# Predictors of left ventricular dysfunction in patients with Takayasu's or giant cell aortitis

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**ABSTRACT**

**Objectives.** *The aim of this study was to determine the clinical and angiographic predictors of left ventricular systolic dysfunction (LVSD) from a relatively large and angiographically characterized Takayasu's or Giant Cell aortitis (TA/GCA) population.*

**Background.** *LVSD in patients with TA/GCA has been described in case reports and attributed variously to hemodynamic and immunologic factors. The predictors of LVSD in patients with angiographically confirmed TA/GCA are not known.*

**Methods.** *We identified 78 patients with angiographically confirmed TA/GCA that underwent transthoracic echocardiography (TTE) at Mayo Clinic. Echocardiograms were then reviewed independently by reviewers blinded to clinical and angiographic data. LVSD was defined as an ejection fraction (LVEF) less than 50%.*

**Results.** *The study population was 84% Caucasian (54/78), 91% female (58/78), and had a mean age of disease onset of 30 years (±15 years). LVSD was present in 14 of 78 patients (18%) with TA/GCA. The mean LVEF in the LVSD group (n = 14) was 37% ± 7%, compared to an LVEF of 62% ± 6% (p < 0.0001) in those without LVSD (n = 64). LVSD was not associated with hypertension or aortic regurgitation (p > 0.5). However, LVSD was found in 43% (9/21) of patients with aortic arch involvement, versus only 9% (5/57) of patients without aortic arch involvement (p = 0.0013). Patients with LVSD had a median of 2 (range 1-4) involved aortic segments compared to a median of 1 (range 1-4) among those without LVSD (p=0.013).*

**Conclusions.** *In TA/GCA aortitis, LVSD is associated with involvement of the aortic arch and with the greater extent of aortic involvement. The hemodynamic variables, aortic regurgitation and systemic hypertension, were not associated with LVSD, consistent with reports that cardiac inflammation is responsible for LVSD in a majority of cases. Ours is the first study to estimate an incidence of LVSD in patients with TA/GCA aortitis, which was 18%.*

## Introduction

Inflammation of the aorta and its large branches from Takayasu's or Giant Cell arteritis (TA/GCA) results in gradual stenosis and less often dilatation and aneurysm formation of the involved vessels. Direct sequelae from this process may include upper extremity claudication, visual disturbances, pulmonary hypertension, mesenteric ischemia, stroke, and myocardial infarction. Systemic effects such as fever, arthralgias, hypertension, and skin lesions have also been associated with these vasculitides. Myocardial dysfunction in the setting of TA/GCAhas previously only been described in case reports or in small case series (1-3).

Heart disease is the major cause of death in patients with TA (4-8). In most cases, cardiac mortality has been associated with heart failure (CHF). Cases of CHF have usually been attributed to the hemodynamic effects of coronary artery involvement, aortic valvular disease, or systemic hypertension (6, 8-11). However, left ventricular dysfunction (LVSD) resulting in CHF has been observed in TA/GCA patients without the presence of these hemodynamic factors (3,12,13). Myocarditis defined by either the Dallas criteria or immunoperoxidase staining was detected in many of these cases, suggesting an inflammatory etiology of LVSD in TA/GCA(13,14).

The purpose of this study was to examine the incidence and predictors of LVSD in patients with angiographically confirmed TA/GCA. Our hypothesis was that the local inflammatory and/or immune effects of large vessel inflammation would more likely predict the

development of LVSD than would the hemodynamic effects of coronary artery lesions, aortic regurgitation, or systemic hypertension in this population.

## Methods

*Patient population*

We retrospectively identified 255 patients with an angiographic diagnosis of TA/GCA at the Mayo Clinic from 1975-2003. Transthoracic echocardiography (TTE) was obtained in 117 patients. Of those, 78 patients had an angiographically confirmed diagnosis of TA/GCA with available TTE tapes for independent review. Clinical and ECHO data were summarized separately for patients with and without LVSD. LVSD was defined as an ejection fraction (LVEF) of less than 50%. Coronary stenosis as a contributing mechanism in the LVSD group was excluded by normal coronary angiography in 11 patients and by negative stress echocardiogram in 2 patients.

