Determinants of Arterial Stiffness in Female Patients with Takayasu Arteritis

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ABSTRACT. ***Objective.*** The assessment of pulse wave velocity (PWV) in Takayasu arteritis (TA) is complex because of many confounding factors. We evaluated PWV in female patients with TA and controls with comparable anthropometric and clinical variables and assessed a possible association of TA with disease variables.

Methods. We evaluated 27 patients with TA consecutively. Exclusion criteria were menopause, smoking, diabetes, renal insufficiency, poorly controlled hypertension, cardiac arrhythmias, obesity, inflammatory comorbidities, pregnancy, and surgical procedures involving the aorta. Disease activity was determined by clinical and laboratory variables. As healthy controls, 27 subjects with comparable age, blood pressure, height, and weight were selected. Carotid-femoral PWV measurements were obtained using the Complior system.

Results. The mean PWV in patients with TA was higher than in healthy controls (9.77 ± 3.49 vs 7.83 ± 1.06 m/s; p = 0.009). Despite our strict selection criteria, patients with TA had an average systolic blood pressure (SBP) 8 mmHg higher than controls (p = NS), and significantly higher pulse pressure values. The multivariate linear regression model shows that 93.8% of the PWV variability is explained by the variables age, mean BP, and the disease itself (adjusted R^2 = 0.938). Stepwise logistic analysis using the PWV cutoff value established by the receiver-operator characteristic curve (> 8.34 m/s) as dependent variable, and measures with significance in univariate analysis as independent variables revealed that TA (OR 4.69; 95% CI 1.31–16.72; p = 0.017) and mean BP (OR 1.06; 95% CI 1.00–1.12; p = 0.048) were independently associated with higher PWV. Further analysis of disease variables revealed that PWV values were not correlated with erythrocyte sedimentation rate, C-reactive protein, cumulative dose of glucocorticoid, or ejection fraction (p > 0.05).

Conclusion. In our cohort of female patients with TA, the disease itself and mean BP were the strongest determinants associated with arterial stiffness. (First Release June 1 2014; J Rheumatol 2014;41:1374–8; doi:10.3899/jrheum.131110)

Key Indexing Terms:
ARTERIAL STIFFNESS TAKAYASU ARTERITIS PULSE WAVE VELOCITY
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Takayasu arteritis (TA) predominantly affects arteries of large and middle size and is related to increased cardiovascular (CV) risk[1,2]. The increase in arterial stiffness is associated with atherosclerosis and is a known independent risk factor for CV events[3,4]. A recent review of techniques for early assessment of vascular function in rheumatic conditions determined that a standard indicator of arterial stiffness in this context is pulse wave velocity (PWV)[5].

The only study in TA that analyzed arterial stiffness described increased PWV and augmentation index in a limited number of patients. However, the nonadjustment of confounding variables age and blood pressure (BP) made it difficult to interpret their results[6]. In fact, these 2 conditions reduce arterial distensibility and therefore are major risk factors for PWV changes[7,8].

We examined arterial stiffness in female patients with TA and in comparable controls by analyzing carotid-femoral (CF) PWV, the possible contribution of the disease itself, and clinical and laboratory variables for study outcomes.

MATERIALS AND METHODS

Ethics. The study was approved by the local ethics committee (CAPPesq — Comissão de Ética para Análise de Projetos de Pesquisa do Hospital das

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Clinicas da Faculdade de Medicina da Universidade de São Paulo, # 0712/10), and all patients provided written informed consent.

Patient selection. Eligible patients met 1990 American College of Rheumatology (ACR) criteria for TA[9]. All patients attended the Vasculitis Outpatient Clinic of the Rheumatology Division, Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, Brazil. Inclusion criteria were female patients with a maximum age of 50 years and ability to remain in a supine position for 30 min. Exclusion criteria were menopause[10], diabetes[7,11], fasting glycemia > 100 mg/dl, renal insufficiency[7,11], or estimated creatinine clearance < 75 ml/min, current or past smoking[12], poorly controlled hypertension [HTN; SBP > 140 mmHg and diastolic (D) BP > 90 mmHg on an outpatient basis][3,13], cardiac arrhythmias[14], body mass index (BMI) > 30 kg/meter square[15], presence of other inflammatory comorbidities, pregnancy[16], aortic aneurysms, aortic endoprosthesis, aorta-related bypass surgeries, or refusal to participate. Male patients were excluded. BP was evaluated in 4 limbs, and the highest value was taken into account. Creatinine clearance was estimated by using the Cockroft-Gault formula[17], and a value of 75 ml/min was arbitrarily chosen as cutoff to exclude patients with kidney impairment.

