Original Research

Effect of Long-Term TNF-α Inhibition with Infliximab on Left Ventricular Torsion in Patients with Rheumatoid Arthritis

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Introduction: We evaluated the impact of tumor necrosis factor alpha (TNF-α) inhibition on left ventricular torsion (LVtor) in patients with rheumatoid arthritis (RA) using speckle-tracking echocardiography (STE).

Methods: Thirty-eight RA patients without cardiovascular disease and 30 healthy subjects were enrolled in the study. Twenty patients received infliximab, a monoclonal antibody against TNF-α, and 18 patients received increasing doses of prednisolone for 180 days. Global systolic longitudinal strain (G-LS), global systolic radial strain (G-RS) and global systolic circumferential strain (G-CS) were determined by STE. LV basal and apical rotations from the base and apex were obtained and used for calculation of LVtor. Pre-treatment LVtor levels were compared with LVtor levels after therapy in both treatment groups.

Results: RA patients had lower G-LS (-16.5 ± 2.9; p<0.01), G-RS (37.6 ± 1.5; p<0.01) and higher G-CS (-23.6 ± 3.5; p=0.04) compared with control subjects (-20.0 ± 2.8, 40.7 ± 4.8, -22.4 ± 2.5, respectively; p<0.01). LVtor levels were significantly higher in RA patients compared to controls (16.4 ± 2.7 vs. 15.1 ± 2.5; p=0.04), which might be attributed to higher values of apical rotation (9.7 ± 2.4 vs. 8.8 ± 2.3; p=0.01). Patients treated with infliximab experienced a significant decrease in LVtor (p=0.04), and a significant increase in G-LS (p<0.01) and G-RS (p<0.01). No significant changes were observed among patients treated with prednisolone. Percentage changes in LVtor were correlated with percent changes in C-reactive protein CRP (r=0.58; p<0.01), disease activity score (r=0.78; p<0.01), and G-LS (r=-0.40; p=0.04) in patients treated with infliximab.

Conclusions: RA is characterized by increased LVtor. Long term TNF-α inhibition improves LV longitudinal and radial systolic deformation and decreases LVtor.

Rheumatoid arthritis (RA) is a chronic inflammatory disease, with a prevalence of 1-2% in Western countries.[1] Systemic inflammation associated with RA contributes to the increased cardiovascular morbidity and mortality.[2,3] Tumor necrosis factor alpha (TNF-α) plays a key role in the pathogenesis of RA, which may cause development of left ventricular (LV) dysfunction, LV remodeling, cardiomyocyte apoptosis, and endothelial cell dysfunction.[4] TNF-α inhibitors could reduce the frequency of heart failure in patients with RA.[5] Infliximab is a monoclonal antibody against TNF-α, and is one of the treatment options for RA that also contributes to an improvement in LV systolic function and

a reduction of brain natriuretic peptide.[6,7] LV torsion (LVtor) is defined as left ventricular rotation around the long axis and is an important component of LV systolic and diastolic performance that has recently been recognized as a sensitive indicator of cardiac performance.[8,9] LVtor have been assessed in different diseases and clinical scenarios. Both an increase and a decrease in LVtor have been found to be associated with (sub)clinical myocardial dysfunction, while it can also be used as a surrogate marker of future myocardial dysfunction and structural changes.[10-15] Speckle-tracking echocardiography (STE) is a new imaging modality for the evaluation of LVtor.[16] In this study, we aimed to investigate the effect of infliximab on LVtor in patients with RA.