*Data collection*

Clinical data was obtained through chart reviews by one investigator. All transthoracic echocardiograms were reviewed in an independent analysis by one echocardiographer, who was blinded to the clinical and angiographic data. Off line measurements of the aortic wall thickness at specified locations (Figs. 1 and 2) were performed using ImageVue work station (Nova Microsonic, Allendale, PA). LV function and valvular regurgitation (Fig. 3) were assessed in accordance with previously published criteria (15,16). Certain parameters could not be measured in some patients due to limitations of the TTE studies (i.e., lack of color Doppler).

*Statistical analysis*

Chi-square or Fishers exact tests were utilized as appropriate for categorical or nominal variables. Wilcoxon rank-sum tests were used for comparisons of continuous variables. P-values $< 0.05$ were considered to be statistically significant.

## Results

As displayed in Table I, the study pop-

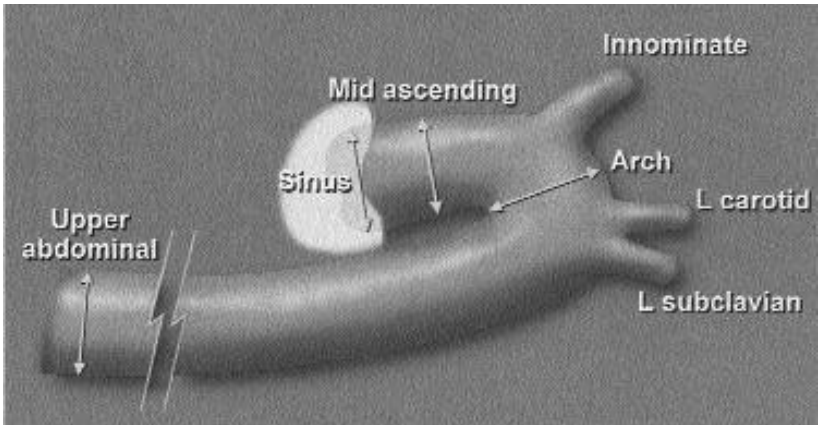


**Fig 1.** The aortic arch with arrowed bars illustrating the location of width measurements in Table II.

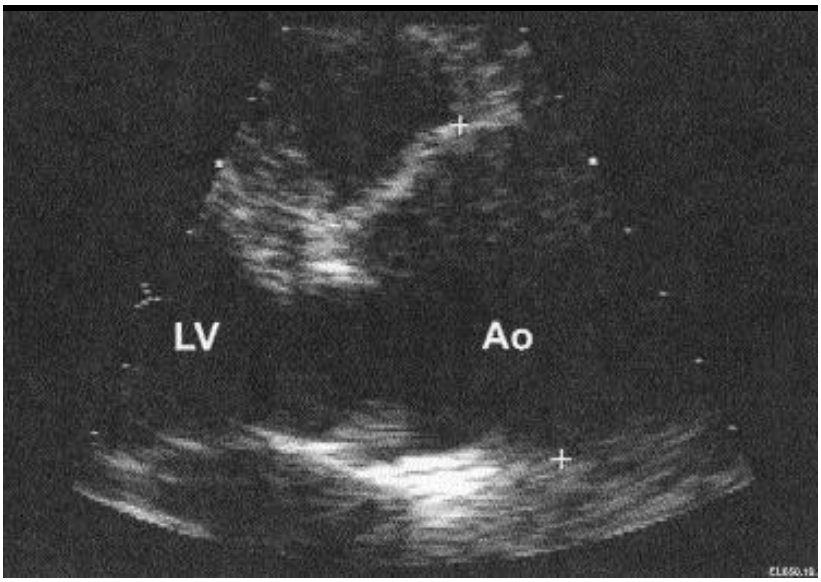


**Fig 2.** Echocardiograph illustrating a typical ascending aortic aneurysm in a patient with Takayasu arteritis. LV, left ventricle. Ao, Aorta. + signs denote the width measurement locations in the mid ascending aorta.