Smoking status was defined according to the US Centers for Disease Control and Prevention[18].

One hundred nineteen patients fulfilled ACR criteria for TA. Nineteen patients were men; 73 patients were excluded: age above the established limit (22), loss to followup (15), death (2), aortic aneurysm correction (2), aortic endoprosthesis (8), aorta-related bypass surgeries [aorto-aortic (2), aorto-renal (1), and aorto-carotid (1)], pregnancy (1), diabetes (1), presence of inflammatory comorbidities (5), smoking (3), endstage renal disease (5), and refusal to participate (5).

To avoid the possible bias of CV risk factors, a rigorous selection of healthy subjects was performed. Controls with comparable sex, age, BP, height, and weight were consecutively selected from a preventive health examination cohort from the Heart Institute, which consisted of asymptomatic subjects with no evidence of CV disease or use of medications.

Study protocol. CF-PWV measurements were obtained by 2 observers (ECT, LAB) in the morning using the Complior system (Colson). The intraobserver and interobserver coefficients of this method were 0.935 and 0.890, respectively[19]. The right common carotid and right common femoral arteries were assessed, and we used the direct distance between points. Two measurements were made for each patient, and the average value was selected. Because it is not recommended to analyze arteries with high-grade stenosis and because patients with TA may present with severe stenosis or occlusion, we used echo tracking and pulse wave analysis in the right common carotid artery to evaluate high-grade stenosis that would require the contralateral measurement or exclusion of the patient.

Patients and controls were not allowed to drink beverages containing caffeine, alcohol, or any stimulant, or to perform any physical activity on the protocol day, to avoid short-term interference with testing, as is recommended. At the beginning of the protocol, height and weight were assessed, and subjects rested comfortably in a supine position for 15 min in an air-conditioned room (with a stable temperature of 22 ± 2ºC)[20,21,22].

Clinical data were obtained by chart review (to December 1999) and from an ongoing electronic database protocol established in January 2000. It consisted of extensive clinical and laboratory evaluation performed for all patients. Clinical disease activity was defined based on the presence of a new or worsening fever or musculoskeletal complaints, vascular ischemia or inflammation such as claudication, diminished or absent pulse, bruit, carotidynia or asymmetric blood pressure[23,24]. Laboratory findings of disease activity were defined as a high erythrocyte sedimentation rate (ESR ≥ 20 mm/h) and/or C-reactive protein (CRP; ≥ 5 mg/l) levels in the absence of infection[24].

Serum samples (after 12 h overnight fast) were obtained at the beginning of the protocol. Serum levels of total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and triglycerides (TG) were measured by spectrophotometry on a Modular Hitachi analyzer (Roche Diagnostics GmbH). Low-density lipoprotein cholesterol (LDL-C) levels were estimated using the equation: TC = HDL-C + TG/5 + LDL-C[25].

Statistical analysis. Results are presented as mean and SD for continuous variables and percentages for categorical variables. Data for continuous variables were compared by the Student's t test to assess differences between patients and controls. Pearson or Spearman correlation coefficients and probability were estimated, and the relationship between PWV and the variables was assessed by comparing the values by Student's t test, and multivariate linear and logistic regressions. Logistic regression analysis was performed using variables that showed statistical significance in the univariate analysis, and controlling age.

SPSS for Windows, version 15.0 was used for statistics. Values of $p < 0.05$ were considered significant.

RESULTS

Twenty-seven female patients and 27 female healthy controls were enrolled. The mean age, height, weight and BMI were similar in both groups ($p > 0.05$, Table 1).

