

The effects of golimumab treatment on systolic and diastolic left ventricular function in ankylosing spondylitis

SC Heslinga^{1,2}TC Konings³

IE van der Horst-

Bruinsma^{1,2}O Kamp³VP van Halm^{3,4}HACM de Bruin-Bon⁴MJ Peters⁵MT Nurmohamed^{1,2}

¹Department of Rheumatology, Amsterdam Rheumatology and Immunology Center, Reade, Amsterdam, The Netherlands;

²Department of Rheumatology, Amsterdam Rheumatology and Immunology Center, VU University Medical Center, Amsterdam, The Netherlands; ³Department of Cardiology, VU University Medical

Center, Amsterdam, The Netherlands; ⁴Department of Cardiology, Academic Medical Center, Amsterdam, The

Netherlands; ⁵Department of Internal Medicine, VU University Medical Center, Amsterdam, The Netherlands

Correspondence: SC Heslinga
Department of Rheumatology,
Amsterdam Rheumatology and
Immunology Center, Reade, Jan van
Breemenstraat 2, 1056 AB, Amsterdam,
The Netherlands
Tel +31 20 242 1100
Email s.heslinga@reade.nl

Background: Diastolic left ventricular (LV) dysfunction appears more prevalent in ankylosing spondylitis (AS). The effects of tumor necrosis factor alpha (TNF- α) blocking therapy, a strong and effective anti-inflammatory drug, on diastolic LV function in AS are unknown. The objective of the study was to find the effects of 1-year treatment with golimumab 50 mg subcutaneously once per month on systolic and diastolic LV dysfunction in AS patients.

Methods: Forty consecutive AS patients were treated with TNF- α blocking therapy for 1 year. Transthoracic echocardiography was performed in all patients at baseline and after 1 year of treatment.

Results: Diastolic LV function improved after treatment in four out of six (67%) AS patients who completed follow-up ($P=0.125$), and did not develop or worsen in any of the other patients. Treatment with TNF- α blocking therapy had no effect on systolic LV function.

Conclusion: These findings give support to the hypothesis that diastolic LV dysfunction improves during treatment with TNF- α blocking therapy.

Keywords: ankylosing spondylitis, cardiovascular disease, anti-TNF

Introduction

Ankylosing spondylitis (AS) is a chronic inflammatory rheumatic disease that affects the spinal column causing pain and decreased spinal flexibility.^{1,2} Extra-spinal manifestations including cardiac pathology are common in AS.³⁻⁵ The cardiac pathology linked to AS includes valvular dysfunction, in particular of the aortic valve, conduction disorders and heart failure (HF).^{3,6-9}

It is conceivable that these cardiac abnormalities originate due to the systemic inflammatory process inherent to AS, as inflammation may affect the aortic root, aortic and mitral valve cups, the atrioventricular node and the proximal septum.^{10,11} Also, inflammation accelerates the process of atherosclerosis, increasing the chance of developing ischemic heart disease and HF.¹²⁻¹⁴ Finally, inflammation might affect the myocardium and endocardium itself, leading to an abnormal filling pattern termed diastolic left ventricular (LV) dysfunction.¹⁵ Diastolic LV dysfunction is caused by impaired relaxation of the left ventricle and may eventually lead to HF with preserved ejection fraction.¹⁶ Failing pump function of the heart is termed systolic LV dysfunction and may lead to HF with reduced ejection fraction.¹⁶

Recently, we performed a review that suggested a higher prevalence of diastolic LV dysfunction in AS patients, an important precursor to chronic HF that may contribute to the enhanced morbidity and mortality in AS.⁸ Considering this, in this study we

investigated the precise magnitude of LV dysfunction, particularly diastolic LF dysfunction, in AS patients and we examined the effect of tumor necrosis factor alpha (TNF- α) blocking therapy on LV function during a treatment period of 1 year.

Methods

Study population

Consecutive AS patients were included at the rheumatology departments of the VU University Medical Center (VUmc) and Reade, Amsterdam, The Netherlands, from November 2012 to May 2014. All patients fulfilled the 1984 Modified New York criteria for AS.¹⁷ Patients were included when they were eligible for treatment with TNF- α blocking therapy and were treated for 1 year with golimumab (Simponi[®]; Merck Sharp & Dohme B.V., Haarlem, The Netherlands) 50 mg subcutaneously once a month. Switching to another TNF- α blocker during the study was allowed. Cardiac function was assessed with transthoracic echocardiography (TTE) at baseline and after 1 year of treatment. Approval was obtained from the local ethics committee (Ethics Committee of the Slotervaart Hospital and Reade, Amsterdam, The Netherlands) and all participating patients gave written informed consent.