Methods

Study population and protocol

Thirty-eight patients with RA from the rheumatology department who fulfilled the revised American Rheumatism Association criteria,[17] and 30 age- and sex-matched healthy subjects (controls) from the cardiology department were recruited to the study between January 2011 and 2012. Patients with known or suspected epicardial coronary artery disease, cardiovascular and renal disease, or ischemic and arrhythmic events during the previous year were excluded. RA patients had an inadequate response to disease-modifying anti-rheumatic drugs (DMARDs) and corticosteroids. RA patients had been treated with methotrexate 15 mg/week, leflunomide 20 mg/day, and prednisolone 5-7.5 mg/day before recruitment in this study. The patients had occasionally been treated with non-steroidal anti-inflammatory drugs for 6 months. Composite inflammatory disease activity score (DAS), which consists of C-reactive protein (CRP), a visual analogue score of wellbeing, and the number of tender and swollen joints, was used in order to assess disease activity in RA.[18] We used the Duke Activity Status Index (DASI), a brief self-administered questionnaire designed to estimate patients' exercise capacity measured in metabolic equivalents.[19] Twenty patients received infliximab (initially 3 mg/kg; 3 mg/kg 2 and 6 weeks after the first infusion; and thereafter the same dose applied every 8 weeks), and 18 patients received prednisolone (average dosage 40 mg/day) for 180 days in both groups. Methotrexate was continued in 14 patients in the infliximab group and 12 patients in the prednisolone group. Patients were seen in the outpatient clinic every month to evaluate their clinical status and compliance with therapy. Both infliximab and prednisolone-treated RA patient groups underwent biochemical tests and analysis of LV function with echocardiography at baseline and after 180 days of therapy. The healthy control subjects had single baseline measurements of the aforementioned parameters. Our study was approved by the local ethics committee and informed consent was obtained from each participant.

2D echocardiography and tissue Doppler imaging

All echocardiographic evaluations were made by a single experienced physician who was blinded to the participants' clinical and laboratory features. Transthoracic echocardiographic studies were performed using a 2.5-3.5 MHz transducer (ie33, Philips Medical System, Bothell, Washington, USA). Apical four-chamber and parasternal views of the LV were obtained at end-expiratory apnea in the left lateral decubitus position. Three cardiac cycles were stored from each view in cineloop format for subsequent offline analysis by an investigator blinded to the patients' information.

We measured the following parameters from cross-sectional echocardiographic images of the cardiac chambers: End-diastolic interventricular septum thickness (IVS), end-diastolic LV posterior wall thickness (PW, mm), end-diastolic (EDV) and end-systolic (ESV) volumes (mL), and ejection fraction (%) using Simpson's method, according to American Society of Echocardiography criteria.[20,21] Mitral inflow and annular velocities were measured using conventional Doppler and tissue Doppler tracings. The latter included peak systolic mitral annular velocity (S), peak early diastolic mitral annular velocity (E'), and late peak diastolic annular velocity (A).[22]

Speckle-tracking echocardiography

Speckle tracking analysis was performed off-line using commercially available software (QLAB 6.0; Philips Medical Systems, Bothell, Washington, USA). The methods of image acquisition and post-processing of strain measurement with speckle tracking have been described previously.[23] All images were obtained at a frame rate of 50 to 80 /s. Briefly, the observer traced the endocardial and epicardial borders on an end-diastolic frame and the software automatically tracked the border on the subsequent frames.

Adequate tracking can then be verified in real-time and corrected by adjusting the region of interest or manually by correcting the border to ensure optimal tracking. The aortic valve closure measured by Doppler was defined 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.

Left ventricular torsion study

The parasternal short-axis basal plane of the LV was acquired at the level of the mitral valve, and the apical plane was acquired distal to the papillary muscles. In each plane, we aimed to obtain circular cross-sections of the LV. Rotation was obtained by tracking the images at the basal and apical level. Torsion of the LV was auto-computed by the software from the values of basal and apical rotation as:

LVtor = Apical rotation – Basal rotation.[24]

As viewed from the apex, counterclockwise rotation was expressed as a positive value and clockwise rotation as a negative value. In order to analyze the LV short-axis function, global systolic longitudinal strain (G-LS), global systolic radial strain (G-RS), and global systolic circumferential strain (G-CS) were determined by STE.

Statistical analysis

All statistical analyses were performed using SPSS for Windows (version 15.0, SPSS Inc., Chicago, IL, USA). Continuous variables were tested for normality using the Kolmogorov–Smirnov test. Normally distributed variables were expressed as mean ± SD. Spearman correlation analysis was used to determine bivariate correlations. Because the biomarkers had a non-normal distribution, data were expressed as median (interquartile range) and were analyzed after transformation into ranks. Propensity scores, which were used to compare the effectiveness of different treatments and to examine whether patients included in two treatment groups (i.e. infliximab vs. prednisolone) were adequately balanced for atherosclerosis, were compared using a two-tailed t-test. Pearson's chi-square or Fisher's exact test (i.e. when five patients or less were included in each cell) were used to compare categorical variables between study groups. Comparisons between normal controls and each treatment group at baseline and at 180 days were performed using an unpaired t-test for normally distributed variables and the Mann–Whitney test for non-normally distributed variables. P-values <0.05 were tabulated as significant.

