Predictors of left ventricular dysfunction in patients with Takayasu's arteritis

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Abstract

Objective

To determine the factors (clinical, biochemical, angiographic, and echocardiographic) which predict left ventricular (LV) dysfunction in Takayasu's arteritis (TAK). TAK causes inflammation of the aorta and its large branches. Systemic hypertension, aortic valvular disease, and coronary artery involvement are probable contributors to LV dysfunction in some patients. In other patients, inflammation and resulting myocarditis play an essential role. However, the prevalence and relative contribution of such predictors of LV dysfunction in TAK patients is unknown.

Methods

We enrolled 87 patients with angiographically confirmed TAK in the study after proper informed consent. A complete clinical, biochemical, and echocardiographic evaluation of all the cases was done. We defined LV systolic dysfunction as an ejection fraction below 50% and diastolic dysfunction by ASE 2016 criteria into grades I, II, and III.

Results

We evaluated 87 consecutive angiographically proven TAK patients. The incidence of LV systolic and diastolic dysfunction in our study was 19.5% (17/87) and 100% (87/87), respectively. All the patients with LV dysfunction (n=17, 100%) had an ITAS 2010 score of more than two suggestive of active disease. In 15 (88%) out of 17 patients with LV systolic dysfunction, we could identify a significant haemodynamic cause of LV dysfunction (untreated hypertension HTN, descending thoracic or abdominal aorta stenosis, renal artery stenosis, coronary stenosis, significant valvular regurgitation). In the rest 2 cases, no important haemodynamic factor was present, and here LV dysfunction was probably because of myocarditis and its sequalae.

Conclusion

This study represents the largest cohort of TAK patients to estimate LV systolic and diastolic dysfunction. We have found LV systolic and diastolic dysfunction multifactorial, with haemodynamic and inflammatory factors contributing to its pathophysiology.

Key word

Takayasu's arteritis, left ventricular systolic dysfunction, ejection fraction

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Introduction

Takayasu's arteritis (TAK) causes inflammation of the aorta and its large branches. TAK often leads to stenosis or aneurysmal dilatations in the inflamed vessel. This inflammatory process most commonly involves the aortic arch and its branches, leading to the involvement of the subclavian arteries or the carotid arteries (1). Other arteries like the renal arteries, coronary arteries, mesenteric arteries, cerebral arteries may be involved leading to renal artery stenosis, myocardial ischaemia, mesenteric ischaemia, stroke, etc. Patients may also have constitutional symptoms like fever, weight loss, reduced appetite during active disease. These diseases could be associated with a relevant burden of mortality and morbidity if not recognised early treated (2). Moreover, even if they are usually rare diseases, their incidence and prevalence seem to be increasing in the last decade, partially because of improved awareness and management of vasculitis from physicians (2).

Cardiac disease is a significant cause of death in patients with TAK. Commonly patients develop congestive heart failure (CHF) secondary to haemodynamic effects of systemic hypertension, aortic valvular disease, or coronary artery involvement (3). In other patients, CHF develops without the presence of these haemodynamic factors. Myocarditis has been detected in many of these patients, indicating an inflammatory cause of myocarditis (4).

We designed this study to study the incidence and predictors of LV dysfunction in patients with angiographically proven TA. We hypothesise that haemodynamic factors like untreated systemic hypertension, aortic valve disease, coronary artery disease, and local inflammatory and immune effects of large-vessel vasculitis are essential to the development of LVSD.

Methods

Patient population

Eighty-seven patients with TAK diagnosed as per American College of Rheumatology (ACR) 1990 criteria (5) and proven on CT angiography were retrospectively identified. We evaluated all the patients with a detailed history, physical examination, blood biochemistry, including ESR and CRP. ECG and 2D echocardiogram were done for all patients to evaluate LV dimensions and LV ejection fraction. We summarised clinical and echo data separately for patients with or without LV systolic dysfunction (LVSD). LVSD was defined as an LV ejection fraction below 50%. LV diastolic function was measured by calculation of E/A ratio, deceleration time, and left atrial volume index (LAVI) according to American Society of Echocardiography 2016 guidelines (6). E/A ratio <0.8 with E<50cm/sec was classified as grade I diastolic dysfunction. E/A ratio <0.8 with E >50cm/sec or E/A ratio 0.8-2.0, LAVI >34 ml/m2, E/e' >14 and DT >160msec was classified as grade II diastolic dysfunction. E/A ≥2 was classified as grade III diastolic dysfunction (6).