Regarding the clinical characteristics of patients, according to Hata, *et al*[26], 23 (85.2%) were rated Class V; 2 (7.4%) Class IIb, and 2 (7.4%) Class I. The mean disease duration was 10 ± 7.29 years (range 1–26). Twelve patients (44.4%) were considered in remission, without the use of glucocorticoids or immunosuppressive drugs and without clinical symptoms. Among the remaining 15 patients, 9 (33.3%) were taking glucocorticoids and 11 (40.7%) were taking immunosuppressive drugs [methotrexate (6); azathioprine (2); methotrexate + azathioprine (1); mycophenolate mofetil (2)]. The mean dose of prednisone per day was 6.4 ± 11.9 mg, and mean cumulative dose of prednisone was 14,592 ± 17,141 mg. Eighteen patients (66.7%) had a previous diagnosis of HTN at baseline, but only 14 continued antihypertensive medication. They were considered under control on an outpatient basis (inclusion criteria). Six patients (22.2%) were taking statins, and 22 (81.5%) were using aspirin. Six patients (22.2%) had undergone at least 1 vascular procedure because of complications of the disease. The procedures included renal and mesenteric artery angioplasty (1), renal artery angioplasty (1), mesenteric artery angioplasty + hepatic artery ligation

Table 1. Demographic and clinical data of patients with Takayasu arteritis (TA) and controls.

	TA, n = 27	Controls, n = 27	p
Age, yrs	32.37 ± 8.26	33.89 ± 10.12	0.55
Height, m	1.60 ± 0.06	1.60 ± 0.08	0.86
Weight, kg	56.93 ± 7.42	60.70 ± 8.26	0.08
BMI, kg/m^2	22.3 ± 2.64	23.7 ± 2.99	0.07
SBP, mmHg	121 ± 20	113 ± 13	0.07
DBP, mmHg	68 ± 15	73 ± 10	0.13
MBP, mmHg	86 ± 13	86 ± 10	0.83
PP, mmHg	54 ± 22	40 ± 9	0.004
CF-PWV, m/s	9.77 ± 3.49	7.83 ± 1.06	0.009

Data are expressed in mean ± SD. SBP: systolic blood pressure; DBP: diastolic blood pressure; MBP: mean blood pressure; PP: pulse pressure; CF-PWV: carotid-femoral pulse wave velocity; BMI: body mass index.

(1), right renal artery angioplasty and left nephrectomy (1), left renal artery angioplasty and left renal autotransplantation (1), and aortic valve replacement (1).

Although SBP (121 ± 20 vs 113 ± 13 mmHg) and diastolic BP (DBP; 68 ± 15 vs 73 ± 10 mmHg) were comparable in patients with TA and controls ($p > 0.05$ for all), pulse pressure was statistically different (54 ± 22 vs 40 ± 9 mmHg; $p = 0.005$).

Distribution of PWV values was normal (Kolmogorov-Smirnov normality test: TA: $p = 0.98$; controls: $p = 0.67$). The mean PWV was higher in patients with TA than in healthy controls (9.77 ± 3.49 vs 7.83 ± 1.06 m/s; $p = 0.009$).

When comparing patients considered in remission with those with active disease, mean SBP, DBP, and mean BP, weight, height, BMI, and disease duration were not statistically different ($p > 0.05$). The mean age was significantly higher in patients considered in remission (36.75 ± 7.48 vs 28.87 ± 7.28; $p = 0.01$). There was no difference between the values of PWV in these groups (9.89 ± 2.86 vs 9.67 ± 4.01; $p = 0.88$). The multivariate linear regression model included 3 variables: age (coefficient 0.078; $p = 0.026$), mean BP (coefficient 0.060; $p < 0.001$), and TA (coefficient 2.097; $p = 0.002$). It concluded that 93.8% of the PWV variability is explained by those 3 variables (adjusted $R^2 = 0.938$). An increase in age of 1 year leads to an increase of 0.078 in PWV, and an increase in mean BP of 1 mmHg results in an increase of 0.06 in PWV values. Female patients with TA have mean PWV values 2.097 higher than controls. The fit of the model was verified with residual analysis and there is no deviation from the assumptions of the model.

