensity score is a methodology used to compare the effectiveness of different treatments and to examine whether patients included in two treatment groups are adequately balanced for atherosclerosis,

and in the present study, a two-tailed t test was used to compare propensity scores for the infliximab-treated and prednisolone-treated patients. Categorical data were compared by contingency tables and between each treatment group, and normal controls by the $\chi^2$ test or Fisher exact test when five patients or fewer were included in each cell. Continuous variables were tested for normality using the Kolmogorov-Smirnov test. Normally-distributed variables are given as mean (SD). Spearmen correlation analysis was used to determine bivariate correlations. Because biomarkers had a non-normal distribution, data are expressed as median (interquartile range) and were analysed after transformation into ranks. Analysis of variance (ANOVA) for repeated measurements was applied to compare the effects of infliximab versus prednisolone, with measurements at baseline and 180 days post-treatment used as a within-subject factor, and type of treatment as between-subject factor. The F and p values of interaction between time measurement of the examined markers and type of treatment were calculated. Post-hoc comparisons were performed within Bonferroni's correction. Comparisons between normal controls and each treatment group at baseline or at 180 days were performed using the unpaired t test (normally-distributed variables) and Mann-Whitney test (non-normally distributed variables). Statistical significance was considered as $p<0.05$. All statistical analyses were performed using SPSS for Windows (release 15.0, SPSS Inc., Chicago, Illinois).

## RESULTS

Table 1 illustrates the demographic, clinical and laboratory characteristics at baseline and at 180 days. All RA patients were seropositive. Twenty three RA patients had restricted mobility caused by arthropathy, with 13% limited due to dyspnea. Median disease duration was 85.7 months (range, 63.8 to 107.8 months). Left ventricular diastolic filling pressure (E/e'), isovolumetric relaxation time (IVRT) and CRP were significantly higher in RA patients ($p=0.03$, $p<0.01$, $p<0.01$, respectively). By logistic regression analysis, including age, sex, hypertension, hyperlipidemia, smoking, cardioactive medication, statins, baseline creatinine, aortic strain and distensibility, the calculated logit propensity scores were similar between the two treatment groups. Thus, the two groups were adequately balanced for markers of atherosclerosis. None were withdrawn from the study because of the adverse effects of drugs or inadequate response to treatment. Patients' physical activity was improved significantly only in the infliximab-treated group (from 5.4±1.1 to 6.4±1.0 METs, F for interaction with treatment= 8.1, $p<0.01$). At baseline, the DASI (METs) was related to DAS ($r=-0.56$, $p=0.02$) and CRP levels ($r=-0.46$, $p=0.03$). Furthermore, the percentage improvement in physical activity as assessed by DASI was related to the percentage improvement of DAS ($r=-0.43$, $p=0.04$). No other significant association between changes in physical activity and changes in aortic or biochemical parameters was observed.

### Inter-relations between 2D speckle-tracking parameters, tissue Doppler, and aortic elasticity indices at baseline

As shown in Table 1, tissue Doppler imaging showed a significant increase in E/E' measured from basal septum mitral annulus (9.0±2.6 *vs.* 7.8±2.0, $p<0.01$) and impaired isovolumetric relaxation time (93.7±10.4 ms *vs.* 86.8±5.5 ms, $p<0.01$) in RA patients compared with the controls. Table 2 illustrates that RA patients had similar aortic maximal diameter (Ao max) (34.0±2.9 mm *vs.* 33.6±2.1 mm, $p=0.47$), increased Ao minimal diameter (Ao min) (32.5±3.0 mm *vs.* 31.2±2.1 mm, $p=0.04$), lower aortic strain and distensibility (4.8±2.9% *vs.* 7.7±3.5%, 0.22±0.14 $cm^2$ dyne-1 10-6 *vs.* 0.37±0.18 $cm^2$ dyne-1 10-6; $p<0.01$ and $p<0.01$, respectively), and higher aortic stiffness index (0.10±0.04 *vs.* 0.06±0.03, $p<0.01$) when compared with the controls. Aortic elasticity parameters were not related to the duration of disease. LV systolic longitudinal basal-, mid-, and apical strain, systolic mid- and apical SR, basal-, mid- and apical early SR were reduced in RA patients compared to controls ($p<0.01$, for both comparisons). LV systolic circumferential apical strain and systolic SR were reduced in RA patients compared to controls ($p=0.04$ and $p<0.01$, respectively). LV systolic radial basal-, mid-, apical strain, basal- and apical systolic strain were reduced in RA patients compared to controls ($p<0.01$, for both comparisons). Aortic stiffness was related to longitudinal mid- and apical strain ($r=-0.41$, $p=0.05$ and $r=-0.59$, $p<0.01$, respectively) and systolic mid- and apical systolic SR ($r=-0.25$; $p=0.04$ and $r=-0.42$; $p=0.04$, respectively), circumferential basal strain ($r=-0.31$, $p=0.04$) and systolic apical SR ($r=-0.47$, $p=0.03$), radial systolic basal-, and apical strain