Data collection

All patients included in the study were diagnosed as cases of TAK based on ACR 1990 criteria. An independent reviewer reviewed CT angiograms of the included patients. Clinical data were obtained through chart review by one investigator. An independent echocardiographer examined all transthoracic echocardiograms, who was blinded to the clinical and angiographic data.

Statistical analysis

P-values <0.05 were considered statistically significant. For comparison of continuous variables, Wilcoxon rank-sum tests were used. Fisher's exact tests or Chi-square tests were utilised for categorical or nominal variables.

Results

Table I shows the demographic profile and inflammatory markers in patients of TAK with or without LV dysfunction. Seventy patients of TAK with normal LV systolic function and 17 patients of TAK with LV systolic dysfunction on 2D-echocardiography were identified. In patients with normal LV function, 15 males and 55 females were present with a male to female ratio of 1:3.6. In patients with LV dys-

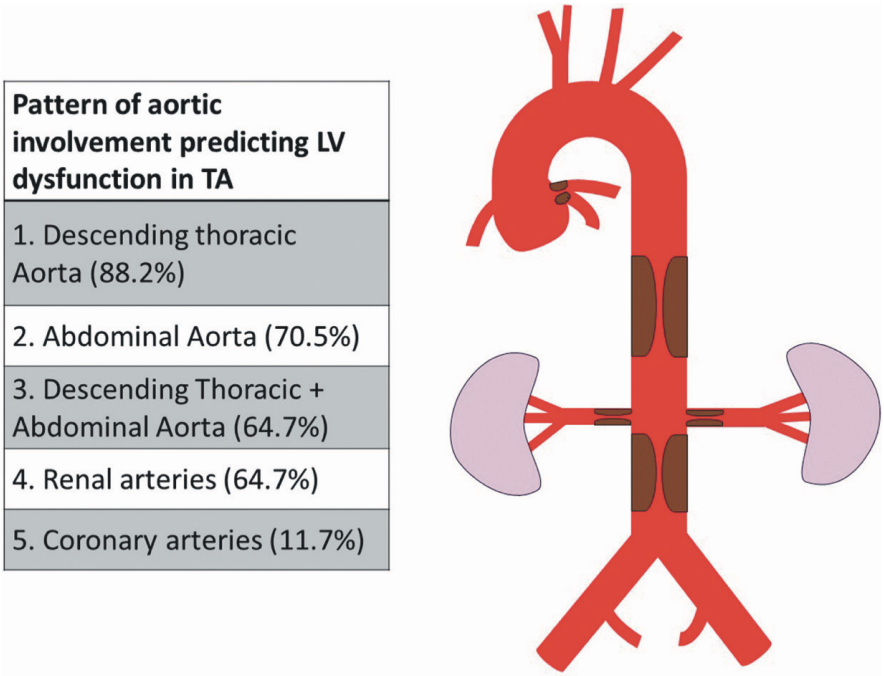

Fig. 1. The pattern of aortic involvement in TAK.

Table I. Demographics of 87 patients with Takayasu's arteritis.

Parameters	Study Groups		*p*-value
	Normal LV function (n=70)	Reduced LV function (n=17)	
	Gender		
Male	15 (21.4%)	4 (24%)	NS
Female	55 (78.6%)	13 (76%)	NS
	Clinical characteristics		
Age (years) mean ± SD	30.85 ± 9.61	25.75 ± 9.55	<0.001
BMI (kg/m^2) mean ± SD	21.62 ± 2.37	21.52 ± 2.55	NS
Hypertension n (%)	35 (50%)	15 (89%)	<0.001
Type 2 diabetes n (%)	7 (10%)	2 (11.7%)	NS
ESR (mm/hr) mean ± SD	7.18 ± 2.75	40.01 ± 2.17	<0.001
CRP (mg/dl) mean ± SD	2.01 ± 1.75	7.68 ± 0.35	<0.001
TNF alpha (pg/ml) mean ± SD	5.59 ± 3.38	10.40 ± 2.88	<0.001
IL-6 (pg/ml) mean ± SD	9.64 ± 3.18	20.10 ± 4.20	<0.001
IL-18 (pg/ml) mean ± SD	6.22 ± 2.58	22.13 ± 4.01	<0.001
Steroid	Yes Yes	NS	
ITAS 2010 mean±SD	3 ± 1.2	6 ± 1.6	<0.001
ITAS ≥2 n (%)	47 (67.14)	17 (100)	<0.001
Duration from the first symptom to diagnosis (months) Median (IQR)	27 (7.5)	16 (8.1)	<0.001

