Aortic stiffness evaluated by echocardiography in female patients with Takayasu's arteritis

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Key words: echocardiography, aortic stiffness, pulse wave velocity, Takayasu's arteritis, cardiovascular risk

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ABSTRACT

Objective. *The aim of this study was to evaluate the aortic stiffness (AS) in young female patients with Takayasu's arteritis (TAK) and comparable controls by measuring carotid-femoral PWV (PWV_{cf}) using echocardiography with pulse wave Doppler. The clinical feasibility and reproducibility of this echocardiographic method were also investigated.*

Methods. *Twenty-five TAK female patients (mean age 28.3±6.2 years) and 25 strictly matched healthy controls were included according to rigorous inclusion and exclusion criteria. The PWV_{cf} of all subjects were measured by echocardiography based on the principle that PWV_{cf} could be calculated by pulse wave spreading distance divided by the transmit time. Reproducibility of the echocardiographic measured PWV_{cf} were performed randomly in 15 TAK patients and 15 healthy controls.*

Results. *The patients with TAK had a higher PWV_{cf} value measured by echocardiography, compared with healthy controls (8.37±2.23 vs. 6.46±1.15 m/s; $p<0.001$). The echocardiographic measured PWV_{cf} was significantly dependent on the TAK ($p=0.003$), age ($p=0.032$) and pulse pressure ($p=0.025$). PWV_{cf} did not correlate with the echocardiographic measured cardiac systolic and diastolic parameters and the laboratory variables in TAK patients ($p>0.05$ for all). The intra- and inter-observer coefficients of variation were low and the Bland-Altman plots indicated a satisfactory reproducibility.*

Conclusion. *Our results indicated that AS in female patients with TAK is increased, which may predict a higher cardiovascular risk. This manifestation is prior to the impairment of cardiac diastolic function. This elevated AS can be detected by echocardiographic measured PWV_{cf} with a good reproducibility.*

Introduction

Takayasu's arteritis (TAK) is a rare, idiopathic autoimmune rheumatic disease (ARD), characterised by chronic inflammatory granulomatous arteriopathy within the aorta and its major branches (1). This inflammatory disorder primarily in arterial intima can result in the pathogenesis of atherosclerosis, which can stiffen and damage the arterial wall, then leading to an extensive clinical cardiovascular manifestations such as cardio-cerebrovascular events, systemic and pulmonary hypertension, arterial stenosis or occlusions, aneurysms, heart failure, etc. (2-6). These cardiovascular complications are the major cause of death in TA (7). In addition, growing evidences have shown that ARDs patients often develop atherosclerosis, contributing to a considerable higher cardiovascular morbidity and mortality than in the general population (8-10). Therefore, early diagnosis and treatment for cardiovascular complications in TAK or other ARDs warrant early detection of subclinical atherosclerosis.

The accelerated atherosclerosis has become increasingly recognised not only in TAK but also in other ARDs including rheumatoid arthritis, systemic lupus erythematosus, spondyloarthropathies and vasculitides (8, 9, 11). The persistent autoimmune condition and chronic inflammation are the major contributory factors for the accelerated atherosclerosis, together resulting in structural damage as well as biomechanical property (*e.g.* elasticity) change in the arterial wall, even though the pathophysiological mechanism remains incompletely understood (8). Aortic stiffness (AS) is one of the earliest detectable manifestations of adverse structural and functional changes within the arterial wall (12). AS is increasingly recognised as a surrogate end point for cardiovascular disease

and now considered as a strong independent predictor of cardiovascular adverse events and all-cause mortality in different patients as well as the general population (13, 14). Aortic pulse wave velocity (PWV) has been confirmed to be the most validated and "gold standard" index of AS. Echocardiography is a useful tool for non-invasively determining aortic PWV through pulse wave Doppler, with a considerable high correlation (r=0.83) with the applanation tonometry (15). The wide availability and practicability make echocardiography as an advantageous tool for future routine AS evaluation in ARDs. However, so far, information is extremely limited regarding AS evaluation in TAK patients and there is still no study reporting the validation of echocardiographic measuring aortic PWV in TAK patients.

The objective of this study was to evaluate the AS in young TAK female patients by measuring carotid-femoral PWV (PWV_{cf}) using echocardiography with pulse wave Doppler. The clinical validation and reproducibility of this echocardiographic method were also investigated in the present study.