**Table 1. Clinical, biochemical and conventional echocardiographic characteristics of the study population**

| | Controls (n=30) | RA patients (n=38) | Infliximab-treated patients (n=20) | Prednisolone-treated patients (n=18) | p* | p** |
|---|---|---|---|---|---|---|
| Disease acitivity score (DAS-28) | – | 6.4±0.7 | 6.4±0.5 | 6.1±0.8 | – | 0.06 |
| Disease duration (months) | – | 85.7±66.8 | 98.4±77.4 | 71.6±51.1 | – | 0.21 |
| RF (mg/dl) | – | 226.8 (25.2-366.1) | 194.4 (25.2-321.8) | 165.8 (30.5-366.1) | – | 0.57 |
| Age (years) | 50.7±3.4 | 52.1±11.1 | 53.4±13.5 | 50.7±7.6 | 0.52 | 0.44 |
| Body mass index (kg/m$^2$) | 30.5±3.7 | 30.5±5.5 | 31.0±5.9 | 29.9±5.2 | 0.91 | 0.70 |
| Obesity (%) | 7 (23) | 5 (13) | 2 (10) | 3 (16) | 0.21 | 0.47 |
| Hypertension (%) | 10 (33) | 17 (44) | 9 (45) | 8 (44) | 0.24 | 0.63 |
| Current smoking (%) | 8 (26) | 5 (13) | 2 (10) | 3 (16) | 0.13 | 0.32 |
| Dyslipidemia (%) | 8 (26) | 8 (21) | 3 (15) | 5 (27) | 0.39 | 0.56 |
| Diabetes mellitus (%) | 2 (6) | 8 (21) | 4 (20) | 4 (22) | **0.09** | 0.24 |
| Medication | | | | | | |
| RAAS-blocker (%) | 5 (16) | 11 (28) | 6 (30) | 5 (27) | 0.18 | 0.48 |
| β-blocker (%) | 5 (16) | 4 (10) | 1 (5) | 3 (16) | 0.34 | 0.43 |
| CCB (%) | 4 (13) | 4 (10) | 3 (15) | 1 (5) | 0.50 | 0.62 |
| Statins (%) | 7 (23) | 4 (10) | 2 (10) | 2 (11) | 0.13 | 0.36 |
| SBP (mmHg) | 121.6±9.8 | 124.7±13.9 | 122.1±14.4 | 127.4±13.2 | 0.33 | 0.24 |
| DBP (mmHg) | 79.0±6.6 | 78.7±8.9 | 75.5±9.1 | 82.2±7.5 | 0.92 | 0.12 |
| HR (beats/min) | 70.6±6.3 | 74.4±10.5 | 74.9±12.2 | 71.1±7.7 | 0.45 | 0.50 |
| Total cholesterol (mg/dl) | 171.1±29.7 | 163.0±24.6 | 170.3±20.2 | 166.5±10.8 | 0.40 | 0.74 |
| HDL cholesterol (mg/dl) | 39.1±8.1 | 41.3±11.3 | 40.4±12.9 | 43.7±9.5 | 0.36 | 0.53 |
| LDL cholesterol (mg/dl) | 112.4±16.4 | 117.2±26.6 | 115.6±25.4 | 119.0±22.9 | 0.44 | 0.76 |
| Glucose (mg/dl) | 96.7±10.7 | 98.4±15.9 | 102.3±13.1 | 98.6±10.0 | 0.77 | 0.47 |
| Creatinine (mg/dl) | 0.8±0.1 | 0.8±0.2 | 0.8±0.1 | 0.8±0.1 | 0.62 | 0.82 |
| CRP (mg/dl) | 1.2 (0.6-4.3) | 20.4 (8.0-34.9) | 20.4 (10.5-34.9) | 17.6 (8.0-33.5) | **<0.01** | 0.16 |
| LV EDV (ml) | 80.1±10.1 | 83.2±6.1 | 85.7±6.6 | 83.9±4.7 | 0.74 | 0.20 |
| LV ESV (ml) | 29.3±5.6 | 28.8±6.2 | 28.3±4.2 | 29.2±5.3 | 0.49 | 0.51 |
| LV EF (%) | 64.6±4.1 | 64.2±3.0 | 63.8±4.0 | 64.1±3.3 | 0.35 | 0.70 |
| IVS (mm) | 9.5±0.6 | 9.7±0.5 | 9.7±1.7 | 9.5±2.5 | 0.39 | 0.06 |
| PW (mm) | 8.5±0.6 | 8.5±0.4 | 8.6±0.6 | 8.5±0.8 | 0.91 | 0.82 |
| LAV (ml) | 38.7±4.8 | 39.8±4.0 | 39.4±3.3 | 40.4±4.6 | 0.29 | 0.43 |
| S' (cm/s) | 7.6±2.9 | 7.3±3.2 | 7.2±1.8 | 7.4±2.5 | 0.16 | 0.10 |
| E' (cm/s) | 9.0±3.1 | 8.6±2.1 | 7.9±2.5 | 8.3±1.9 | 0.18 | 0.09 |
| E/ E' | 7.8±2.0 | 9.0±2.6 | 9.4±3.9 | 8.5±2.5 | **0.03** | **0.02** |
| IVRT (ms) | 86.8±5.5 | 93.7±10.4 | 96.7±10.8 | 90.3±10.1 | **<0.01** | 0.56 |