LV: left ventricle; BMI: body mass index; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein, TNF: tumour necrosis factor; IL: interleukin.

function, four males and 13 females were there with a male to female ratio of 1:3.2, similar to patients with normal LV function. The average age of presentation of patients with normal LV function was 30.85±9.61years. At the same time, patients with LV dysfunction appeared to present earlier at the age of 25.75±9.55 years. This might be attributed to the earlier development of symptoms in patients with LV dysfunction, thus seeking medical care earlier. No significant differences were noted in BMI (25.75±9.55 vs. 21.52±2.55) and incidence of type 2 diabetes (10% *vs.* 11.7%) in the patient's normal LV function compared to patients with LV dysfunction. Hypertension was much more frequent in patients with LV dysfunction (89% *vs.* 50%, $p<0.001$) than those with normal LV function. Untreated hypertension may be one of the contributory causes of LV dysfunction in these patients.

Assessment of markers of inflammation revealed significantly raised inflammatory markers in patients with LV dysfunction. Patients with LV dysfunction had significantly higher ESR (40.01±2.17 *vs.* 7.18±2.75 mm/hr, $p<0001$) and CRP (7.68±0.35 *vs.* 2.01±1.75 mg/dl, $p<0001$) compared to patients with normal LV function. The further evaluation also revealed significantly higher levels of serum TNF-α (10.40±2.88 *vs.* 5.59±3.38 pg/ml, $p<0001$), IL-6 (20.10±4.20 *vs.* 9.64±3.18 pg/ml, $p<0001$) and IL-18 (22.13±4.01 *vs.* 6.22±2.58 pg/ml, $p<0001$) in patients with LV dysfunction showing a significantly higher systemic inflammatory response in these patients.

ITAS 2010 score was 6±1.6 in patients with LV dysfunction compared to 3±1.2 in patients without LV dysfunction. A significantly higher proportion of patients with LV dysfunction (n=17, 100%) had an ITAS 2010 score of more than two suggestive of active disease. In contrast, an ITAS score of more than two was recorded in 47 (67.14%, $p<0.001$) patients without LV dysfunction. Patients with LV systolic dysfunction presented earlier (median 16 mth, IQR 8.1 mth) as compared to patients without LV dysfunction (median 27 mth, IQR 7.5 mth, $p<0.001$). All the patients were on guideline-recommended doses of systemic steroids.

Table II shows the pattern of involvement of aorta and aortic branches in the two sub-set of patients. Patients with LV dysfunction had, on average, three aortic segments ($p=0.02$) involved compared to 1 segment involvement in patients without LV dysfunction. Descending thoracic aorta (88.2% *vs.* 68.5%, $p<0.001$) and abdominal aorta (70.5% *vs.* 47.1%, $p<0001$) were involved more frequently in patients of LV dysfunction. Both Descending thoracic and abdominal aorta involvement in the same patient was also higher in patients with LV dysfunction (64.7%

vs. 38.5%, *p*<0001). Renal artery stenosis was seen in 64.7% patients with LV systolic dysfunction compared to 10% patients with normal LV function (*p*<0.001). Stenotic coronary artery disease was seen more frequently in patients with LV systolic dysfunction (11.7% *vs*. 4.2%, *p*<0.001). Ascending aorta, aortic arch, carotid, subclavian, brachiocephalic, vertebral, and mesenteric arteries were affected with a similar frequency in both groups.