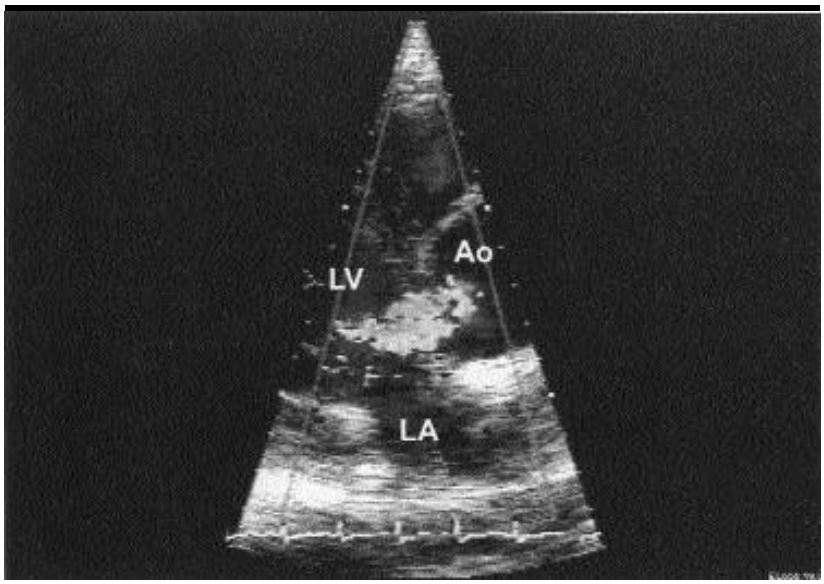


**Fig 3.**. Echocardiogram illustrating aortic valve regurgitation in a patient with Takayasu arteritis. LV, left ventricle. Ao, Aorta, LA, left atrium.

ulation was 84% Caucasian (54/78), 91% female (58/78), and had a mean (±SD) age of disease onset of 30 ± 15 years. The mean LVEF was 57% (±11%). The average time between symptom onset and diagnosis was 46 months, and the average time between diagnosis and echocardiography was 24 months. Of the 78 patients, 18% (14) had an LVEF less than 50% (mean of 37% ± 7%). If one assumes that cardiac function was normal in the remainder of the 255 subjects with angiographically confirmed GCA/TA, the incidence of LVSD was 5.5%, over five times higher than would be expected in a healthy female population of similar age (24).

Table II illustrates the distribution of involved vessels in this patient population. The presence of LVSD was found in 43% (9/21) of patients with aortic arch involvement, versus 9% (5/57) of patients without aortic arch involvement (p = 0.0013). Patients with LVSD had a median of 2 (range 1-4) involved aortic segments compared to a median of 1 (range 1-4) among those without LVSD (p = 0.013).

Echocardiographic measurement characteristics are represented in Figure 1, while predictors of LVSD by univariate analysis are shown in Table III. LVSD was present in 14 of 78 patients (18%) with TA/GCA. The mean LVEF in the LVSD group was 37 ± 7%, compared to an LVEF of 62% ± 6% (p < 0.0001) in those without LVSD. Aortic root, ascending aorta, and aortic arch diameters were significantly larger in patients with LVSD. There was a trend toward significance (p = 0.084), suggesting an increased posterior wall thickness of the aorta in those with LVSD. Pulmonary valve regurgitation of at least moderate degree was more frequent in those with LVSD (p = 0.039). No significant difference in the severity and frequency of other valvular lesions were noted. LV EDD and ESD dimensions were significantly larger in those with LVSD (p = 0.002 and p < 0.0001, respectively).

The following factors were not associated with the presence of LVSD: aortic thickness, aortic regurgitation, the number of involved extra-aortic vessels, aneurysm, hypertension, diabetes, tobacco use, sedimentation rate, leukocyte count, hemoglobin, retinopathy, and progressive course of arteritis.