Values are expressed as mean±SD. Values for CRP and RF are median and interquartile range. *For comparisons between RA and controls. **For comparisons between infliximab-treated patients and prednisolone-treated patients. RF: Rheumatoid factor; RAAS: Renin-angiotensin-aldosteron system; CCB: Calcium channel blocker; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; HR: Heart rate; CRP: C-reactive protein; LV: Left ventricle; EDV: End-diastolic volume; ESV: End-systolic volume; EF: Ejection fraction; IVS: Interventricular septum; PW: Posterior wall; LAV: Left atrial volume; IVRT: Isovolumetric relaxation time.

(r=-0.39, p<0.01 and r=-0,.37, p=0.04), radial systolic basal SR (r=-0.27, p=0.02).

### 2D speckle-tracking derived parameters and aortic elasticity parameters post-infliximab versus post-prednisolone

The reduction in LV systolic circumferential basal-, mid- and apical strain (p<0.01 for both comparisons) and systolic radial apical strain (p=0.04) was significantly higher in the infliximab group when compared to reductions in the prednisolone group. The reduction in systolic radial basal- and mid strain (p=0.13, p=0.32, respectively) did not reach statistical significance between the two groups.

**Table 2. Comparison of myocardial deformation and vascular indices between RA patients and controls**

| | Controls (n=30) | RA patients (n=38) | *p* |
|---|---|---|---|
| | Mean±SD | Mean±SD | |
| Aortic maximum diameter (mm) | 33.6±2.1 | 34.0±2.9 | 0.47 |
| Aortic minimum diameter (mm) | 31.2±2.1 | 32.5±3.0 | **0.04** |
| Aortic strain (%) | 7.7±3.5 | 4.8±2.9 | **<0.01** |
| Aortic distensibility | 0.37±0.18 | 0.22±0.14 | **<0.01** |
| Aortic β index | 0.06±0.03 | 0.10±0.04 | **<0.01** |
| Longitudinal strain (%) | | | |
| Basal | -10.6±2.3 | -9.2±2.3 | **<0.01** |
| Mid | -21.3±5.1 | -17.7±3.3 | **<0.01** |
| Apical | -28.1±4.4 | -22.5±3.9 | **<0.01** |
| Longitudinal systolic strain rate (1/s) | | | |
| Basal | -1.4±0.2 | -1.3±0.3 | 0.12 |
| Mid | -1.0±0.2 | -0.9±0.1 | **<0.01** |
| Apical | -1.0±0.2 | -0.9±0.3 | **<0.01** |
| Longitudinal early diastolic strain rate (1/s) | | | |
| Basal | 0.9±0.1 | 0.7±0.2 | **<0.01** |
| Mid | 1.0±0.2 | 0.9±0.2 | **<0.01** |
| Apical | 1.1±0.2 | 1.0±0.1 | **<0.01** |
| Circumferential strain (%) | | | |
| Basal | -23.6±3.4 | -22.3±5.2 | 0.20 |
| Mid | -17.6±2.0 | -17.8±4.0 | 0.84 |
| Apical | -29.6±5.7 | -27.2±4.4 | 0.04 |
| Circumferential systolic strain (1/s) | | | |
| Basal | -0.7±0.2 | -0.7±0.1 | 0.88 |
| Mid | -0.8±0.2 | -0.8±0.2 | 0.14 |
| Apical | -1.1±0.2 | -0.9±2.0 | **<0.01** |
| Circumferential early diastolic strain rate (1/s) | | | |
| Basal | 1.1±0.2 | 1.0±0.3 | **0.05** |
| Mid | 0.9±0.2 | 1.0±0.2 | 0.25 |
| Apical | 1.1±0.2 | 1.0±0.3 | 0.89 |
| Radial strain (%) | | | |
| Basal | 41.7±10.0 | 35.6±8.2 | **<0.01** |
| Mid | 44.5±9.6 | 39.0±11.4 | **<0.01** |
| Apical | 43.8±12.3 | 38.8±8.4 | **<0.01** |
| Radial systolic strain rate (1/s) | | | |
| Basal | 1.6±0.2 | 1.4±0.3 | **<0.01** |
| Mid | 1.4±0.2 | 1.3±0.3 | 0.10 |
| Apical | 1.3±0.2 | 1.2±0.1 | **0.03** |
| Radial early diastolic strain rate (1/s) | | | |
| Basal | -1.2±0.1 | -1.1±0.3 | 0.32 |
| Mid | -1.0±0.3 | -1.1±0.2 | 0.15 |
| Apical | -0.9±0.2 | -0.8±0.2 | 0.10 |

RA: Rheumatoid arthritis; SD: Standard deviation.

**Table 3. Chronic effects of infliximab on vascular and LV deformation parameters versus prednisolone-treated patients**