Table III summarises the echocardiographic parameters of LV systolic function assessed in both groups. LV systolic function was assessed by measuring LV ejection fraction and chamber dimensions. The ejection fraction was calculated by the biplane method using modified Simpson's rule. The ejection fraction was 62.6±2.3% in patients with normal LV function. In contrast, the ejection fraction in patients with LV dysfunction was significantly lower at 27.7±3.4%. Assessment of LV chamber revealed significant chamber dilatation and chamber wall hypertrophy in patients with LV dysfunction. LV end-diastolic dimension (58.8±4.3 *vs*. 49.1±5.1, *p*<0.001) and LV end-systolic dimension (46.2±4.4 *vs*. 30.8±3.3, *p*<0.001) was significantly higher in patients of LV dysfunction signifying chamber dilatation. Also, patients with LV dysfunction showed evidence of concentric hypertrophy with the increased interventricular septum (IVS) and posterior wall (PW) thickness. There was no evidence of asymmetrical septal hypertrophy, systolic anterior movement of the anterior mitral leaflet, or mid cavitary gradient. IVS thickness: PW thickness was less than 1.3 in all cases.

Table IV summarises the echocardiographic parameters of LV diastolic function assessed in both groups. In patients with normal LV function, the E/A ratio was 0.7±0.1, the deceleration time was 216±13 ms, and the LA volume index was 28.6±1.9 ml/m2. 61 patients with normal LV function had Type 1 diastolic dysfunction, seven patients had type 2 diastolic dysfunction, and two patients had type 3 diastolic dysfunction. In contrast, the E/A ratio was 2.4±0.2, the Deceleration time was 113±11 ms, and the LA volume index was 34.4±7.2 ml/m2 in patients with LV dysfunction. Significantly higher E/A ratio and LAVI with lower deceleration time indicate a more severe diastolic dysfunction in these patients. 7 patients had type 2 diastolic dysfunction, eight patients had type 3 diastolic dysfunction, and only two patients had type 1 diastolic dysfunction.

Table V summarises the echocardiographic evaluation for valvular regurgitation assessed in both groups. Aortic root dilatation was seen more com-

Table II. Pattern of involvement of aorta and aortic vessels.

Vessel (stenosis)	Normal LV function (n=70)	Reduced LV function (n=17)	*p* value
Ascending aorta	18 (25.7%)	4 (23.5%)	NS
Aortic Arch	35 (50%)	9 (52.9%)	NS
Descending thoracic aorta	48 (68.5%)	15 (88.2%)	<0.001
Abdominal aorta	33 (47.1%)	12 (70.5%)	<0.001
Desc Thoracic + Abd Aorta	27 (38.5%)	11 (64.7%)	<0.001
Carotid	56 (80%)	13 (76.4%)	NS
Subclavian	59 (84.2%)	14 (82.3%)	NS
Brachiocephalic	34 (48.5%)	7 (41.1%)	NS
Vertebral	6 (8.5%)	2 (11.7%)	NS
Mesenteric	3 (4.2%)	1 (5.8%)	NS
Renal	7 (10%)	11 (64.7%)	<0.001
Coronary	3 (4.2 %)	2 (11.7%)	<0.001
Aortic segments	1 (median)	3 (median)	0.02

Table III. Echocardiographic measures of LV systolic function.

Parameter Diameter (Mean ± SD mm)	Normal LV function (n=70)	Reduced LV function (n=17)	*p* value
• EF (%)	62.6 ± 2.3	27.7 ± 3.4	<0.001
• LVEDD	49.1 ± 5.1	58.8 ± 4.3	0.001
• LVESD	30.8 ± 3.3	46.2 ± 4.4	<0.001
• IVSd	9 ± 1.3	13 ± 2.6	<0.001
• IVSs	10 ± 1.2	16 ± 3.4	<0.001
• PWd	7 ± 2.1	12 ± 2.9	<0.001
• PWs	9 ± 1.1	15 ± 3.1	<0.001

EF: ejection fraction; LVEDD: left ventricle end diastolic dimension; LVESD: left ventricle end systolic dimension; IVSd: interventricular septal thickness in diastole; IVSs: interventricular septal thickness in systole; PWd: posterior wall thickness in diastole; PWs: posterior wall thickness in systole.

Table IV. Echocardiographic measures of LV Diastolic function.

Parameter	Normal LV function (n=70)	Reduced LV function (n=17)	*p* value
• E/A ratio	0.7 ± 0.1	2.4 ± 0.2	<0.001
• Deceleration time (ms)	216 ± 13	113 ± 11	<0.001
• LAVI (ml/m2)	28.6 ± 1.9	34.4 ± 7.2	<0.001
• Type I DD	61 (87.1)	2 (11.76%)	<0.001
• Type II DD	7 (10%)	7 (41.2%)	<0.001
• Type 3 DD	2 (2.8%)	8 (47.05%)	<0.001

Table V. Echocardiographic evaluation for valvular regurgitation.