The PWV cutoff value established by the receiver-operator characteristic curve was 8.34 m/s (sensitivity: 59.3%; specificity: 70.4%). The multivariate logistic analysis using PWV > 8.34 m/s as a dependent variable and TA, age, mean BP as independent variables showed that TA (OR 4.69; CI 95% 1.31–16.72; $p = 0.017$) and mean BP (OR 1.06; 95% CI 1.00–1.12; $p = 0.048$) were independent risk factors for higher PWV. Further analysis of disease variables (continuous variables) in TA patients showed that the PWV values were not correlated with ESR, CRP, cumulative dose of steroid, ejection fraction, or lipid levels ($p > 0.05$, Table 2). Moreover, evaluation of binary variables demonstrated that vascular procedure only was significantly associated with CF-PWV ($p = 0.03$), whereas no association was observed for disease activity, history of HTN, or disease duration (≤ 5 yrs and > 5 yrs; $p > 0.05$, Table 3).

Table 2. Correlation of CF-PWV and disease variables in 27 patients with Takayasu arteritis.

Variables	Correlation	p
SBP, mmHg	0.242	0.23
DBP, mmHg	0.296	0.13
ESR, mm/h	–0.274	0.17
CRP, mg/l	–0.075	0.71
Ejection fraction, %	–0.008	0.97
Cumulative steroid dose, mg	0.102	0.61*

* Spearman correlation. SBP: systolic blood pressure; DBP: diastolic blood pressure; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; CF-PWV: carotid-femoral pulse wave velocity.

Table 3. Comparison of CF-PWV in 27 patients with Takayasu arteritis.

Variables	CF-PWV, m/s	p	
Disease activity	Active, n = 15	9.89 ± 3.97	0.83
	Remitted, n = 12	9.59 ± 2.80	
History of HTN	Yes, n = 18	9.29 ± 3.87	0.32
	No, n = 9	10.72 ± 2.47	
Disease duration	≤ 5 yrs, n = 7	8.82 ± 1.49	0.23
	> 5 yrs, n = 20	10.03 ± 3.09	
Vascular surgery	Yes, n = 6	12.40 ± 4.42	0.03
	No, n = 21	9.01 ± 2.87	

Data are expressed as mean ± SD. HTN: hypertension; CF-PWV: carotid-femoral pulse wave velocity.

DISCUSSION

The results of our study suggest that the higher arterial stiffness assessed by carotid-femoral PWV in female patients with TA is determined by mean BP (MBP), age, and disease itself and that TA and MBP are independent risk factors for elevated arterial stiffness.

The stiffening of the central arteries, particularly the aorta, is recognized as an independent predictor of CV mortality in hypertensive patients and in the general population[3,4,27], and PWV is definitely associated with age and BP[8,28]. The evaluation of PWV is an easy indirect measure to assess arterial stiffness[5].

The finding of elevated PWV in our patients may represent a major issue in managing those affected by this vasculitis because TA is known to be associated with increased CV morbidity and mortality[1,29]. Arterial stiffness and carotid artery atherosclerosis have been evaluated in TA. Raninen, *et al*[30] evaluated arterial stiffness in 16 patients with TA using carotid and femoral ultrasound (US). They found diminished compliance in the carotid but not in the femoral artery. Seyahi, *et al*[31] evaluated 30 patients with TA and younger than 50 years. The study compared the formation of atherosclerotic plaques in patients with TA to patients with systemic lupus erythematosus, and findings were considered similar because both diseases are associated with systemic premature atherosclerosis. The authors stated that the utility of B-mode carotid US is not good enough to differentiate between an increased intima-media thickness owing to TA itself or the associated atherosclerosis.

The only study available on PWV in TA evaluated only 10 patients and 11 controls. Patients were older and had

significantly higher BMI and SBP compared to controls, hindering interpretation of their results because age and BP are associated with elevated PWV[6]. We tried to limit the influence of those variables on our results by establishing an age limit of 50 years and excluding patients with poorly controlled hypertension in an outpatient setting. In direct comparison with the previous study, our patients were younger (mean age 32 vs 41 yrs), and had better BP values (mean SBP 121 vs 141.4, and mean BP 86 vs 96.6).