| | İnfliximab (n=20) | | | Prednisolone (n=18) | | | | |
|---|---|---|---|---|---|---|---|---|
| | Baseline | 6-months | p | Baseline | 6-months | p | F | p |
| | Mean±SD | Mean±SD | | Mean±SD | Mean±SD | | | |
| Aortic strain (%) | 4.3±3.2 | 9.2±5.7 | **<0.01** | 5.4±2.6 | 5.9±2.0 | 0.24 | 11/01/14 | **0.01** |
| Aortic distensibility | 0.18±0.14 | 0.43±0.27 | **<0.01** | 0.25±0.13 | 0.29±0.19 | 0.13 | 09/08/14 | **0.03** |
| Aortic β index | 0.12±0.04 | 0.06±0.05 | **<0.01** | 0.08±0.03 | 0.10±0.05 | 0.16 | 11/08/14 | **0.01** |
| Longitudinal strain (%) | | | | | | | | |
| Basal | -9.3±2.8 | -10.5±1.9 | **0.04** | -9.1±1.6 | -9.3±2.0 | 0.61 | 15.0 | **0.04** |
| Mid | -17.5±2.6 | -18.7±3.4 | 0.19 | -18.0±3.9 | -18.3±5.6 | 0.79 | 01/01/14 | 0.29 |
| Apical | -22.6±2.7 | -24.5±2.6 | **0.02** | -22.5±5.1 | -24.2±5.6 | 0.04 | 15/06/14 | **0.01** |
| Longitudinal systolic strain rate (1/s) | | | | | | | | |
| Basal | -1.30±0.09 | -1.43±0.10 | **0.01** | -1.34±0.10 | -1.36±0.09 | 0.49 | 11/03/14 | **0.01** |
| Mid | -0.98±0.08 | -1.05±0.91 | **<0.01** | -1.00±0.08 | -1.02±0.12 | 0.66 | 10/05/14 | **0.02** |
| Apical | -0.91±0.04 | -0.98±0.08 | **0.02** | -0.92±0.09 | -0.93±0.09 | 0.55 | 09/02/14 | **0.01** |
| Longitudinal early diastolic strain rate (1/s) | | | | | | | | |
| Basal | 0.73±0.12 | 0.81±0.10 | **<0.01** | 0.84±0.11 | 0.80±0.10 | 0.04 | 02/02/14 | 0.16 |
| Mid | 0.89±0.12 | 0.98±0.13 | **0.03** | 0.92±0.14 | 0.90±0.12 | 0.46 | 02/02/14 | 0.14 |
| Apical | 1.08±0.13 | 1.17±0.12 | **<0.01** | 1.08±0.13 | 1.03±0.15 | 0.27 | 01/01/00 | 0.30 |
| Circumferential strain (%) | | | | | | | | |
| Basal | -18.4±2.8 | -18.2±3.4 | 0.89 | -26.6±3.5 | -25.0±5.6 | 0.08 | 01/04/14 | 0.23 |
| Mid | -15.8±3.7 | -15.9±4.8 | 0.94 | -20.0±4.7 | -20.1±5.7 | 0.94 | 0.1 | 0.89 |
