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Concise Report

Takayasu's arteritis: a cause of prolonged arterial stiffness

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Objectives. **Cardiovascular disease is a major cause of mortality and morbidity in patients with Takayasu's arteritis (TA). Increased arterial stiffness is an independent risk factor and predictor of cardiovascular mortality in a variety of diseases. Pulse wave velocity (PWV) and the augmentation index (AI) are used as clinical measurements of arterial stiffness.**
Methods. **Data are presented from 10 patients with TA and 11 normal controls obtained between 2000 and 2004. Arterial compliance was assessed non-invasively by measurement of PWV, using the Complior® system, and calculation of the aortic AI.**
Results. **TA patients (mean age 40.8 ± 13.2 yr) were compared with a control group of healthy women from a parallel study (mean age 32.3 ± 5.5 yr). The mean carotid–femoral PWV (PWV-CF) was higher in TA patients ($P = 0.03$). In addition, both aortic AI derived from the radial artery ($P = 0.002$) and carotid AI ($P = 0.03$) were higher in TA patients compared with controls. PWV-CF did not correlate with CRP ($r = -0.23$, $P = 0.23$) or ESR ($r = -0.19$, $P = 0.27$). Similar results were obtained for the correlation of carotid–radial PWV with CRP ($r = 0.15$, $P = 0.32$) and ESR ($r = 0.33$, $P = 0.14$).**
Conclusions. **Our data show that TA is associated with elevated arterial stiffness in the central aorta, which may persist when the disease is quiescent. These data suggest that PWV represents a means by which cardiovascular risk can be detected and monitored in TA, and highlights the importance of effective management of cardiovascular risk factors in these patients.**

KEY WORDS: Takayasu's arteritis, Arterial stiffness, Vasculitis, Pulse wave velocity, Vascular dysfunction, Augmentation index.

Takayasu's arteritis (TA), a chronic inflammatory granulomatous arteriopathy, affects predominately large elastic arteries. It is associated with significantly increased risk of cardiovascular complications, including cerebrovascular accident, systemic and pulmonary hypertension, ruptured aortic aneurysm, and renal and congestive heart failure. These complications are the major cause of death in TA [1].

The pathophysiology that links TA to late cardiovascular complications remains to be fully elucidated. Endothelial dysfunction and chronic vascular injury progressing to irreversible structural damage to the vessel wall, due to increased intima–media thickness and progressive intimal and adventitial fibrosis, are the major contributory factors. Aortic stiffness is a likely consequence of these vascular abnormalities, as evidenced by reduced carotid artery compliance in TA [2]. Moreover, emerging data suggest that increased arterial stiffness is an independent risk factor for cardiovascular morbidity and mortality in hypertension [3] and renal failure [4], and predicts the risk of coronary artery disease in patients under 60 yr [5].

Direct measurement of arterial stiffness requires invasive techniques unsuitable for routine clinical use. However, indirect assessment of arterial stiffness, through measurement of pulse wave velocity (PWV) and the augmentation index (AI), is achieved using simple, non-invasive techniques [4–8]. PWV and AI are strongly correlated to direct measurements of arterial distensibility and can be considered a good surrogate for the evaluation of arterial stiffness, both PWV and AI having been shown to positively correlate with arterial stiffness [8].

In this paper we present our clinical data on patients with TA who underwent PWV and AI measurements between January 2000 and June 2004. Our aim was to determine whether patients with TA have increased arterial stiffness and, if so, whether this is related to disease activity.

Materials and methods

Patients

All patients ($n = 10$) attended the rheumatology department at Hammersmith Hospital, London and fulfilled the American College of Rheumatology (ACR) TA classification criteria (1990) [9]. Disease duration was between 2 and over 20 yr. Eight patients were treated with immunosuppressive therapy, three with statins and eight with antihypertensive medication at baseline (Table 1). The cardiovascular analysis of the patients included in the study was performed as part of their routine clinical management and verbal consent was obtained for each investigation.