Comparison of patients with TA and healthy subjects may be influenced by CV risk factors associated with the disease itself. Taking into account the age of patients, the recruitment of controls with similar CV risk profile would be difficult to perform. We could have included patients with other rheumatic diseases as controls — with known increased CV risk and similar ages, but there would probably be differences, inherent in the pathophysiology of diseases, interfering with analysis of the results.

Previous guidelines for CV screening in the asymptomatic population at risk established CF-PWV cutoff value of 12.0 m/s as a sign of target organ damage[27]. This value has also been recognized for the detection of early atherosclerotic lesions in hypertensive patients[5]. Importantly, the recent consensus statement established a lower default cutoff value of 10.0 m/s[21]. This study raises the possibility that this cutoff value may still be too high when considering younger patients (≤ 50 yrs) taking into account that TA was found to be an independent risk factor for higher PWV using the value of 8.34 m/s.

In patients with essential hypertension, PWV has been shown to be moderately correlated with levels of CRP, interleukin 6, and tumor necrosis factor-α, suggesting that inflammation plays a major role in the development and maintenance of endothelial dysfunction[32,33,34]. In reference to TA, CRP and ESR may not be ideal indicators of disease activity because about half of histopathological analyses of arterial biopsies in TA revealed inflammation in patients considered in remission[23]. However, we found no association with disease activity or inflammatory markers and PWV values in our patients. In contrast, with steroid treatment in polymyalgia rheumatica, which was associated with reduced arterial stiffness, no association was found in our study in relation to the current use of glucocorticoid and PWV[35].

Despite the exclusion criteria for vascular procedures involving the aorta, PWV was significantly higher in patients who had undergone any vascular procedure. This finding may suggest that, in TA, structural vascular damage can be of great importance for arterial stiffening. Our group has recently shown that in Behçet disease, which affects arteries of all sizes, PWV is more useful than carotid US in detecting structural and functional vascular damage and that the disease itself has a major role in promotion of these changes[36].

The strengths of our study are the number of enrolled patients and controls, with comparable age, BMI, and SBP values and the fact that all were premenopausal women. Limitations of our study include its cross-sectional design, in which data from only 1 visit were analyzed. Also, when assessing patients with rheumatic and particularly vasculitic conditions, other issues may be present that may influence PWV analysis and results, such as the use of immunosuppressive or antihypertensive therapies, steroids, and statins. The patients used at least 1 of these therapies at some point and it is unclear to what extent this may have influenced our results. Moreover, we did not obtain information on family history of CV diseases.

Despite our strict selection criteria, patients with TA still had (although not statistically significant) an average of 8 mmHg higher SBP than controls. The elevated SBP and decreased DBP — and consequently the elevated pulse pressure — compared to the control population are probably the result of aortic infiltration. This finding may have influenced our results. However, logistic regression showed that both MBP and TA were associated with high PWV. The 95% CI for patients with TA in the logistic regression was wide, probably because of small sample size. This suggests an association, but results must be verified in a larger population sample.

A large group of patients with TA is difficult to recruit. Patients may have different disease presentations and the effect seen on the arteries may be heterogeneous, with both dilations and stenosis occurring at the same time[1], and patients may present with high-grade stenosis in the common carotid artery that can hinder proper analysis of PWV. No difference was observed in PWV in relation to the presence of narrow or dilated vascular involvement in our patients. However, the small representation of patients with aneurysms and exclusion of aneurysms requiring surgery in this study preclude any definitive interpretation.

It should be stated that the PWV is a prognostic rather than a diagnostic tool for vasculitides. The relationship between TA-associated active inflammation and atherosclerosis is not completely understood. In this regard, routine PWV measurement in patients with TA should not be recommended until further studies elucidate the clinical significance of our findings.

In this group of female patients with TA, mean BP and the disease itself were the strongest determinants associated with arterial stiffness.

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