| Apical | -29.3±4.1 | -30.3±9.6 | 0.60 | -25.2±3.6 | -26.3±8.1 | 0.47 | 0.7 | 0.38 |
| Circumferential systolic strain rate(1/s) | | | | | | | | |
| Basal | -0.78±0.09 | -0.83±0.10 | **<0.01** | -0.79±0.11 | -0.78±0.09 | 0.66 | 0.1 | 0.74 |
| Mid | -0.83±0.09 | -0.86±0.10 | 0.13 | -0.87±0.08 | -0.85±0.10 | 0.92 | 01/01/14 | 0.29 |
| Apical | -0.97±0.10 | -1.07±0.12 | 0.56 | -0.95±0.16 | -0.94±0.14 | 0.78 | 04/04/14 | 0.53 |
| Circumferential early diastolic strain rate (1/s) | | | | | | | | |
| Basal | 1.07±0.09 | 1.05±0.12 | 0.43 | 1.10±0.20 | 1.06±0.12 | 0.45 | 01/02/14 | 0.27 |
| Mid | 0.96±0.20 | 0.95±0.18 | 0.93 | 0.94±0.25 | 0.95±0.16 | 0.81 | 0.1 | 0.84 |
| Apical | 1.05±0.11 | 1.03±0.14 | 0.61 | 1.07±0.13 | 1.10±0.10 | 0.47 | 0.1 | 0.94 |
| Radial strain (%) | | | | | | | | |
| Basal | 38.0±9.5 | 39.1±8.3 | 0.75 | 37.2±8.3 | 38.9±5.6 | 0.29 | 0.2 | 0.46 |
| Mid | 37.5±14.9 | 40.1±14.11 | **<0.01** | 39.6±9.3 | 39.9±11.6 | 0.84 | 13/06/14 | **<0.01** |
| Apical | 35.6±13.8 | 42.5±15.6 | **<0.01** | 38.3±8.3 | 40.2±10.1 | 0.03 | 0.1 | 0.75 |
| Radial systolic strain rate (1/s) | | | | | | | | |
| Basal | 1.45±0.12 | 1.41±0.18 | 0.38 | 1.49±0.15 | 1.51±0.26 | 0.72 | 0.1 | 0.78 |
| Mid | 1.45±0.09 | 1.48±0.16 | 0.62 | 1.42±0.10 | 1.41±0.20 | 0.89 | 0.2 | 0.71 |
| Apical | 1.23±0.10 | 1.32±0.11 | 0.02 | 1.30±0.15 | 1.26±0.16 | 0.28 | 01/01/14 | 0.28 |
| Radial early diastolic strain rate (1/s) | | | | | | | | |
| Basal | -1.26±0.12 | -1.24±0.16 | 0.74 | -1.31±0.17 | -1.25±0.18 | 0.35 | 01/01/00 | 0.34 |
| Mid | -1.04±0.12 | -1.03±0.14 | 0.89 | -1.10±0.10 | -1.10±0.14 | 0.99 | 0.1 | 0.92 |
| Apical | -0.91±0.17 | -0.99±0.19 | 0.18 | -0.83±0.18 | -0.90±0.21 | 0.28 | 03/02/14 | **0.08** |