Results

Our study enrolled 38 RA patients and 30 healthy controls. Left ventricular diastolic filling pressure (E/E'), isovolumic relaxation time (IVRT), and CRP were significantly higher in patients with RA ($p=0.03$, $p<0.01$, $p<0.01$, respectively). None of the other aforementioned characteristics showed a statistically significant difference between RA patients and healthy controls. RA patients were divided into two subgroups: 20 received infliximab and 18 were treated with prednisolone. E/E' values were significantly higher in patients treated with infliximab ($p=0.02$), while other baseline characteristics were similar between the two treatment groups (Table 1). DAS-28 and CRP levels were significantly lower after 6 months of treatment in both groups ($p<0.001$ for both comparisons). Although there was no significant difference in CRP levels at 180 days after treatment, DAS-28 was significantly lower in the infliximab-treated group ($p=0.038$). Initial LVEDV and LV ejection fraction (LVEF) were similar in the two subgroups. The reduction in LVEDV and the increase in LVEF were greater in the infliximab-treated group after 6 months ($p=0.044$ and $p=0.011$, respectively; Table 2). LV G-LS and G-RS were significantly lower in RA patients than in controls ($p<0.01$ for both comparisons), but G-CS was higher in the former group. LV basal rotation did not differ significantly between the study groups ($p=0.94$), but apical rotation and LVtor were significantly lower in patients with RA ($p<0.01$ for both comparisons; Table 3). Both treatment modalities increased G-RS significantly ($p=0.02$ in the prednisolone group, $p<0.01$ in the infliximab group). Pre-treatment G-RS was significantly lower in infliximab-treated patients ($p=0.001$) and, after 180 days of treatment, infliximab-treated patients showed a better improvement in terms of G-RS than patients treated with prednisolone ($p=0.002$; Table 4). CRP and DAS-28 decreased significantly after 180 days of medical treatment in both groups and there was no statistically significant between-group difference in CRP values ($p=0.150$); however, DAS-28 values were significantly lower after therapy in patients treated with infliximab ($p<0.038$). Percentage changes of LVtor in patients treated with infliximab were correlated with percentage changes in

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

Clinical and biochemical variables	Healthy controls (n=30)	RA patients (n=38)	Infliximab-treated patients (n=20)	Prednisolone-treated patients (n=18)	p*	p†
Disease duration (months)	N/A	85.7 ± 66.8	98.4 ± 77.4	71.6 ± 51.1	N/A	0.21
Age (years)	50.7 ± 3.4	52.1 ± 11.1	53.4 ± 13.5	50.7 ± 7.6	0.52	0.44
BMI (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
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
DAS-28	N/A	6.4 ± 0.7	6.4 ± 0.5	6.1 ± 0.8	N/A	0.06
RF (mg/dL)	N/A	226.8 (25.2-366.1)	194.4 (25.2-321.8)	165.8 (30.5-366.1)	N/A	0.57
Medication						
RAAS-blocker (%)	5 (16)	11 (28)	6 (30)	5 (27)	0.18	0.48
B-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
Echocardiography						
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
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. RA – rheumatoid arthritis; BMI – body mass index; SBP – systolic blood pressure; DBP – diastolic blood pressure; HR – heart rate; HDL – high-density lipoprotein; LDL – low-density lipoprotein; CRP – C-reactive protein; DAS-28 – disease activity score; RA – rheumatoid arthritis; RF – rheumatoid factor; RAAS – renin–angiotensin–aldosterone system; CCB – calcium channel blocker; LV – left ventricle; EDV – end-diastolic volume; ESV – end-systolic volume; EF – ejection fraction; IVS – interventricular septum; PW – posterior wall; S – mitral annulus early diastolic velocity; E' – mitral annulus early diastolic velocity; IVRT – isovolumic relaxation time; N/A – not applicable.

LV apical and basal rotation, G-LS, LVEF, CRP, and DAS-28, as shown in Table 5 and Figure 1.

Discussion

Our results demonstrated that LVtor values were elevated in patients with RA. The improvement in clinic condition (DAS-28) and LV function (G-LS, G-RS, LVEF and LVtor) was greater in patients treated with infliximab than in those treated with prednisolone.