**Table I.** Demographics of 78 patients with TA/GCAlarge vessel arteritis.

| | Normal LVfunction (n = 64) | | LVSD (n = 14) | | p-value |
|---|---|---|---|---|---|
| Age of onset | 28.6 | (13.3) | 34.7 | (19.7) | NS |
| Female gender | 58 | (91%) | 12 | (86%) | |
| Race: | | | | | NS |
| Caucasian | 54 | (84%) | 11 | (79%) | |
| Hispanic | 4 | (6%) | 1 | (7%) | |
| African-American | 1 | (1.5%) | | 0 | |
| Native American | 1 | (1.5%) | 0 | | |
| Asian | 5 | (7%) | 2 | (14%) | |
| Diabetes | 6 | (8%) | 0 | NS | |
| Hypertension | 34 | (53%) | 8 | (57%) | NS |
| Tobacco use: | | | | | \NS |
| Current | 9 | (14%) | 1 | (7%) | |
| Previous | 19 | (30%) | 5 | (36%) | |
| Takayasu | 58 | (91%) | 11 | (79%) | |
| GCA | 6 | (9%) | 3 | (21%) | |
| Hemoglobin | 12.0 | (2.0) | 12.6 | (2.0) | NS |
| WBC | 9.0 | (2.8) | 8.5 | (3.8) | NS |
| Sedimentation rate | 34.1 | (30.5) | 32.8 | (34.5) | NS |
| Steroid use | 52 | (81%) | 14 | (100%) | NS |
| EF (%) | 61.7 ± 5.7 | | 37.5 ± 7.3 | | **< 0.0001** |

**Table II.** Distribution of affected vessels in 78 patients with TA/GCAlarge vessel arteritis.

| | Normal LVfunction (n = 64) | | LVSD (n = 14) | | p-value |
|---|---|---|---|---|---|
| Ascending aorta | 19 | (30%) | 6 | (43%) | NS |
| Aortic arch | 12 | (19%) | 9 | (64%) | **0.0013** |
| Descending thoracic aorta | 30 | (47%) | 10 | (71%) | **0.096** |
| Abdominal aorta | 27 | (42%) | 7 | (50%) | NS |
| No. of aortic segments (of 4) | 1 | (median) | 2 | (median) | **0.013** |
| Carotid | 38 | (59%) | 9 | (64%) | NS |
| Subclavian | 52 | (81%) | 11 | (79%) | NS |
| Brachiocephalic | 7 | (11%) | 3 | (21%) | NS |
| Vertebral | 17 | (27%) | 3 | (21%) | NS |
| Mesenteric | 17 | (27%) | 4 | (29%) | NS |

## Discussion

This study adds to existing data regarding the cardiac sequelae of large vessel vasculitis associated with TA/GCA. We estimated the incidence of LVSD, and its predictors, in a subpopulation of patients with large vessel arteritis from angiographically proven TA/GCA.

Historically, hemodynamic mechanisms such as aortic regurgitation and/or systemic hypertension have been suggested to be the predominant etiologies for the development of heart failure in Takayasu's aortitis (6, 11). The development of aortic valvular incompetence has been proposed to result from proximal aortic inflammation with dilatation of the aortic ring (9,17). The evolution of long-standing systemic hypertension in these patients has been postulated to result from large vessel stenoses, especially those involving the renal arteries (6, 9). Interestingly, our study group did not display a statistically significant association between LVSD and the presence of these hemodynamic variables. Therefore, the

**Table III.** Echocardiographic predictors of LVSD in 78 patients with TA/GCAarteritis.

| | Normal LVfunction (n = 64) | | LVSD (n = 14) | | p-value |
|---|---|---|---|---|---|
| Pericardial disease (n)% | (6/63) | 9.5% | (2/14) | 14.3% | NS |
| Diameter mean ± SD (mm) | | | | | |
| LVEDD mean | 48.1 ± 6.1 | (n = 57) | 54.1 ± 5.3 | (n = 13) | **0.002** |
| LVESD mean | 30.1 ± 5.7 | (n = 57) | 42.2 ± 6.1 | (n = 13) | **< 0.0001** |
| Aorta root | 28.3 ± 6.8 | (n = 58) | 32.7 ± 5.0 | (n = 13) | **0.034** |
| Mid ascending aorta | 29.2 ± 8.9 | (n = 44) | 35.9 ± 11.0 | (n = 10) | **0.044** |
| Aortic arch | 28.8 ± 6.7 | (n = 50) | 37.3 ± 8.9 | (n = 10) | **0.001** |
| Descending abdominal aorta | 17.7 ± 4.8 | (n = 26) | 14.3 ± 2.7 | (n = 3) | NS |
| Wall thickness mean ± SD (mm) | | | | | |
| Anterior sinus | 4.6 ± 1.3 | (n = 58) | 5.0 ± 1.2 | (n = 13) | NS |
| Posterior sinus | 5.2 ± 1.5 | (n = 58) | 6.1 ± 2.0 | (n = 13) | NS |
| Mid ascending aorta | 4.8 ± 1.8 | (n = 38) | 6.1 ± 2.8 | (n = 8) | NS |
| Aortic arch | 4.8 ± 1.8 | (n = 30) | 4.7 ± 1.2 | (n = 6) | NS |
| Valve regurgitation > mild (n) % | | | | | |
| Aortic | (14/64) | 21.9% | (4/14) | 28.6% | NS |
| Mitral | (1/64) | 1.6% | (1/14) | 7.1% | NS |
| Tricuspid | (0/63) | | (1/13) | 7.7% | NS |
| Pulmonary | (2/63) | 3.2% | (3/14) | 21.4% | **0.04** |