SD: Standard deviation. F and p indicate the interaction between speckle tracking parameters and treatment with infliximab versus treatment with prednisolone at baseline and after 180 days.

Compared to baseline, there was an improvement in longitudinal basal and apical strain, basal-, mid-, and apical systolic and diastolic SR, as well as circumferential basal systolic SR and radial basal and apical strain and apical systolic SR after 180 days of infliximab treatment (Table 3). In the prednisolone-treated group, significant changes were observed only in basal longitudinal and radial apical strain after treatment compared to baseline. Furthermore, increases in longitudinal strain, systolic and early diastolic SR, as well as radial strain and systolic SR were higher in patients after infliximab treatment than after prednisolone treatment.

## DISCUSSION

In this study, we showed that LV deformations were impaired in RA patients without clinical cardiovascular disease despite normal LV ejection fraction by STE, in association with increased aortic stiffness. To our knowledge, this is the first prospective study demonstrating that chronic infliximab treatment caused a greater improvement in LV deformation in association with improvement of aortic elasticity and with reduction of systemic inflammation when compared to prednisolone treatment.

### Aortic elasticity and functions

Arterial stiffness, a progressive, diffuse and age-related process that occurs in all vascular beds, is one of the earliest detectable manifestations of adverse structural and functional changes within the vessel wall.[22] Aortic stiffness as a marker of vascular dysfunction is influenced by complex interaction between endothelial cell function, vascular smooth muscle tone, and the extracellular matrix containing elastin, collagen and fibrillin fibers. It should be differentiated from atherosclerosis, which is defined as the occlusive result of vascular inflammation.[18,23] Aortic stiffness is the resistance to deformation of the vessel wall subjected to blood pressure. Increased arterial stiffness is an important marker of increased LV load and a predictor of cardiovascular morbidity and is associated different diseases.[24-28] Aortic stiffness may influence the structure of the heart and cardiac systolic-diastolic functions. It is well known that patients with RA have a higher arterial stiffness than their age-matched healthy counterparts, and thus have a higher cardiovascular risk.[29,30] Increased circulating levels of TNFα have been reported in RA patients and TNFα antagonists may have a beneficial effect on arterial stiffness, and therefore cardiovascular risk.[29-31] Cytokines promote production of metalloproteinases that degrade the collagen and elastin content of the aortic intima, and may thus contribute to impaired function and dilatation of the aorta.[32] Increased nitrooxidative stress, interleukin-6 and endothelin-1 by an injured endothelium may sustain cytokine-induced matrix degradation within the aortic layers over time.[33] We have shown that chronic TNFα blockade improved aortic elasticity compared with prednisolone. Furthermore, we demonstrated a parallel improvement in LV deformation, Aoε, AoD and Aoβ index. Patients treated with prednisolone had impaired aortic elasticity compared with healthy controls at baseline, but there was no improvement after treatment at 180 days.[34]

In our study, aortic elasticity indices were associated with impaired LV deformation indices and prolonged DT and higher LV diastolic filling pressure, suggesting a link between increased aortic stiffness and impaired myocardial systolic and diastolic dysfunction as described previously.[9,10,35-37] Increased aortic stiffness augments LV afterload and impairs myocardial perfusion, causing LV dysfunction.[38] Thus, impaired aortic elasticity may represent one of the mechanisms of decreased LV deformation indices in RA patients.