Patient and disease characteristics

Medical history included AS history, medication use, hypertension, diabetes mellitus type 2 and CV events. Patients with a history of CV events were subsequently excluded. Physical examination included height, weight and blood pressure measurements. Body mass index was calculated. Hypertension was defined as present if a patient was treated with antihypertensive medication or had an indication for treatment. Blood sample measurements included standard hematological assessment, C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR). Disease activity was measured with the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Functional Index (BASFI) and the Ankylosing Spondylitis Disease Activity Score – CRP (ASDAS).

Transthoracic echocardiography

TTE was performed by experienced echo technicians at the VUmc. To exclude inter-observer variability, all recordings of echocardiography data from both AS patients and controls were stored digitally and were afterwards analyzed offline by a single investigator (T.K.). TTE was performed according to the following protocol based on the guidelines provided by American Society of Echocardiography.¹⁸ Evaluation of cardiac function consisted of 2D, spectral and color flow

Doppler recordings. The 2D recordings were performed in parasternal long- and short-axis views, and apical four-, three- and two-chamber views. Left atrial and ventricular diastolic and systolic diameters, posterior wall thicknesses (PWT) and interventricular septum thicknesses (IVS) were measured during systole and diastole by 2D imaging. Left ventricular mass was calculated with the following formula: $0.8 (1.04) (\text{end diastolic diameter [EDD]} + \text{IVS} + \text{PWT})^3 - (\text{EDD}^3) + 0.6$ (in grams). The relative wall thickness was calculated as following: $(\text{IVS} + \text{PWT}) / \text{EDD}$. Left ventricular systolic and diastolic volumes and ejection fraction (EF) were calculated from the apical four chamber view using 3D echocardiography or modified Simpson's method.¹⁸ Left atrial volume was measured using modified biplane Simpson's rule. Aortic and mitral valve function was evaluated using color Doppler flow. Pulsed-Doppler spectral recordings of the mitral inflow were obtained with the sample volume placed at the tips of the mitral leaflets. From the transmitral pulsed-Doppler recordings, peak E and A velocities, the E/A ratio and the E wave deceleration times (DT) were obtained. Pulse wave tissue Doppler imaging was performed in the apical views to acquire mitral annular velocities. The sample volume was positioned at, or within 1 cm of the septal (e' sept) and lateral (e' lat) insertion sites of the mitral leaflets.

Definitions

Systolic LV dysfunction was defined as an EF <50%. Expert opinion defined the presence of systolic LV dysfunction if the EF could not be determined due to image quality or other. Diastolic LV dysfunction was graded into three categories: mild (grade I), pseudonormal (grade II) and restrictive (grade III), using criteria based on the recommendations by Nagueh et al.¹⁹ Diastolic LV dysfunction was present when at least two out of three measurements (ie, e' sept, e' lat, left atrial volume) were abnormal. The specific grade of diastolic LV dysfunction (normal, mild, pseudonormal or restrictive) was defined when at least two of the three measurements (ie, E/A ratio, DT, E/e' ratio) met that specific grade. Valvular function and aortic diameters were evaluated according to the most recent echocardiographic guidelines.^{18,20}

Statistical analysis

For data analysis, SPSS Version 19.0 (IBM Corp., Armonk, NY, USA) was used. Demographic and disease characteristics were summarized using descriptive statistics. Distribution of data was analyzed with histograms. Values are expressed as mean \pm SD, median (interquartile range) or numbers (percentages, %) where appropriate. Independent samples

t-tests were used for comparisons of normally distributed continuous variables and Mann–Whitney *U*-test for non-normally distributed continuous variables. Fisher's exact test was performed on dichotomous variables. Echocardiographic data of all patients completing the follow-up at 1 year were analyzed using the paired samples *t*-test, Wilcoxon signed-rank test or McNemar test, where appropriate. A level of $P < 0.05$ was considered statistically significant.

Results

Patient, control and disease characteristics

In total, 47 consecutive AS patients were included. Three patients refused echocardiography, and four patients had a history of CV events (myocardial infarction $n=2$, cerebrovascular accident $n=2$) and were subsequently excluded (Figure 1). Baseline data are shown in Table 1. Of all AS patients, 33 (83%) were HLA-B27 positive. Before initiation of TNF- α blocking therapy, the mean BASDAI score was 5.6 ± 1.7 and the mean ASDAS score was 3.2 ± 1.2 . Six (15%) AS patients had a history of hypertension compared to none in the control group ($P=0.011$).