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Table 1. Clinical characteristics of patients with Takayasu's arteritis

Patients	Age (yr)	Disease duration (yr)	Arteries involved	Drug treatment at time of study		
				Immunosuppression	No. of antihypertensives	Statin
1	24	2	Aorta, L-SCA	P, A	–	–
2	30	5	R-SCA, IMA, L-RenA	P	2	–
3	61	>20	Aorta, R-RenA	P, A	1	–
4	61	>20	R-VA, R-SCA, L-SCA, R-BrA	P, A	1	–
5	34	4	Aorta, L-CCA, L-SCA	P, MTX	2	–
6	30	2	Aorta, R-CCA, L-CCA, L-SCA	P, MTX	–	Yes
7	43	3	Aorta, SMA, L-RenA	–	3	–
8	44	5	R-SCA, L-SCA, L-RenA	P, MTX	3	–
9	40	3	L-SCA, SMA, L-RenA	–	1	Yes
10	43	8	Aorta, L-CCA, R-SCA, L-SCA	P, A	2	Yes

Arterial involvement was determined by magnetic resonance imaging. L, left; R, right; SCA, subclavian artery; RenA, renal artery; IMA, inferior mesenteric artery; VA, vertebral artery; BrA, brachial artery; CCA, common carotid artery; SMA, superior mesenteric artery; P, prednisolone; A, azathioprine; MTX, methotrexate.

Clinical details

The coexistence of any conventional cardiovascular risk factors and the history of drugs used were obtained from case notes. Measurements of fasting glucose, lipids, CRP and ESR are part of our standard care for patients with TA.

Arterial compliance measurement

Patients were rested before testing and remained supine throughout the measurement. Blood pressure and pulse rate were measured from the right arm using an automated digital sphygmomanometer (Omron-705 CP), except when there was a known unilateral stenosis of the right subclavian or brachial artery. PWV was measured using the Complior® system (Colson Medicals, Paris), which calculates the time interval between two pulse waves recorded simultaneously. Distances between the two applanation sites, over the carotid artery and femoral artery or over the carotid artery and radial artery, were measured as a straight line on the surface between the two arteries. The velocity was calculated as transit distance/transit time; the carotid–femoral PWV (PWV-CF) and carotid–radial PWV (PWV-CR) were recorded and the average of 10 recordings was calculated.

The carotid AI was calculated using SphygmoCor® (AtCor Medical, Australia) performed on the right carotid artery. A tonometer (Miller, USA) was applied to the carotid artery, compressing the vessel wall sufficiently to record the pulse trace. Arterial waveforms were processed using dedicated software. This gave a measure of carotid artery AI. There was no transfer function applied. The aortic AI (derived from the radial artery) was then recorded by placing the tonometer on the right radial artery. The transfer function, which is part of the SphygmoCor system software, was applied and this provided a derived aortic AI. This was recorded and referred to as the aortic AI derived from the radial artery. Although these measures of PWV and AI have been shown to be reproducible [10], there is some controversy regarding the central aortic pressures obtained using the SphygmoCor system [11]. However, in this study, only the aortic AI data were used and not the derived central aortic pressure measurements. Pressure waveforms not achieving the automatic quality controls specified by the SphygmoCor software were rejected. The derived aortic waveform was subject to further analysis by the SphygmoCor software to calculate the aortic AI. The AI was defined as the ratio of augmentation (dP) to pulse pressure (PP) and was expressed as a percentage [$AI = (dP/PP) \times 100\%$]. Two recordings were performed at each site and the mean of the two recordings was taken for each subject.

Control group

The control group of 11 healthy women (mean age 32.4 ± 5.5 yr), with no known cardiovascular disease and not taking any medication, was obtained from a parallel study performed in the same laboratory under similar conditions. In view of the younger mean age of this control group and the potential influence of this on arterial stiffness, further comparisons were made with two older control groups obtained from our other studies [7, 12]. The PWV was recorded using Complior (Artech, Pantin, France) and AI (SphygmoCor) was calculated using applanation tonometry. Written informed consent was obtained from the normal volunteers who were involved in this study, according to the guidelines set down by the Hammersmith Hospitals Trust Research Ethics Committee.

Statistical analysis

Means and standard deviations were calculated for continuous variables. To determine whether arterial stiffness correlated with systemic inflammatory markers, the Pearson correlation coefficient (r) and probability (P) were calculated using SPSS for Windows, Version 11.0; $P < 0.05$ was considered significant. An unpaired t-test was performed to compare the values of the study population with those of the control group and to examine differences in PWV when classified by the Kerr criteria for disease activity [13]. A model of multiple regression was performed to explain the variance of the PWV-CF.

Results

Between January 2000 and June 2004, 10 patients with TA underwent PWV and AI measurements. All were female; the mean age was 41.0 ± 12.5 yr (range 24–61 yr).