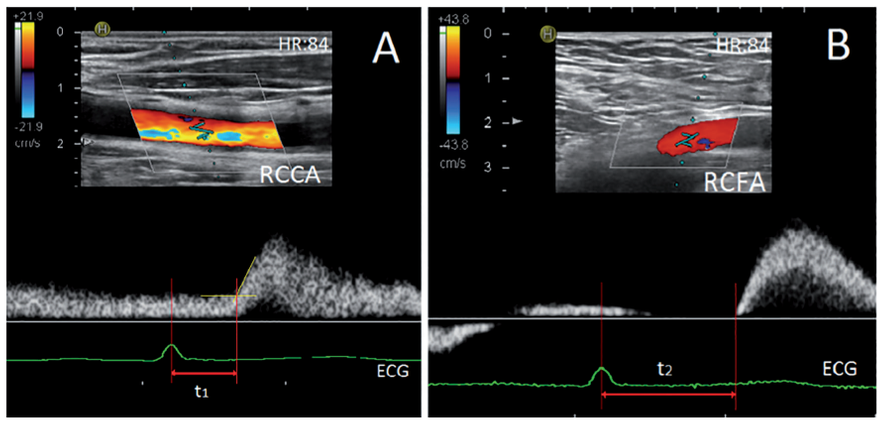

Fig. 1. The methodology for measuring pulse wave transit time in the PWV_{cf} determination by echocardiography.
The flow velocity spectra at RCCA (A) and RCFA (B) were recorded by pulse wave Doppler in each participant at a stable heart rate (HR variation ≤3 bpm). The simultaneous ECG were shown at the bottom. The time intervals of peak R wave of ECG to pulse wave foot at RCCA and RCFA (t_1 and t_2, respectively) were carefully measured. The pulse wave transit time between this two sites (Δt) was calculated as $\Delta t = t_2 - t_1$. PWV_{cf}: carotid-femoral pulse wave velocity; RCCA: right common carotid artery; RCFA: right common femoral artery; HR: heart rate.

Methods

Subjects

All patients of this study (n=25) were recruited from the hospitalised patients in the Rheumatology Department of Tangdu Hospital, from February 2015 to December 2016, according to the American College of Rheumatology criteria for TA (16). The carefully matched healthy controls (n=25) were enrolled from participants in the Health Checking Centre in the hospital during the same time period. This study was approved by the Ethics Committee of Tangdu Hospital, Fourth Military Medical University and was conform to the principles of the Declaration of Helsinki. Written informed consent was obtained from each participant after study explanation.

Rigorous inclusion and exclusion criteria were performed for the subject selection. Inclusion criteria for TAK patients were: female patients with the age between 18 and 40 years, newly diagnosed TAK and without previously using any corticosteroids and/or immunosuppressive medication, non-smokers. Exclusion criteria were: severe stenosis or occlusion in the right common carotid artery (RCCA), hypertension, hyperlipidaemia, diabetes mellitus, arrhythmia, renal insufficiency or any other known established cardiovascular disease. The healthy controls with comparable sex, age, height and weight were selected based on a careful medical assessment. All their examination results suggested no evidence of cardiovascular disease or medication use.

PWV_{cf} measurements

The echocardiographic measurement of PWV_{cf} in each subject was performed by a trained sonographer (Y.Y) unaware of the participants' status, using a Hi Vision Preirus ultrasonography system (Hitachi, Japan) with a 5–13 MHz linear array transducer (EUP-L74M). All the participants were asked to refrain from tea, alcohol and coffee for at least 24 h before the study. All participants adopted a supine position and had at least 10 min rest before any testing in a quiet, temperature-controlled (22±1°C) room in order to have a steady blood flow state and heart rate, according to the recommendations (6, 17). Blood pressure was measured 3 times in 5-minute intervals from the right arm by an automated digital sphygmomanometer (Omron HEM-7052), and if there was a known stenosis at the right subclavian or brachial artery, the measurements of blood pressure from left brachial artery were taken into account.

The method for PWV_{cf} measurement by echocardiography is illustrated in Figure 1. The pulse wave Doppler velocity spectra with simultaneous ECG were recorded at two sites, the RCCA and right common femoral artery (RCFA), respectively. The time interval (t_1 and t_2 in Fig. 1) between peak R wave of ECG and initial point of pulse wave (*i.e.* wave foot) at each site was carefully measured. Intersecting tangent method (18) was used for wave foot detection on the spectra with a high sweep speed aiming to improve measurement accuracy (19). Ten heart beat measurements were taken and then averaged as the result. The transit time (Δt) of the pulse wave between RCCA and RCFA was calculated as $\Delta t = t_2 - t_1$. In this study, we used 80% of the tape measured direct straight carotid-femoral distance as the pulse wave traveled distance (ΔD), according to the new recommendation (17). Three distance measurements were averaged for each participant. Thus, the PWV_{cf} can be calculated as $PWV_{cf} = \Delta D/\Delta t$.