Parameter	Normal LV function (n=70)	Reduced LV function (n=17)	*p* value
• Aortic Regurgitation	7 (10%)	3 (17.6%)	0.01
• Mitral Regurgitation	4 (5.7%)	4 (23.3%)	<0.001
• Tricuspid Regurgitation	0 (0%)	1 (5.8%)	<0.001
• Aortic Root diameter mm	26 ± 1.2	34.4 ± 4.0	0.015
• Mitral annulus diameter mm	31 ± 7.1	40 ± 4.3	<0.001
• Tricuspid annulus diameter mm	38 ± 4.5	39 ± 3.1	NS
• RV systolic pressure by TR jet mmHg	NA	42 ± 11	NA

monly in patients with LV dysfunction (34.4±4.0 *vs*. 26±1.2 mm, $p<0.015$), leading to more frequent moderate to severe aortic regurgitation in these patients (17.6% *vs*. 10%, $p<0.01$). Moderate to severe Mitral regurgitation was more frequent in patients with LV dysfunction (23.3% *vs*. 5.7%, $p<0.001$). Significant Mitral annular dilatation was seen in patients with LV dysfunction (40±4.3 *vs*. 31±7.1 mm, $p<0.001$). Tricuspid regurgitation was more frequent in patients with LV dysfunction (5.8% *vs*. 0%, $p<0.001$) with a calculated RV systolic pressure of 42±11 mmHg.

Discussion

TAK is an inflammatory disease of unknown aetiology involving the aorta and its branches that predominantly affect women with its onset during the second or third decades of life. Left ventricular dysfunction is a leading cause of morbidity and mortality in patients with TAK. LV systolic dysfunction appears to be multifactorial. Haemodynamic reasons like untreated hypertension due to significant vessel stenosis (*i.e*. renal artery stenosis, aortic stenosis, and carotid stenosis), aortic regurgitation due to aortic root dilatation, and coronary artery stenosis have been historically suggested cause of LV systolic dysfunction (3). Few studies have failed to establish haemodynamic causes as the primary reason for this and have argued for alternative myocardial inflammation and myocarditis (4).

In our study, 87 patients diagnosed with TAK have been evaluated. Of the enrolled cases, 17 were found to have LV systolic dysfunction, and 87 were found to have LV diastolic dysfunction. The incidence of LV systolic and diastolic dysfunction in our study was 19.5% (17/87) and 100% (87/87), respectively. Female preponderance was seen in both patients with or without LV systolic dysfunction with F: M 3:1. The patients with LV systolic dysfunction presented at a younger age compared to patients without LV dysfunction. This may be because patients with LVSD appear to have a more extensive disease and develop symptoms earlier and present earlier. The incidence of CHF also is much higher in children in previous studies (7).

Echocardiographic evaluation of the patients revealed dilated LV in patients of LV systolic dysfunction. Concentric hypertrophy was seen with increased thickness of both the interventricular septum and posterior wall. Diastolic dysfunction was seen in all the patients; however, the severity of diastolic dysfunction was higher in the patients with underlying LV dysfunction. Due to the combined effects of systolic and diastolic dysfunction, these patients appeared to have higher LA volume suggestive of LA dilatation.

Evaluation of markers of systemic inflammation revealed elevated ESR, CRP, serum TNF-α, IL-6, and IL-18 in all the cases enrolled. However, in patients who had LV dysfunction, these markers were elevated to a greater extent, pointing towards a higher systemic inflammatory burden in these cases, which may cause myocardial involvement leading to myocarditis and fibrosis (8). ITAS 2010 disease activity score was significantly higher in patients with LV systolic dysfunction. A substantially higher proportion of patients with LV dysfunction had an ITAS score of more than 2, suggesting the active disease is associated with LV dysfunction at presentation. Primary myocardial involvement is well documented in previous clinical as well as autopsy studies (7). Chopra *et al*. have reported four patients with TAK and congestive cardiac failure with the absence of significant haemodynamic factors like hypertension or valvular regurgitation (9). Cardiac histological data were characteristic of dilated cardiomyopathy in these cases with interstitial fibrosis and myonecrosis. Arora *et al*. have also reported patients with TAK and congestive cardiac failure diagnosed as having dilated cardiomyopathy with the absence of hypertension, coronary arterial, or valvar disease (10). Autopsy data revealed biventricular hypertrophy, areas of myonecrosis, and fibrosis with occasional mononuclear cell infiltration. Thickening of the left atrial and ventricular endocardium has been reported at autopsy by Shrivastava *et al*. (11) and Chetri *et al*. (12). Endomyocardial biopsies (EMB) were not performed in our study, mainly because of the perception that EMB is a relatively low yield and high-risk procedure. The result of clinically useful information with EMB among patients with dilated cardiomyopathy is expected, around 10%, and the risks of cardiac perforation are approximately 1: 250 (4). Alternative modalities such as gadolinium-enhanced MRI and PET scanning may provide adequate non-invasive data to recognise or follow LVSD and cardiac inflammation in giant vessel arteritis.