Arterial stiffness of central, large arteries is increased in TA

The baseline characteristics were largely comparable between patients and controls, although there were some differences (Table 2). As expected, systolic blood pressure (SBP) was higher in TA patients, as was the body mass index (BMI), the latter probably reflecting the effect of prednisolone therapy. Finally, there was a difference in age, with TA patients 41 ± 12.5 yr and controls 32.4 ± 5.5 ($P = 0.05$).

PWV-CF and PWV-CR were obtained in nine patients. The measurements of PWV-CF in one patient and PWV-CR in another

were abandoned due to technical difficulties. Comparing the two groups, we found that the mean PWV-CF was higher among TA patients (12.0 ± 4.3 *vs* 8.3 ± 1.1 m/s, $P = 0.03$) (Table 2). In contrast, there was no difference between the two groups in PWV-CR ($P = 0.65$). We also measured aortic AI in these patients (Table 2). Carotid AI and aortic AI, derived from the radial artery, were obtained in nine and eight patients, respectively. Consistent with the data on PWV, the mean estimated carotid AI (40.0 ± 13.8 *vs* $26.6 \pm 8.7\%$; $P = 0.03$) and aortic AI derived from the radial artery (33.1 ± 10.3 *vs* $14.9 \pm 9.9\%$; $P = 0.002$) was higher in TA patients compared with controls.

A multiple regression analysis with PWV-CF as dependent variable and SBP, diastolic blood pressure (DBP), BMI, the presence or absence of TA, and age as independent variables showed that PWV-CF was dependent upon DBP ($P = 0.007$), the presence or absence of TA ($P = 0.011$) and BMI ($P = 0.035$), but independent of SBP and age. Inclusion of the mean blood pressure (MBP) in the multiple regression showed that PWV-CF was dependent upon the presence or absence of TA ($P = 0.011$) and BMI ($P = 0.035$), but independent of age, DBP, MBP and SBP.

TABLE 2. Laboratory data obtained from TA patients and controls

	Takayasu's arteritis	Control group	*P*
Number of subjects	10	11	
Age (yr)	41.0 ± 12.5	32.4 ± 5.5	0.05
Sex	All female	All female	
SBP (mmHg)	141.4 ± 32.3	115.2 ± 3.4	0.03
DBP (mmHg)	74.2 ± 12.2	70.5 ± 6.2	0.41
MBP (mmHg)	96.6 ± 14.4	85.4 ± 7.2	0.05
BMI (kg/m^2)	26.3 ± 3.1	22.2 ± 1.9	0.003
Cholesterol (mmol/l)	5.6 ± 2.2	5.0 ± 1.1	0.44
PWV-CF (m/s)	12.0 ± 4.3	8.3 ± 1.1	0.03
PWV-CR (m/s)	10.4 ± 2.8	10.9 ± 1.4	0.62
AI carotid (%)	40.0 ± 13.8	26.6 ± 8.7	0.02
AI radial (%)	33.1 ± 10.3	14.9 ± 9.9	0.001

Values are mean ± S.D.

Arterial stiffness in TA correlates poorly with disease activity

All PWV-CF measurements were analysed in relation to disease activity. In total, up to 15 measurements were made, with three patients undergoing serial measurements. Disease activity was assessed by measurement of CRP and ESR. In addition, patients were classified as having active or inactive disease according to Kerr's criteria [13], in which TA is considered active when there is new onset or worsening of two or more of the following: (i) fever or arthralgia; (ii) raised ESR; (iii) new claudication, bruits or vascular pain; and (iv) new typical angiographic features.

As shown in Fig. 1, PWV-CF did not correlate with CRP ($r = -0.23$, $P = 0.23$) or ESR ($r = -0.19$, $P = 0.27$). Similar results were obtained with PWV-CR (CRP, $r = 0.15$, $P = 0.32$; ESR, $r = 0.33$, $P = 0.14$). Using the Kerr criteria, the mean PWV-CF during active disease ($n = 6$ readings) was 11.25 ± 1.55 m/s compared with 13.86 ± 7.20 m/s during clinical remission ($P = 0.19$) ($n = 7$ readings), indicating that PWV-CF did not correlate with clinical disease activity. Similar results were obtained with PWV-CR (10.80 ± 2.53 and 9.67 ± 2.50 m/s in active and inactive patient groups, respectively; $P = 0.21$).