Reproducibility of echocardiographic measured PWV_{cf}

Intra- and inter-observer variability of

the echocardiographic measured PWV_{cf} were performed randomly in 15 TAK patients and 15 healthy controls by two blinded observers (Y.Y and Z.W). The measurements were performed in the same condition with an interval of 1 day.

Statistical analysis

Data are expressed as the mean±SD for normally distributed continuous variables. Measurements and group profiles were compared with unpaired Student's *t*-test. Spearman correlation was used to investigate the correlations between PWV_{cf} and cardiac systolic and diastolic parameters by echocardiography, as well as the laboratory variables in TAK patients. Bland-Altman analysis was performed to determine precision and bias between the echocardiographic PWV_{cf} measurements. The coefficient of variation (CV) of the measurements were calculated as the SD of the differences between paired measurements divided by the mean of all measurements. The results were analysed using the statistical software SPSS 15.0 (SPSS, Chicago, IL, USA). A *p*-value <0.05 was regarded as statistically significant.

Results

The demographic and clinical data of TAK patients and controls are shown in Table I. For TAK patients, the mean disease duration was 14.6±8.2 months (ranged from 3 to 36 months). According to the clinical angiographic features, 10 patients (40%) were classified as Type II; 8 (32%) Type I and 7 (28%). All of the patients had relating clinical symptoms (malaise, pain, absent or diminished pulses and loss of blood pressure, etc.) and were then newly diagnosed as TAK. Before the study, six of them (24%) had some Chinese traditional medicine (ingredient unknown) for a short time (≤2 months). The demographic and clinical characteristics were largely comparable between the two groups, except systolic blood pressure (SBP, 123±11.3 *vs*. 116±10.3 mmHg; *p*=0.03) and pulse pressure (PP, 57±8.2 *vs*. 48±7.5 mmHg; *p*=0.02), as shown in Table I.

Compared with the healthy controls, the TAK patients had a higher PWV_{cf} value measured by echocardiography (8.37±2.23 *vs*. 6.46±1.15 m/s; *p*<0.001). In this study, a multiple linear regression analysis showed that PWV_{cf} was significantly dependent on the presence or absence of TAK (*p*=0.003), age (*p*=0.032) and PP (*p*=0.025), but independent of body mass index (BMI), SBP, mean blood pressure (MBP) and diastolic blood pressure (DBP).

As shown in Table II, Spearman correlation analyses showed that PWV_{cf} were not correlated with the cardiac systolic and diastolic parameters by echocardiography, as well as the laboratory variables in TAK patients (*p*>0.05 for all).

The results of the variability of PWV_{cf} measurements by echocardiography in 15 TAK patients and 15 healthy controls were demonstrated in Table III and Figure 2. The intra- and inter-observer coefficients of variation were relatively low and the Bland-Altman plots indicated a satisfactory reproducibility.

Table I. Demographic and clinical data of the TAK patients and healthy controls.

	TA (n=25)	Controls (n=25)	*p* value
Age (year)	28.3 ± 6.2	27.1 ± 4.2	0.45
Height (cm)	159.9 ± 10.7	161.3 ± 10.8	0.43
Weight (kg)	53.1 ± 7.2	54.8 ± 8.2	0.30
BMI (kg/m^2)	20.7 ± 2.9	20.9 ± 3.0	0.38
SBP (mmHg)	123 ± 11.3	116 ± 10.3	0.03
MBP (mmHg)	85 ± 8.1	84 ± 8.0	0.13
DBP (mmHg)	66 ± 7.2	68 ± 7.3	0.11
PP (mmHg)	57 ± 8.2	48 ± 7.5	0.02
HR (bpm)	76.3 ± 9.9	72.1 ± 9.2	0.09
BG (mmol/L)	4.66 ± 0.52	4.53 ± 0.51	0.42
TC (mmol/L)	4.06 ± 0.12	4.01 ± 0.11	0.37
E/A	1.51 ± 0.31	1.42 ± 0.29	0.11
e/a	1.32 ± 0.27	1.28 ± 0.25	0.08
LVEF (%)	66 ± 3.1	67 ± 4.2	0.22
PWV_{cf} (m/s)	8.37 ± 2.23	6.46 ± 1.15	<0.001

Values are mean±SD. TAK: Takayasu's arteritis; BMI: body mass index; SBP: systolic blood pressure; MBP: mean blood pressure; DBP: diastolic blood pressure; PP: pulse pressure; HR: heart rate; BG: blood glucose; TC: total cholesterol; LVEF: left ventricular ejection fraction; E/A: mitral early diastolic flow/late diastolic flow by pulse wave Doppler; e/a: mitral annulus early wave/late wave by tissue Doppler; PWV_{cf},: carotid-femoral pulse wave velocity.