Baseline echocardiography

In total, 13 (33%) AS patients had cardiac pathology (ie, one or more of the following: systolic and/or diastolic LV dysfunction, aortic valve dysfunction and/or aortic dilatation; one AS patient had two disorders), see Table 2.

Nine (23%) AS patients had diastolic LV dysfunction at baseline. The mean age of patients with diastolic LV dysfunction was 52.2 ± 7.2 years compared to 38.7 ± 9.8 years in patients with a normal diastolic LV function ($P < 0.001$), and the prevalence of hypertension was 44% in patients with

diastolic LV dysfunction compared to 6% in patients with a normal diastolic LV function ($P=0.005$) (Table 3). Levels of CRP: 4 (1–12) mg/L vs 9 (6–20) mg/L, and ESR: 6 (5–25) mm/h vs 14 (6–46) mm/h were higher in the group of patients with diastolic LV dysfunction, however, these differences did not reach statistical significance.

Follow-up echocardiography after 1 year of treatment

Results are shown in Table 4. Of all 40 patients, 31 (78%) completed the study. Two patients switched to adalimumab during follow-up due to treatment failure. The reasons for dropping out of the study were treatment failure ($n=5$) or loss to follow-up ($n=4$). There were no baseline differences between these two groups regarding age and inflammation levels, except that the BASDAI (6.8 ± 1.6 vs 5.2 ± 1.6 , $P=0.016$) and BASFI (6.4 ± 2.8 vs 4.0 ± 2.0 , $P=0.016$) scores were significantly higher in the group of dropouts compared to those who completed the study. Treatment with TNF- α blocking therapy resulted in a significant decrease in inflammatory and disease activity, with median CRP levels decreasing from 5.0 (2.0–12.0) mg/L to 2.0 (1.9–3.2) mg/L ($P < 0.001$), mean BASDAI decreasing from 5.2 ± 1.6 to 3.7 ± 2.3 ($P=0.001$) and mean ASDAS decreasing from 3.1 ± 1.2 to 2.0 ± 1.0 ($P < 0.001$).

In four out of six AS patients, diastolic LV function improved during treatment ($P=0.125$), see Figure 2. In three patients, diastolic LV dysfunction grade I improved to normal function, and one patient with diastolic LV dysfunction grade II had a normal function after 12 months. In none of the other patients, the grade of diastolic LV function worsened, and no new cases of diastolic LV dysfunction were found. Treatment with TNF- α blocking therapy had no effect on LV mass, left atrial volume or systolic LV function.

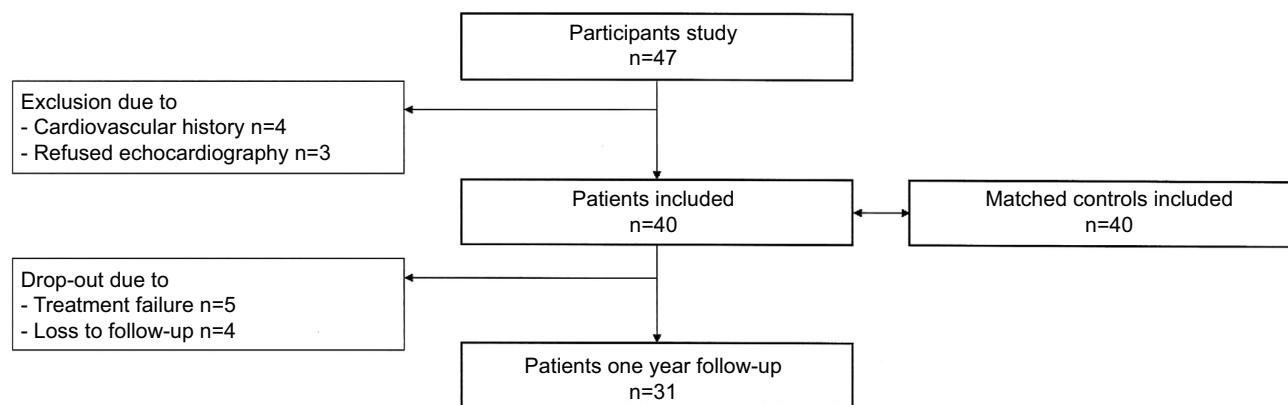


Figure 1 Flowchart of included patients.

