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Increased Arterial Stiffness Measured By Carotid Femoral (Aortic) Pulse Wave Velocity In Patients with Inactive Behçet's Disease

Introduction Behçet's disease (BD) is a chronic, multisystemic disease characterised by vascular involvement. Acute and chronic inflammatory processes associated with BD may cause endothelial dysfunction, which can then lead to a subsequent increase of arterial stiffness and altered pressure wave reflections. The aim of this study was to evaluate the pulse wave velocity (PWV) measurements in patients with inactive BD and control subjects.

Methods We studied 50 patients with inactive BD and 49 healthy control subjects without known cardiovascular disease. Carotid-femoral PWV was determined in all subjects by the same expert research clinician using Complior device (Colson, Paris, France).

Results Mean disease duration was 3.23±2.31 years. Patients with BD (mean age 36.04±9.94 years) had significantly higher PWV levels compared to controls (9.57±1.88 vs. 8.47±1.13 m/s; p=0,003). PWV was found to be positively correlated with age, systolic, diastolic, mean blood pressure, waist, and waist/hip ratio.

Conclusion In our study we demonstrated that patients with BD exhibit significantly increased arterial stiffness assessed by increased carotid-femoral PWV compared to healthy control subjects.

Keywords Behçet's disease, arterial compliance, pulse wave velocity, arterial stiffness

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Introduction

Behçet's disease (BD) is a systemic disease characterized by recurrent oral aphthae followed by genital ulcers, arthritis, variable skin and ocular lesions, gastrointestinal and central nervous system involvement and also vascular disease [1, 2]. Vascular involvement or disease, a term used to indicate the involvement of small to large vessels (predominantly of veins), is observed in ranging from 7 to 29% of patients [3]. Acute and chronic inflammatory processes associated with BD may cause endothelial dysfunction, which can then lead to a subsequent increase of arterial stiffness, vascular damage and altered pressure wave reflections [4, 5]. The histopathology results from studies indicate that there is fibrous thickening in all layers of the vessel wall, with focal aneurysmal dilatation and thick thrombus formation over the aneurysms. Vessel wall membrane is infiltrated by lymphocytes, monocytes, and neuthrophils [6].

Reduced arterial elasticity and increased arterial stiffness occur as results of endothelial injury and dysfunction due to the effects of ageing, hypertension, and other cardiovascular risk factors. Acute and chronic inflammation have been associated with endothelial dysfunction, altered pressure wave reflection and decreased arterial compliance that may lead to increased central blood pressures (BP) even in the absence of increased peripheral BP. Arterial stiffness is a reliable predictor of subsequent cardiovascular mortality and vascular damage which can be assessed by noninvasive pulse wave velocity (PWV) measurements [7]. PWV estimates central systolic-diastolic pressure and determines the influence of pulse wave reflection on the central pressure waveform. The pressure wave contour in any artery is the summation of the forward transmission of the cardiac pressure impulse and a backward reflection generated by the peripheral vascular system at the interface between the large arteries and resistance vessels [8]. Carotid-femoral (aortic) PWV is a technique according to which large artery elasticity is measured from analysis of the peripheral arterial waveform [7], in patients with chronic inflammatory conditions such as vasculitis. The main propose of the present study is to evaluate the arterial compliance by PWV in patients with BD.

Patients and Methods

This study included 50 patients with BD (40 male) diagnosed according to the International Study Group for BD [9] and 49 healthy subjects (31 male).

All of the patients were inactive during the investigation. If a patient has no signs of ulcer, erythema nodosum, active neurologic involvement, and gastrointestinal involvement; the patient was accepted as inactive. Exclusion criteria were a previous myocardial infarction, peripheral arterial disease, carotid artery disease, congestive heart failure, renal failure (plasma creatinine >1.5 mg/dL), arterial hypertension, diabetes mellitus, hyperlipidaemia, valvular heart disease, atrial fibrillation, presence of anemia (hematocrit <35%), obesity with body-mass index >35 kg/m^2 and waist-hip ratio ≥1, use of estrogen, progesterone, antihypertensives, antidiabetics, hormone replacement therapy, and lipid lowering drugs. Fifteen patients were using azathioprine, 23 patients were being treated with colchicine, 10 patients were taking corticosteroid, and 2 patients were on interferon therapy. The study was approved by the Local Ethical Committee and all patients gave informed consent.

Pulse wave velocity measurement

Systolic, diastolic, mean BP and pulse pressure were measured at the office, in compliance with European Society of Cardiology (ESC) and the European Society of Hypertension (ESH) guidelines [10].