LVtor is the net result of counterclockwise rotation of the base and clockwise rotation of the apex around the LV long axis. LVtor is a component of systolic function and contributes to an energy-efficient ejection.[25,26] In this study we found that the increase in LVtor among patients with RA was mostly attributable to increased apical rotation. The reason for this increased LVtor is controversial but it might be due to under-perfusion of the subendocardium, leading to reduced subendocardial myofiber func-

Table 2. Comparison of clinical, biochemical and echocardiographic characteristics in the infliximab and prednisolone sub-study populations before and after 6 months of treatment.

Clinic and biochemical variables	Infliximab-treated RA patients (n=20)			Prednisolone-treated RA patients (n=18)			p*
	Baseline	6-month	p	Baseline	6-month	p	
DAS-28	6.4 ± 0.5	3.9 ± 0.8	<0.001	6.1 ± 0.8	4.6 ± 1.0	<0.001	0.038
BMI (kg/m^2)	31.0 ± 5.9	30.3 ± 4.7	0.656	29.9 ± 5.2	30.2 ± 5.0	0.751	0.789
SBP (mmHg)	122.1 ± 14.4	120.7 ± 10.9	0.543	127.4 ± 13.2	128.0 ± 12.3	0.852	0.066
DBP (mmHg)	75.5 ± 9.1	78.8 ± 11.9	0.895	82.2 ± 7.5	81.0 ± 10.5	0.204	0.343
HR (beats/min)	74.9 ± 12.2	72.5 ± 18.3	0.067	71.1 ± 7.7	70.9 ± 11.0	0.592	0.064
Total cholesterol (mg/dL)	170.3 ± 20.2	182 ± 45.2	0.042	166.5 ± 10.8	172 ± 21.4	0.049	0.528
HDL cholesterol (mg/dL)	40.4 ± 12.9	39.2 ± 20.9	0.654	43.7 ± 9.5	42.6 ± 10.6	0.576	0.465
LDL cholesterol (mg/dL)	115.6 ± 25.4	112.7 ± 31.0	0.528	119.0 ± 22.9	122.5 ± 27.1	0.790	0.442
Glucose (mg/dL)	102.3 ± 13.1	99.5 ± 17.2	0.584	98.6 ± 10.0	102.2 ± 21.0	0.500	0.111
Creatinine (mg/dL)	0.8 ± 0.1	0.8 ± 0.1	0.521	0.8 ± 0.1	0.8 ± 0.1	0.895	0.966
CRP (mg/dL)	20.4 (10.5-34.9)	8.3 (5.2-14.4)	<0.001	17.6 (8.0-33.5)	9.6 (4.8-17.1)	<0.001	0.150
Echocardiography							
LV EDV (mL)	85.7 ± 6.6	79.7 ± 6.9	0.114	83.9 ± 4.7	85.4 ± 9.8	0.868	0.044
LV ESV (mL)	28.3 ± 4.2	27.2 ± 3.6	0.140	29.2 ± 5.3	27.9 ± 2.6	0.557	0.809
LV EF (%)	63.8 ± 4.0	64.6 ± 2.8	0.096	64.1 ± 3.3	64.9 ± 2.8	0.350	0.011
IVS. (mm)	9.7 ± 1.7	9.5 ± 3.9	0.267	9.5 ± 2.5	9.4 ± 4.6	0.316	0.07
PW (mm)	8.6 ± 0.6	8.3 ± 0.4	0.056	8.5 ± 0.8	8.7 ± 0.4	0.381	0.05
S (cm/s)	7.2 ± 1.8	6.8 ± 0.8	0.258	7.4 ± 2.5	7.6 ± 0.6	0.369	<0.001
E' (cm/s)	7.9 ± 2.5	9.0 ± 1.3	0.181	8.3 ± 1.9	7.8 ± 2.4	0.600	0.076
E/E'	9.4 ± 3.9	8.0 ± 1.4	0.004	8.5 ± 2.5	8.8 ± 2.4	0.379	0.076

Values are expressed as mean ± SD. Value for CRP is median and interquartile range. p indicates the interaction between parameters and treatment with infliximab and prednisolone at baseline and after 180 days. p*: For comparisons between infliximab-treated patients and prednisolone-treated patients after 180 days of study. Abbreviations as in Table 1.

Table 3. Comparison of myocardial deformation between patients with rheumatoid arthritis (RA) and healthy controls.