Discussion

Our data suggest that TA is associated with increased arterial stiffness in central elastic arteries (aorta, common iliac and

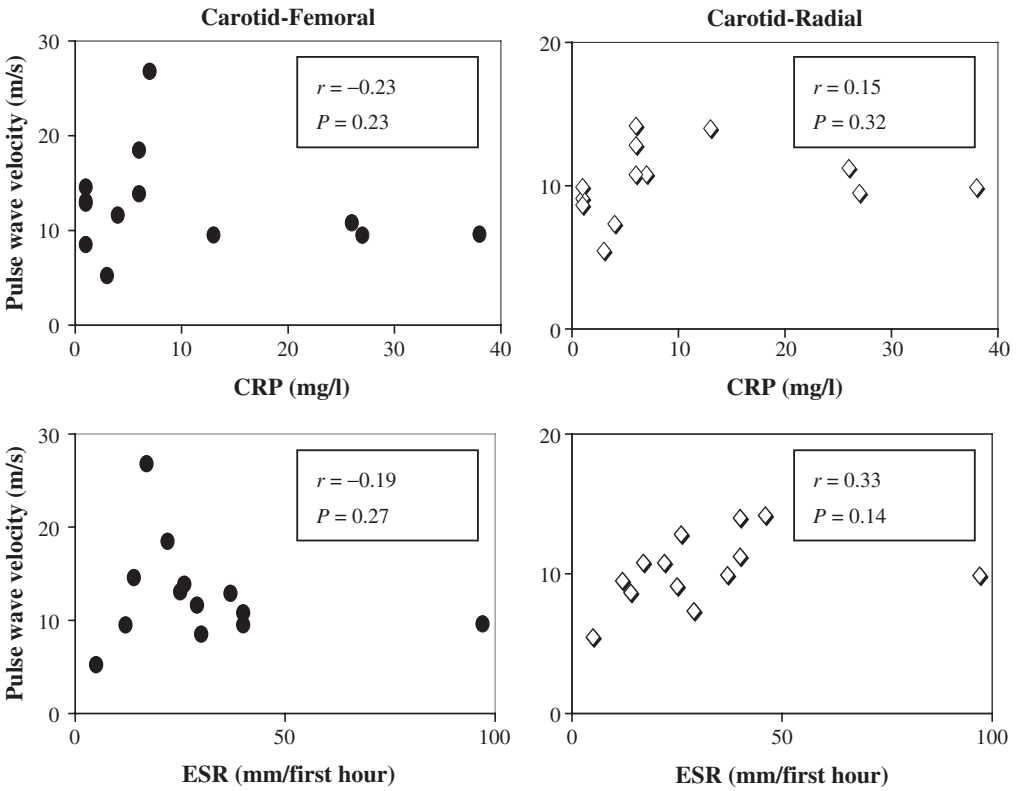

FIG. 1. Carotid–femoral (closed circles) and carotid radial (open diamonds) PWV in relation to CRP and ESR at the time of PWV measurements. Correlation coefficient (r) and probability of any significant correlation using 95% confidence (P) are indicated in each diagram.

femoral), which persists when disease is clinically quiescent. To our knowledge, this is the first report demonstrating increased arterial stiffness in patients with TA, as assessed by PWV-CF and aortic AI. However, in the peripheral muscular arteries (brachial and radial) the values obtained were similar to those in the control group (Table 2). The results support those of a previous study, in which non-invasive ultrasonography was used to estimate the elastic modulus and stiffness constant [2]. The authors concluded that the carotid arterial compliance in TA was reduced [2]. However, the arterial stiffness of peripheral arteries was not measured, and the relationship between disease activity and arterial stiffness was not investigated.

The arterial tree is composed of central elastic and peripheral muscular arteries, TA affecting mainly the former. Accordingly, we found that PWV-CF, a reflection of arterial stiffness of the large elastic arteries, was higher in patients with TA than in controls despite treatment with antihypertensives and statins. There was no significant difference in PWV-CR between the two groups, possibly reflecting the fact that TA is less likely to affect peripheral muscular arteries. The aortic AI, derived from radial artery applanation tonometry (using the transfer function, SphygmoCor), shows that the central aorta has poor compliance. The carotid AI, measured by direct applanation of the right carotid artery, showed increased arterial stiffness, consistent with the fact that TA frequently affects carotid arteries.