Table II. Correlation between PWV_{cf} and the laboratory/echocardiographic findings in TAK patients.

Variables	r	*p*-value
BG (mmol/L)	0.15	0.45
TC (mmol/L)	0.24	0.43
CRP (mg/L)	0.29	0.11
ESR (mm/h)	-0.34	0.13
E/A	-0.32	0.38
e/a	-0.39	0.09
LVEF (%)	0.22	0.30

CRP: C-reactive protein; ESR: erythrocyte sedimentation rate.

Table III. The reproducibility of the PWV_{cf} measurements in healthy controls and TAK patients.

Measurements	Mean ± SD (m/s)	Mean Difference ± SD (m/s)	CV (%)
Controls (intra-observer)	6.22 ± 1.13	-0.047 ± 0.26	4.2
Controls (inter-observer)	6.27 ± 1.15	-0.048 ± 0.48	7.7
TAK patients (intra-observer)	8.22 ± 2.45	-0.047 ± 0.25	3.1
TAK patients (inter-observer)	8.29 ± 2.44	-0.187 ± 0.48	5.8

CV: coefficient of variation; SD: standard deviation.

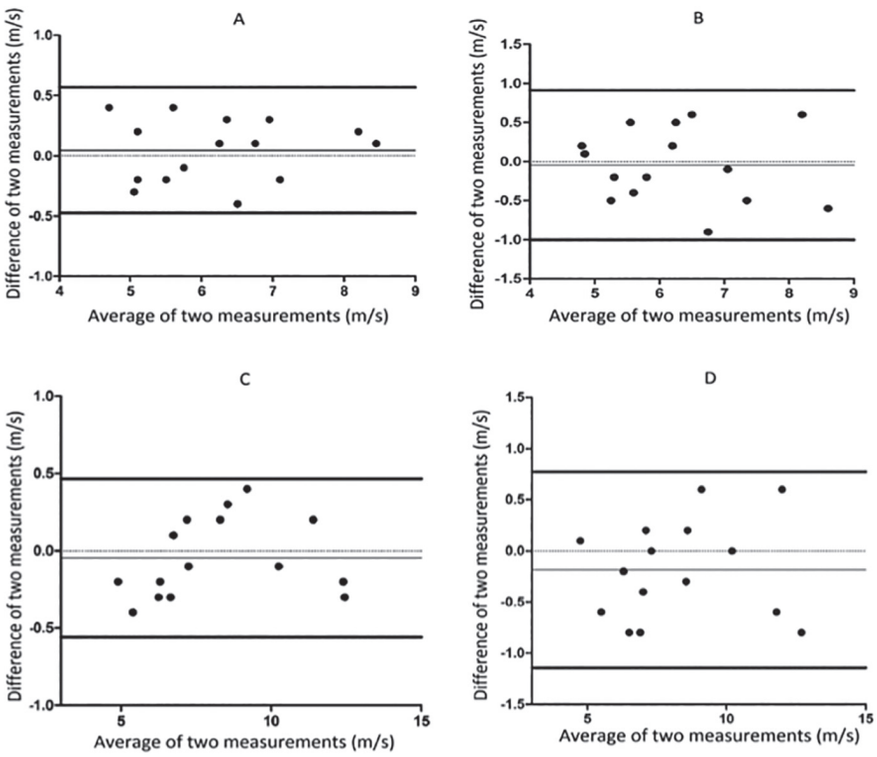

Fig. 2. Intra- and inter-observer variability of the echocardiographic measured PWV_{cf}. Intra- (**A**) and inter- (**B**) observer variability of PWV_{cf} measurements in healthy subjects (n=15), intra- (**C**) and inter- (**D**) observer variability in Takayasu's arteritis patients (n=15) were demonstrated by Bland-Altman plots, respectively.

Discussion

In this study, the AS in young TAK female patients was evaluated by measuring PWV_{cf} using an echocardiographic method. Our findings suggest that AS in female patients with TAK is increased, which may predict a higher cardiovascular risk. This manifestation is prior to the impairment of cardiac diastolic function in these patients. This elevated AS can be detected by echocardiographic measured PWV_{cf} with a good reproducibility.