	Controls (n=30)	RA patients (n=38)	p
LV global systolic strain (%)			
Longitudinal	-20.0 ± 2.8	-16.5 ± 2.9	<0.01
Circumferential	-22.4 ± 2.5	-23.6 ± 3.5	0.04
Radial	40.7 ± 4.8	37.6 ± 1.5	<0.01
LV rotation (°)			
Basal rotation	-6.5 ± 1.1	-6.3 ± 1.0	0.45
Apical rotation	8.8 ± 2.3	9.7 ± 2.4	0.01
Torsion	15.1 ± 2.5	16.4 ± 2.7	0.04

Values are expressed as mean ± SD.

tion, which normally counteracts the LVtor generated by the subepicardial myofibers.[12,13,27] Subendocardial myofiber dysfunction may be secondary to subendocardial fibrosis, asymptomatic subendocardial infarction or reduced subendocardial perfusion.[15] Myocardial abnormalities, as detected by cardiac magnetic resonance imaging, are frequent in RA patients without known cardiac disease and include segmental and non-segmental subendocardial perfusion defects. These findings have been associated with higher RA disease activity, suggesting a role of inflammation in the pathogenesis of myocardial involvement in RA.[28] In this study, LVtor was found to be significantly increased in patients with mild diastolic dysfunction. However, in patients who had advanced diastolic dysfunction with increased filling pressure, LVtor was

Table 4. Chronic effects of infliximab vs. prednisolone on left ventricular deformation parameters.

	Infliximab (n=20)			Prednisolone (n=18)			p†	p‡
	Baseline	6 months	p*	Baseline	6 months	p*		
LV global systolic strain (%)								
Longitudinal	-16.4 ± 2.8	-17.9 ± 2.9	<0.01	-16.5 ± 2.1	-17.2 ± 3.1	0.22	0.893	0.447
Circumferential	-21.2 ± 2.5	-21.1 ± 3.4	0.73	-23.9 ± 2.9	-23.8 ± 4.3	0.90	0.002	0.074
Radial	36.8 ± 3.0	41.8 ± 3.3	<0.01	38.4 ± 3.5	39.8 ± 3.0	0.02	0.001	0.002
LV rotation (˚)								
Basal rotation	-6.6 ± 1.3	-6.6 ± 1.2	0.94	-6.0 ± 0.7	-6.3 ± 1.2	0.21	0.065	0.391
Apical rotation	9.9 ± 1.7	8.7 ± 1.5	<0.01	9.6 ± 1.1	9.5 ± 1.3	0.68	0.488	0.126
Torsion	16.6 ± 1.9	15.4 ± 1.7	0.04	15.6 ± 1.3	15.8 ± 2.0	0.49	0.078	0.562

Values are expressed as mean ± SD. *Comparisons between baseline and 6-month values. †Comparisons between infliximab-treated and prednisolone-treated patients before study. ‡Comparisons between infliximab-treated and prednisolone-treated patients after 6 months of study.

Table 5. Correlations between left ventricular torsion and other parameters in patients treated with infliximab.

	Change (%)	r	p
Apical rotation (˚)	-10.8 ± 9.5	0.73	<0.01
Basal rotation (˚)	3.1 ± 24.1	0.55	0.01
G-LS (%)	11.3 ± 11.1	-0.40	0.04
G-RS (%)	13.5 ± 4.5	-0.03	0.87
G-CS (%)	2.0 ± 19.5	-0.15	0.51
LVEF (%)	3.4 ± 3.1	-0.54	0.02
CRP (mg/dL)	-62.8 ± 37.6	0.58	<0.01
DAS-28	-52.4 ± 14.8	0.78	<0.01

G-LS – global systolic longitudinal strain; G-RS – global systolic radial strain; G-CS – global systolic circumferential strain; LVEF – left ventricular ejection fraction; CRP – C-reactive protein; DAS-28 – disease activity score.