### Myocardial deformations and systolic functions

Studies have reported an increased risk of developing heart failure without documented cardiac dysfunction in patients with RA.[38] Furthermore, RA patients receiving anti-TNFα therapy were less likely to develop overt heart failure.[39] TNFα can affect myocardial function via the effects on both myocyte contractility and extracellular matrix in addition to the effect on myocardial remodelling.[40] The effects of TNFα on myocardial function are complex and time-, concentration- and subtype specific.[41] Otherwise, if intracellular glutathione is present, TNFα will act as an inotrope or vice versa. Heart failure is often characterized by increased TNFα and its soluble receptor that becomes more pronounced as myocardial dysfunction progresses.[42] Furthermore, CRP which is produced predominantly by hepatocytes under the influence of TNFα, is higher in heart failure patients.[43] Higher CRP levels are associated with features of more se-

vere heart failure, and are independently associated with mortality and morbidity.

Speckle-tracking echocardiography is an extremely powerful tool for detection and differentiaiton of regional systolic and diastolic abnormalities of the myocardium, and has numerous advantages compared to conventional 2D echocardiography and tissue Doppler. It allows the observer to analyse the longitudinal, circumferential and radial deformation completely. Ikonomidis et al. showed impaired LV deformation and, following inhibition of interleukin-1 (IL-1) by anakinra, a recombinant IL-1 receptor antognist, improved LV deformation in RA patients.[10] Additionally, significant improvement in endothelial and aortic function contributed to the improvement in LV deformation after treatment. Sitia et al. demonstrated that LV deformation was reduced in the absence of traditional cardiovascular risk factors, and even with short disease duration.[9]

To the best of our knowledge, our study is the first study which used STE to demonsrate that LV deformations were impaired in RA patients, and that chronic infliximab treatment may improve LV deformation in association with aortic elasticity. Chronic inflammation and coronary microcirculatory dysfunction causes regional differences in blood supply, and thus may affect myocardial functions in a heterogeneous way. This could explain segmental heterogenity in myocardial deformation impairment. RA patients have a higher prevalence of diastolic dysfunction than those without RA.[44] Thus, diastolic dysfunction could contribute to the impairment of coronary blood supply, since coronary flow occurs mainly in diastole. In our study, we demonstraed that RA patients have a higher prevalence of diastolic dysfunction and higher left ventricular filling pressure. Furthermore, infliximab treatment decreased E/E', thus improved left ventricular filling.

The significance of early detection of subclinic myocardial injury is highlighted by recognizing that anti- TNFα blockade may halt or delay progression of myocardial dysfunction. Thus, early detection of myocardial dysfunction by STE allow us to identify RA patients at risk of progressive heart failure.

## Study limitations

This study is a single-center, and non-randomized study of relatively small sample size. The study design does not enable exploration of causality for the changes in vascular and LV function after infliximab treatment. The non-invasive assessment of vascular and LV function should also be acknowledged as a limitation. However, several reports have demonstrated the excellent correlation of nonivasively-calculated vascular function and LV function indices.[45] We have not excluded subclinical coronary artery involvement. However, given the lack of clinical findings, the likelihood for coronary artery disease is relatively low.

In this study, we demonstrated by STE that infliximab treatment improves LV deformation, and is related to concomitant improvement of aortic elastic properties and reduction in inflammatory stress in patients with RA. This condition might prevent cardiovascular involvement and impairment in patients with RA.

***Conflict-of-interest issues regarding the authorship or article: None declared***

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*Key words:* Aorta; echocardiography; myocardial deformation; rheumatoid arthritis/drug therapy; Tumor Necrosis Factor-alpha.

*Anahtar sözcükler:* Aort; ekokardiyografi; miyokart deformasyonu; romatoid artrit/ilaç tedavisi; tümör nekroz faktörü-□.