TA is a chronic inflammatory disease characterised by granulomatous inflammation of the large-vessel wall with an unknown aetiopathogenesis. TAK predominantly affects young females before the age of 40 years and mainly involves the large elastic arteries (20-22). As we know, at the beginning a disease is easy to cure but difficult to diagnose, when it comes to a late phase, it becomes easy to diagnose but difficult to cure. Therefore, early diagnosis and detection of subclinical cardiovascular risk are of extreme importance for the managing of TAK because the cardiovascular complication is a major cause of mortality and morbidity in these patients. Now measuring PWV_{cf} is considered as the "gold standard" method to non-invasively assess AS and its predictor value for cardiovascular adverse events and all-cause mortality has been validated in most studies (5, 23-25). Applanation tonometry and some other methods have been developed for non-invasively measuring AS (12, 13). However, these methods usually require specific devices and software, and sometimes high technical expertise, which may hinder their clinical utility for routine evaluation.

Echocardiography is now a widely used tool for non-invasively diagnose cardiovascular diseases. Combined with ECG, it could be used to determine aortic PWV through pulse wave Doppler with the advantages of simplicity, time saved and acceptable accuracy. A strength of our study is the reporting of the echocardiographic methodology for measuring PWV_{cf} and its reproducibility. Our results showed that this method had low intra- and inter-observer variations for PWV_{cf} measurements. We propose that echocardiography, due to its remarkable wide availability, may be used as a routine tool for clinical AS evaluation in TAK as well as other potential patients. The measurement of AS in these patients may predict the risk of late cardiovascular complications and allow timely intervention and non-invasive monitoring of treatment efficacy.

The stiffness of large elastic arteries, usually measured by PWV_{cf} or carotid augmentation index, was found to be increased in TAK patients even though some of the results still remained discrepant (20, 26). Our conclusion was in accordance with these findings. The increased AS measured by PWV_{cf} seems lower than that in previous studies because we used 80% of the tape measured direct straight carotid-femoral distance as the pulse wave traveled distance, not the direct straight distance, which those two studies used.

Regarding the methodology of echocardiographic measured PWV_{cf}, two issues we think are of importance to ensure the precise measurements. The first is the heart rate control during the flow velocity spectra recording, because the peak R wave of ECG is used as a time maker when measuring the transit time (Δt) of the pulse wave, therefore the stable heart rate is necessary for accurate measurements. Based on our preliminary experiments, the heart rate variation ≤3 bpm is acceptable, of course the same heart rate during two recordings would be perfect. In the current study, we used this standard and heart rate variation was carefully controlled during recordings. Another issue is the sweep speed of the flow spectrum. In the time interval determination, the sweep speed of the flow spectrum should be adjusted as high as possible, with the aim to improve the temporal resolution for measuring. Small errors in transit time measurement may cause a significant PWV_{cf} deviation. So, we averaged 10 consecutive time measurements in this study.

The results of this study (Table II) demonstrated that PWV_{cf} measured by echocardiography had no correla-

tion with echocardiographic cardiac diastolic parameters, such as E/A, e/a. This interesting finding may suggest that the structural damage and biomechanical property change in the large arterial wall are prior to the impairment of cardiac diastolic function in in these patients. This vascular abnormality can be detected so early that clinical appropriate intervention on arterial inflammatory disorder could be taken so as to reduce future cardiovascular morbidity and mortality in TAK. Our data also showed that, for untreated patients with TAK, the echocardiographic measured PWV_{cf} did not correlate with laboratory variables such as blood glucose or total cholesterol, as well as disease activity. These results suggest that AS may be an independent factor for the cardiovascular risk in female TAK patients.

However, some limitations are present in this study. The first one is the relative small sample size. A larger sample size is usually needed in order to precisely quantify the PWV, especially for a diagnostic cut-off value, because heterogeneous individual variations are difficult to eliminate in most clinical studies. However, the sample size in this study was comparable or larger than in previous studies, was sufficient to describe the methodology and evaluate its clinical applicability and reproducibility, and it would not change the conclusion. The second limitation was that systolic blood pressure and pulse pressure were higher in the TAK patients, and this may influence our results. However, our and previous studies (20, 26) also showed that the presence of TAK was the major influence in increased PWV_{cf}. Therefore, we proposed that these two uncomparable factors may not change our final conclusion. The third is that this was a cross-sectional study, the later use of immunosuppressive drugs should be followed for long time and their influences on the PWV_{cf} analysis should be further investigated.

In conclusion, our results indicate that AS in female patients with TAK is increased, which may predict a higher cardiovascular risk. This manifestation is prior to the impairment of cardiac diastolic function. This elevated AS can be detected by echocardiographic measured PWV_{cf} with a good reproducibility.

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