etiology of LVSD in TA/GCA may be due to an alternative mechanism or perhaps in some cases multifactorial.

In our study, LVSD was associated with disease involvement of the aortic arch and with a greater extent of aortic involvement. These findings were consistent with other reports that cardiac inflammation, through local inflammatory or cellular mechanisms, contributes to the development of LVSD in a majority of cases (3,5,12,13). Talwar *et al*. examined myocardial involvement of TA by utilizing endomyocardial biopsies to detect the presence of leukocytes with myocyte damage and to follow the response to immunosuppressive therapy. Myocarditis was noted to be present in 8 of 11 patients with active disease and in none with inactive disease. After immunosuppressive therapy, clinical and hemodynamic improvement in each patient was observed.

Other etiologies of LVSD in TA/GCA include coronary arteritis, which has an estimated incidence of approximately 10% (18, 19). However, myocardial infarction associated with TA/GCA was not observed in our study group. Additionally, evaluations to exclude coronary atherosclerosis as a contributing mechanism in the LVSD group were performed in 13 of the 14 patients – 11 patients had negative coronary angiograms and 2 patients had negative stress echocardiograms. The one patient without a cardiac evaluation was a 38 year-old female with aortic, carotid and subclavian involvement of Takaysu arteritis who otherwise displayed no known cardiac risk factors.

Significant limitations of this study include the potential referral biases to a tertiary medical center, which could produce an overestimation of LVSD incidence compared to a community-based cohort. Most studies of patients with TA/GCA have involved patients of Asian decent, whereas ours consisted mostly of Caucasian subjects. Whether or not genetic variations influence responses to disease processes differently is beyond the scope of this paper, but could potentially explain the differences in findings compared to Asian population studies. Few patients in this study underwent pulmonary angiography, which limited our ability to observe the potential associations of pulmonary artery disease with LVSD.

The larger average aortic root diameter and greater degree of pulmonary valve regurgitation in the LVSD group did not likely contribute to the development of LVSD. The resistance vessels, not the proximal aorta, determine afterload on the left ventricle in systole. In diastole, left ventricular wall stress would not be affected by a larger aortic root, providing the aortic valve was competent. In our series the rate of aortic regurgitation was similar in the LVSD and control groups. Pulmonic regurgitation is not a cause of left ventricular failure, and likely reflects higher pulmonary artery pressures transmitted from the left atrium.

Endomyocardial biopsies (EMB) were not performed in our study, largely because of the perception that EMB is a relatively low yield and high-risk procedure. The yield of clinically useful information with EMB among patients with dilated cardiomyopathy is low, around 10%, and the risks of cardiac perforation are approximately 1: 250. Alternative future modalities such as gadolinium-enhanced MRI and PET scanning may provide adequate non-invasive data to recognize or follow LVSD and cardiac inflammation in large vessel arteritis (21-23).

In summary, this study represents the largest cohort of patients with TA/GCA aortitis to estimate an incidence of LVSD. Even if one assumes that all TA/GCApatients without echocardiograms had normal cardiac function, the incidence of LVSD would be 5.5%, which is over 5 times the expected rate in a healthy female cohort of similar age (24).

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