Table 1 Baseline characteristics

Variables	
Age, years (mean ± SD)	41.8±10.8
Gender, male n (%)	27 (68)
Body mass index, kg/m ² (median, range)	24.4 (21.9–28.0)
Hypertension n (%)	6 (15)
Diabetes mellitus type 2 n (%)	1 (3)
Disease characteristics	
Years since disease onset (median, range)	16 (9–24)
Years since diagnosis (median, range)	8 (2–16)
HLA-B27 positive n (%)	33 (83)
Systolic blood pressure, mmHg (mean ± SD)	126±13
Diastolic blood pressure, mmHg (mean ± SD)	81±7
ESR, mm/h (median, range)	10 (6–22)
CRP, mg/L (median, range)	4 (1–12)
BASDAI (mean ± SD)	5.6±1.7
BASFI (mean ± SD)	4.5±2.4
ASDAS (mean ± SD)	3.2±1.2
Prior anti TNF- α medication use n (%)	22 (55)
Current NSAIDs use n (%)	33 (83)
Years of prior anti TNF- α medication use (median, range)	0.3 (0.0–4.0)
Echocardiography	
Cardiac abnormality n (%)*	13 (33)
Systolic LV dysfunction n (%)	0 (0)
Diastolic LV dysfunction n (%)	9 (23)
Grade I/II/III n (%)	7 (18)/2 (5)/0 (0)
Aortic valve dysfunction n (%)	1 (3)
Aortic dilatation n (%)	2 (5)
Structural abnormality n (%)	2 (5)
LV mass index, g/m ² (mean ± SD)	74.7±16.6
LA volume/BSA, mL/m ² (mean ± SD)	24.3±6.9
Aortic root diameter, mm (mean ± SD)	3.1±0.4
Mitral dysfunction n (%)	8 (20)
Ejection fraction, % (mean ± SD)	60.0±4.8
Peak E velocity, cm/s (mean ± SD)	79.7±15.6
Peak A velocity, cm/s (mean ± SD)	60.3±13.4
E/A ratio (mean ± SD)	1.38±0.4
Deceleration time, ms (mean ± SD)	191±33
e' septal, cm/s (mean ± SD)	9.9±2.4
E/e' ratio (mean ± SD)	7.5±1.7

Notes: *Statistically significant: $P < 0.05$.

Abbreviations: ASDAS, Ankylosing Spondylitis Disease Activity Score; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; LV, left ventricular; NSAID, non-steroidal anti-inflammatory drug; TNF- α , tumor necrosis factor alpha.

Discussion

Our observations suggest that TNF- α blocking therapy may favorably influence diastolic LV function in patients with an inflammatory disease. No differences were found in systolic LV function.

Increased diastolic LV dysfunction has previously been reported in AS, comparable to other diseases associated with an increased inflammatory response, such as rheumatoid

Table 2 Echocardiographic data

Cardiac abnormalities	AS patients
Cardiac abnormality n (%)*	13 (33)
Systolic LV dysfunction n (%)	0 (0)
Diastolic LV dysfunction n (%)	9 (23)
Grade I/II/III n (%)	7 (18)/2 (5)/0 (0)
Aortic valve dysfunction n (%)	1 (3)
Aortic dilatation n (%)	2 (5)
Structural abnormality n (%)	2 (5)
Other echocardiography variables	
LV mass index, g/m ² (mean ± SD)	74.7±16.6
LA volume / BSA, mL/m ² (mean ± SD)	24.3±6.9
Aortic root diameter, mm (mean ± SD)	3.1±0.4
Mitral dysfunction n (%)	8 (20)
Ejection fraction, % (mean ± SD)	60.0±4.8
Diastolic LV function variables	
Peak E velocity, cm/s (mean ± SD)	79.7±15.6
Peak A velocity, cm/s (mean ± SD)	60.3±13.4
E/A ratio (mean ± SD)	1.38±0.4
Deceleration time, ms (mean ± SD)	191±33
e' septal, cm/s (mean ± SD)	9.9±2.4
E/e' ratio (mean ± SD)	7.5±1.7

Notes: *Statistically significant: $P < 0.05$, One AS patient and one control had two abnormalities.