The main limitations of this study are the small size of the patient group, reflecting the rarity of TA, and the discrepancy in the age of the controls. Although age and blood pressure may affect the measurement of PWV and AI, the fact that the mean age and blood pressure were lower in the controls is unlikely to account for all the observed differences in PWV-CF and AI between the two groups. Indeed, when the PWV and AI of TA patients were compared with those of older control populations obtained from our other studies [7], we found that, despite their younger age (41.0 ± 12.5 *vs* 54.0 ± 7.3 yr) and comparable blood pressure, the mean PWV-CF in TA was higher than in the reference group (12.0 ± 4.3 *vs* 10.7 ± 0.7 m/s). In contrast, the mean PWV-CR was lower among the patient group (10.4 ± 2.8 *vs* 13.0 ± 2.3 m/s), reflecting their younger age and in keeping with the fact that TA does not affect peripheral muscular arteries. Similarly, compared with an older reference group (mean age 57.5 ± 13.7 yr) [7], the estimated aortic AI derived from the radial artery AI and carotid AI was higher in TA (33.1 ± 10.3 *vs* 31.5 ± 12.8% and 40 ± 13.8 *vs* 36.2 ± 10.8%, respectively) [10]. Thus, the combined data, derived by comparison of arterial stiffness in patients with TA compared with that in three separate control groups (the index control group and controls from our other studies of the West London population [7, 12]) confirm that arterial stiffness is abnormally raised in TA.

Although SBP was higher in the TA patients, a multiple regression model with PWV-CF as a dependent variable and SBP, DBP, the presence or absence of TA and BMI as independent variables showed that SBP did not affect PWV-CF. The only significant contributors were DBP, BMI and the presence or absence of TA. This suggests that TA contributed significantly to the increase in PWV-CF. Moreover, adding MBP to the model did not affect the outcome, suggesting that the presence of TA was the major influence in increased arterial stiffness.

Endothelial cell dysfunction and vascular injury is associated with many rheumatic disorders and is related to premature atherosclerosis and increased cardiovascular and overall mortality. Endothelial dysfunction and elevated arterial stiffness have been reported in ANCA-associated vasculitis (AASV), systemic lupus erythematosus and rheumatoid arthritis [14–18]. In AASV, arterial stiffness is correlated with disease activity [15]. However, we found no correlation between arterial stiffness and disease activity in TA. One explanation for this is that diagnosis of TA is often delayed and irreversible structural damage to the vasculature is established [13]. An alternative and yet not mutually exclusive explanation is that CRP, ESR and available clinical criteria may not accurately reflect disease activity. Indeed, 40% of biopsies from 'inactive' patients revealed evidence of ongoing vasculitis, with new angiographic changes identified in 60% of patients [13]. We have recently shown that [^{18}F]-fluorodeoxyglucose positron emission tomography ([^{18}F]-FDG-PET) may be useful in monitoring vascular inflammation in TA [19]. It will be of interest to look prospectively for any correlation between vascular inflammation detected by [^{18}F]-FDG-PET and increased arterial stiffness.

The presence of narrowed, stenotic or dilated arteries will result in disturbed local blood flow and increased areas of the arterial wall exposed to oscillatory shear stress. It is such areas that are most prone to the development of atherosclerosis. In combination with endothelial dysfunction, these abnormalities are likely to be important in the accelerated atherosclerosis reported at autopsy in young female patients with TA [20]. The measurement of arterial stiffness in patients with TA may predict the risk of late cardiovascular complications and allow timely intervention and non-invasive monitoring of treatment efficacy. The statins represent an attractive strategy for reduction of cardiovascular risk in TA. In addition to their lipid-lowering properties and beneficial effects on vascular function, the statins are anti-inflammatory [21] and significantly reduce arterial stiffness in patients with rheumatoid arthritis [22]. Other potential interventions include the antiplatelet agents aspirin and clopidogrel, and close management of coexisting conventional cardiovascular risk factors, including hypertension.

In conclusion, PWV and AI measurements suggest that patients with TA have increased stiffness of their central arteries. We propose that the use of PWV for early detection of increased arterial stiffness may allow appropriate intervention to reduce future cardiovascular morbidity and mortality. Our data also highlight the importance of effective management of conventional cardiovascular risk factors in these patients.

Rheumatology	Key messages
	• Takayasu's arteritis is associated with increased central arterial stiffness. • Early detection of increased arterial stiffness may allow appropriate intervention to reduce future cardiovascular morbidity and mortality in Takayasu's arteritis.

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