Evaluation of haemodynamic factors revealed that untreated hypertension (HTN) is significantly higher in patients with LV dysfunction (13). These patients appeared to have more extensive aortic involvement (3 segments *vs*. one segment). Stenosis of descending thoracic aorta, abdominal aorta, and renal arteries was more frequent in these patients. Incidence of moderate to severe aortic regurgitation was also higher in patients with LV systolic dysfunction and appeared to be secondary to inflammatory Aortic root dilatation. These patients had a significantly higher incidence of moderate to severe mitral regurgitation and tricuspid regurgitation. Mitral regurgitation was associated with a higher mitral annular diameter, suggesting mitral regurgitation was secondary to LV remodelling and annular dilatation.

In contrast, tricuspid regurgitation was not associated with tricuspid annular dilatation. Calculated RV systolic pressure was higher in these patients, pointing towards possible pulmonary hypertension-induced TR without significant annular dilatation or RV dysfunction. It may be hypothesised that significant stenosis of descending thoracic aorta, abdominal aorta, and renal arteries may be substantial causes of secondary hypertension in these cases, which leads to LV systolic dysfunction. Aortic root dilatation with significant AR and secondary MR also appears to be contributing to LVSD.

In 15 out of 17 patients with LV systolic dysfunction, a significant haemodynamic cause of LV dysfunction (un-

treated HTN, descending thoracic or abdominal aorta stenosis, renal artery stenosis, coronary stenosis, significant valvular regurgitation) could be identified. Similar haemodynamic causes have been previously associated with LV dysfunction in TAK patients in other studies (14). However, these patients also had significantly higher systemic inflammatory markers. It may be possible that even in these patients, inflammatory response and myocardial involvement play an essential role in the pathophysiology of LV dysfunction. In 2 cases, no significant haemodynamic factor was identified. In these cases, LV systolic dysfunction may have been caused primarily due to myocarditis and its sequelae (15).

In contrast, LV diastolic dysfunction was documented in all the cases, including those without systolic dysfunction. Although data on diastolic dysfunction in TAK is lacking, diastolic dysfunction is prevalent and seen in two-thirds of cases of rheumatoid arthritis (16) without evident cardiovascular disease. It may be possible that systemic inflammation and haemodynamic factors hamper cardiac myocyte relaxation and cause diastolic dysfunction. Since this was documented in all cases without LV systolic dysfunction, it may be argued that diastolic dysfunction is strongly linked to a systemic inflammatory state independent of systolic dysfunction.

All the patients with active disease were treated with corticosteroids with a dose of (1 mg/kg/day) prednisolone or equivalents. Other immunosuppressants like methotrexate and mycophenolate mofetil were used in the case of steroid non-responders. In none of the cases biologicals were used. We have documented systolic and diastolic dysfunction even in patients on guideline-directed doses of steroids. The use of biological agents like infliximab or tocilizumab is capable of remedying specific vascular lesions. It may provide additional benefits to patients with TAK who do not sufficiently respond to conventional synthetic disease-modifying antirheumatic drug (DMARD) treatment. Future studies may be needed to study the effect of these agents on systolic and diastolic dysfunction (17). This study represents the largest cohort of TAK patients to estimate LV systolic and diastolic dysfunction. Identification of the cause of systolic and diastolic dysfunction is important as TAK patients have an increased incidence of cardiovascular mortality than the general population (18). We have found LV systolic and diastolic dysfunction multifactorial in origin, with both haemodynamic and inflammatory factors contributing to its pathophysiology.

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