Abbreviations: AS, ankylosing spondylitis; BSA, body surface area; LA, left atrium; LV, left ventricular; n, number.

arthritis, psoriatic arthritis and diabetes mellitus.^{21–24} There is a growing interest in diastolic LV dysfunction as it has been shown to be an increasing problem with its own morbidity and mortality.^{25,26} Diastolic LV dysfunction is poorly understood and the pathophysiology of the disease is speculative at best.^{15,27} Treatment of diastolic LV dysfunction is subject of many studies, all failing to bring improvement.²⁸ Therefore, the present study might attribute to the understanding of this disease and help formulate new points of intervention in order to resolve this growing problem.

Pathogenically, the systemic inflammatory process may cause cardiac fibrosis, subsequently decreasing overall cardiac muscle elasticity and the relaxing abilities.²⁷ In this study, inflammation levels were not significantly different in patients with diastolic LV dysfunction compared to those without. An effect of inflammation can, however, not be disregarded, as it is possible that the cumulative disease and inflammatory burden over several years affects the CV system, which is difficult to establish. Also, the investigated groups might have been too small to detect subtle differences. Patients with diastolic LV dysfunction were older and had a higher blood pressure compared to those without diastolic LV dysfunction, both known risk factors for the development of diastolic LV dysfunction.¹⁶ The prevalence of hypertension is often reported higher in AS compared to controls.^{29–31} The

Table 3 Differences in characteristics of study population between AS patients with and without diastolic LV dysfunction at baseline

Variables	Normal diastolic LV function (n=31)	Diastolic LV dysfunction (n=9)	P-value
Age, years (mean \pm SD)	38.7 \pm 9.8	52.2 \pm 7.2	<0.001*
Years since diagnosis (median, range)	8.0 (2.0–13.0)	8.0 (2.0–19.0)	0.649
HLA-B27 positive n (%)	26 (84)	7 (78)	0.645
CRP, mg/L (median, range)	4 (1–12)	9 (6–20)	0.132
ESR, mm/h (median, range)	6 (5–25)	14 (6–46)	0.292
SBP, mmHg (mean \pm SD)	124 \pm 13	130 \pm 10	0.190
DBP, mmHg (mean \pm SD)	80 \pm 7	83 \pm 2	0.256
Hypertension n (%)	2 (6)	4 (44)	0.002*
Prior anti TNF- α medication use n (%)	18 (58)	4 (44)	0.705
NSAIDs usage n (%)	25 (81)	8 (88)	1.000
BASDAI (mean \pm SD)	5.7 \pm 1.8	5.1 \pm 1.6	0.761
ASDAS (mean \pm SD)	3.2 \pm 1.2	3.3 \pm 1.0	0.405

Note: *Statistically significant: $P < 0.05$.

Abbreviations: ASDAS, Ankylosing Spondylitis Disease Activity Score; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; CRP, C-reactive protein; DBP, diastolic blood pressure; ESR, erythrocyte sedimentation rate; LV, left ventricular; NSAID, non-steroidal anti-inflammatory drug; SBP, systolic blood pressure; TNF, tumor necrosis factor.

Table 4 Effects of TNF- α blocking therapy

Disease variables	Baseline	One year	P-value
CRP, mg/L (median, range)	5.0 (2.0–12.0)	2.0 (1.9–3.2)	<0.001
ESR, mm/h (median, range)	10.0 (6.0–22.0)	4.0 (2.0–7.0)	<0.001
BASDAI (mean \pm SD)	5.2 \pm 1.6	3.7 \pm 2.3	0.001
ASDAS (mean \pm SD)	3.1 \pm 1.2	2.0 \pm 1.0	<0.001
SBP, mmHg (mean \pm SD)	127 \pm 13	124 \pm 11	0.095
DBP, mmHg (mean \pm SD)	82 \pm 7	83 \pm 8	0.472
Echocardiographic variables			
LV mass index, g/m ² (mean \pm SD)	75.1 \pm 17.7	73.1 \pm 15.0	0.389
LA volume / BSA, mL/m ² (mean \pm SD)	24.4 \pm 6.8	25.8 \pm 7.8	0.384
Ejection fraction, % (mean \pm SD)	60.4 \pm 4.5	58.8 \pm 4.7	0.081
LVEDVI (mean \pm SD)	65.1 \pm 13.4	64.1 \pm 12.1	0.313
LVESVI (mean \pm SD)	26.2 \pm 7.2	27.1 \pm 6.3	0.966
Systolic LV dysfunction n (%)	0 (0)	0 (0)	N/A
Diastolic LV dysfunction n (%)	6 (20)	2 (6)	0.125
Grade I/II/III n (%)	4 (13) / 2 (5) / 0 (0)	1 (3) / 1 (3) / 0 (0)	
E/A ratio (mean \pm SD)	1.42 \pm 0.37	1.42 \pm 0.46	0.923
Deceleration time, ms (mean \pm SD)	192 \pm 32	198 \pm 28	0.415
E/e' ratio (mean \pm SD)	7.7 \pm 1.8	7.2 \pm 1.2	0.104