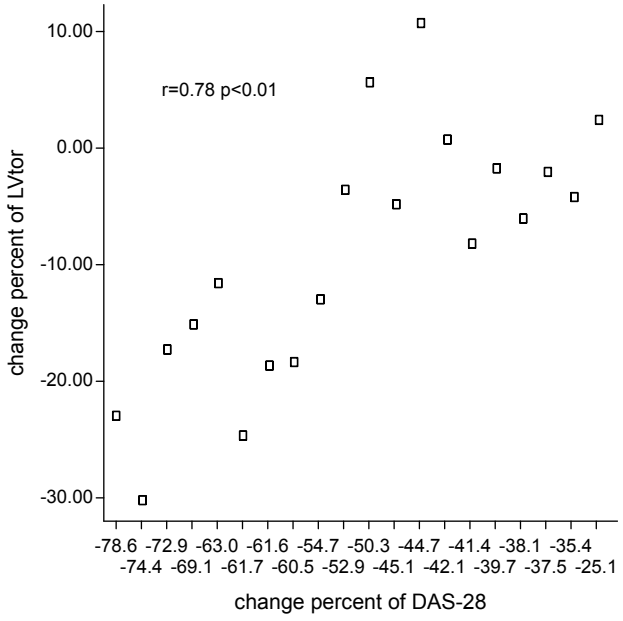

Figure 1. The relationship between percentage changes in disease activity score (DAS-28) and left ventricular torsion (LVtor).

normalized or reduced.[29] RA patients have a higher prevalence of diastolic dysfunction than those without RA. Disease duration and inflammatory cytokine levels are independently associated with diastolic dysfunction, suggesting the impact of chronic autoimmune inflammation on myocardial function in RA.[30] Another explanation of the increased LVtor in RA patients might be the mild diastolic dysfunction and elevated LV filling pressure, expressed by E/E'. In infliximab-treated patients, E/E' decreased after treatment and the percentage change in E/E' was correlated with the percentage change in LVtor. Thus, it can be speculated that LVtor provides the potential energy for subsequent untwisting recoil: therefore, the greater the LVtor, the higher the untwisting recoil rate. In addition, increased LVtor might be related with cardiac dysfunction, as previously suggested by some authors.[14] Increased LVtor may be a compensatory mechanism for reduced relaxation associated with the prolonged duration of RA.

RA patients had altered myocardial deformation, as previously reported.[31,32] However, our results demonstrated an increase in global circumferential strain in contrast to global radial and longitudinal strain, resembling aging and heart failure with preserved ejection fraction.[33] G-CS might be a marker of compensation to sustain LVtor in order to preserve LVEF in RA patients.

In the present study, we showed an improvement in G-LS and G-RS and normalization of LVtor correlated with decreasing apical rotation after 180 days of treatment with infliximab in RA patients. The improvement of myocardial deformation and the normalization of LVtor after infliximab treatment were correlated with DAS-28 and LVEF. Furthermore, the improvement in these parameters was greater in

the infliximab group than the prednisolone group after long-term treatment. These findings suggest that long-term TNF-α inhibition may improve myocardial deformation to a greater extent than corticosteroids, because of its potential effects on ventricular filling pressure and inflammatory stress. Thus, chronic treatment with infliximab may improve myocardial deformation and normalize LVtor, as demonstrated in this study. Furthermore, limitation of myocardial and arterial inflammation might contribute to these favorable effects. TNF-α plays a central role as an inflammatory marker in atherosclerosis and predicts cardiovascular events in healthy subjects and patients who have suffered myocardial infarction.[34] The impaired integration of myocardial and vascular physiology might be related to increased inflammatory activity, which could lead to accelerated atherosclerosis. Endothelial dysfunction and injury,[32,35] lipid abnormalities and atherogenic lipoprotein factors, adhesion molecules, and proinflammatory cytokines may be contributing factors to increased cardiovascular mortality and morbidity.[36] Infliximab treatment shows beneficial effects on the LV function of RA patients, whereas the potential favorable effects on cardiovascular events need to be confirmed by future studies.

Limitations

The study design did not enable any exploration of causality regarding the changes in LVtor after infliximab treatment. The noninvasive assessment of LVtor should also be acknowledged as a limitation. However, Yip et al have demonstrated an excellent correlation between noninvasively calculated LVtor and invasive measurement of LVtor.[24] We did not exclude subclinical coronary artery involvement. However, given the lack of clinical findings, the likelihood of coronary artery disease was relatively low. Finally, all participants were female and the study design did not enable us to test the validity of our findings for the entire RA population.

Conclusions

RA is associated with increased LVtor. The early detection of abnormalities in left ventricular torsion might provide a method for identifying patients with a high risk of progressing to heart failure. This screening modality may be an important part of clinical judgment and optimizing treatment. Moreover, long term TNF-α inhibition improves LV longitudinal and radial systolic deformation, which may also normalize during the course of treatment. Infliximab treatment was more effective than corticosteroids in terms of improvements in LV physiology.

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