Abbreviations: AS, ankylosing spondylitis; ASDAS, Ankylosing Spondylitis Disease Activity Score; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BSA, body surface area; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; LA, left atrial; LV, left ventricular; LVEDVI, left ventricular end-diastolic volume index; LVESVI, left ventricular end-systolic volume index; N/A, not applicable; n, number; TNF- α , tumor necrosis factor alpha.

frequent use of NSAIDs, being the cornerstone of AS treatment, might add to this risk through its anti-natriuretic and vasoconstrictor effects.³² Blood pressure should therefore be monitored regularly in all AS patients and properly treated when necessary.

The development of TNF- α blockers has led to great improvements in the treatment of AS, with major reductions in disease and inflammatory activity.³³ In this study, we found a potential favorable effect of TNF- α blocking

treatment on diastolic LV function, as diastolic LV function normalized in four AS patients during treatment. This potential positive effect may be explained in several ways. First, suppressing inflammation (ie, TNF- α) might lead to improvements in endothelial function through increases in nitric oxide production and a decrease in resting tension in the adjacent cardiomyocytes.^{27,34–36} Second, lowering of disease activity may lead to improvements in physical capabilities and exercise possibilities resulting in better diastolic cardiac

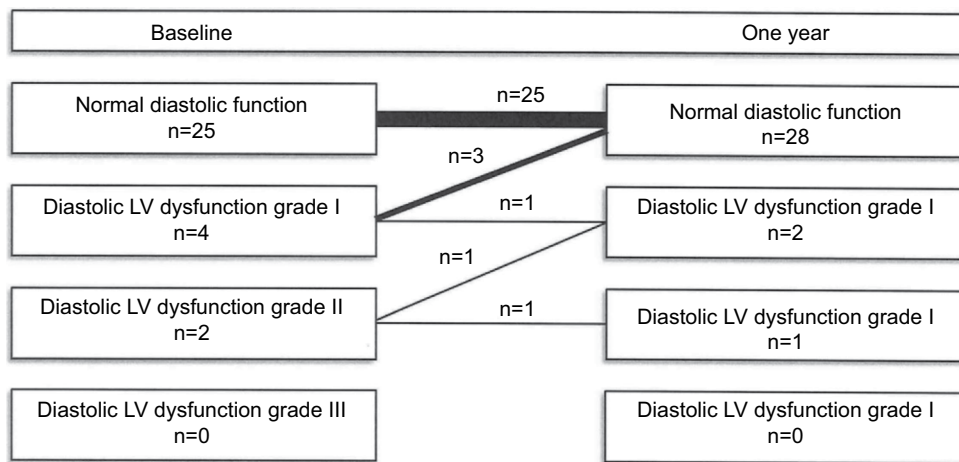


Figure 2 The effect of golimumab treatment on diastolic left ventricular function.

function.^{37,38} Third, decreased use of NSAIDs might positively affect blood pressure levels and lower the cardiac afterload, improving diastolic LV dysfunction.

This study has several strengths and limitations. First we included a homogeneous group of consecutive AS patients with high disease activity. Second, this is one of the first studies investigating the effects of TNF- α blocking therapy on LV function in AS. A limitation of this study is the relatively low number of included patients, which limits the possibility of detecting associations between cardiac pathology and disease characteristics such as inflammation.

Treatment with TNF- α blocking therapy showed a potential favorable effect on diastolic LV dysfunction, but the precise effect of TNF- α blocking treatment and the exact prevalence of cardiac pathology in AS remain to be determined in future studies.

Data sharing statement

The authors have access to raw data for this study and may be contacted for inquiries. According to national data protection rules, these linked raw data cannot be distributed further.

Acknowledgment

This is an investigator-initiated study partly financed by an unrestricted grant from Merck Sharp & Dohme, the Netherlands.

Author contributions

All authors contributed to data analysis, drafting and revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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