Mean BP = [systolic BP + 2×diastolic BP]/3

Carotid-femoral PWV was determined in all subjects by the same expert research clinician using Complior device (Colson, Paris, France). Briefly, common carotid artery and femoral artery pressure wave forms were recorded noninvasively using a TY-306 Fukuda pressure sensitive transducer (Fukuda, Tokyo, Japan). When the operator observed a pulse waveform of sufficient quality, the digital register was stopped and then the delay time between the two pressure upstrokes was calculated. It was repeated at least in five different cardiac cycles and the mean value was used for the final distance analysis. The distance traveled by the pulse wave was measured over the body surface as the distance between the two recording sites (D), while the pulse transit time (t) was automatically determined by Complior (Colson) which calculated PWV as:

$$PWV\ (m/s) = distance\ (m)/transit\ time\ (ms).$$

Table 1. Demographic, clinical and hemodynamic characteristics of patients with Behcet's disease and control group

Parameters	Behcet's disease, n=50	Control group, n=49	p
Age, years	35 (18-61)	36 (18-59)	0.391
Female, n (%)	10 (20)	18 (36.7)	0.40
Duration, years	3.23±2.31		
Weight, kg	75.5 (49-93)	75.0 (49-95)	0.833
Height, cm	172 (150-190)	170 (153-184)	0.126
BMI, kg/m^2	24.6 (17.9–36.3)	25.3 (18.7–34.2)	0.588
Waist, cm	85 (64-103)	88 (57-110)	0.249
Hip, cm	97 (80-113)	100 (80-111)	0.081
Waist/hip	0.87 (0.72–1.01)	0.89 (0.66–0.99)	0.298
SBP, mmHg	120 (90-150)	115 (90-135)	0.844
DBP, mmHg	80 (60-100)	70 (60-85)	0.158
MBP. mmHg	93 (73-116)	83.3 (70–101.6)	0.565
Pulse pressure, mmHg	40 (20-70)	40 (20-65)	0.165
Heart rate, bpm	72 (54-108)	72 (60-96)	0.896
Transit time, s	69 (41-112)	71 (57–93.9)	0.090
PWV, m/s	9.09 (5.63–14.55)	8.52 (5.57–11.7)	0.003

BMI – body mass index; DBP – diastolic blood pressure; MBP – mean blood pressure; PWV – pulse wave velocity; SBP – systolic blood pressure.

The validation and reproducibility of this automatic method have been previously described, with an intra-observer repeatability coefficient of 0.935 [7].

Statistical analysis

Statistics were obtained using the ready-to-use programme of SPSS version 8.0. Data was expressed as n (%) for categorical variables. Pearson chi-square was performed for categorical variable. After fitness to normal distribution analyzed with the Kolmogorov-Smirnov test data were expressed as "median (minimum-maximum)" for abnormal distribution. Pearson's correlation test was performed for correlations between the two parameters. p<0.05 was accepted as statistically significant.

Results

This study consisted of 50 patients with BD and 49 healthy age- and sex-matched subjects. There were no differences in the age, sex ratio, height, weight, other measures known to affect PWV, including BP, heart rate and total cholesterol levels between patients with BD and controls. Mean duration of the disease was 3.23±2.31 years.

The carotid-femoral (aortic) PWV was increased significantly in patients with BD as compared with control group (Table 1). Transit time was non significantly lower in Behçet's patients.

As patients were on anti-inflammatory therapy and were inactive; there were no connection between PWV and clin-

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ical manifestations. Correlation analysis was not performed between PWV and these parameters.

Correlation analysis was performed to evaluate the correlation between PWV and clinical variables separately in the control group and in patients with BD. Age, diastolic BP, mean BP, waist, waist/hip ratio and heart rate were found to be correlated with PWV in patients with Behcet's disease group as shown in Table 2, while PWV was not correlated with the duration of the disease. However, PWV was not correlated with any of these variables in control group (Table 2).

Discussion

In our study we aimed to evaluate arterial compliance in patients with BD. Arterial compliance assessed by transit time is decreased in patients with BD compared to healthy controls. However PWV is increased compared to controls. Furthermore, significant correlations between PWV and age, waist, waist/hip, BP were found. In spite of being inactive and using anti-inflammatory drugs patients in our study had higher PWV compared with controls.

Histopathologically BD is mainly characterized by vasculitis, with prominent neutrophil and monocyte infiltration in the perivascular regions with or without fibrin deposition in the vessel wall. Endothelial dysfunction, the initial lesion in atheromatosis, intermittent inflammation, autoimmune mechanisms and drugs are thought to account for the accelerated atherosclerosis in patients with BD [11].

Arterial stiffness can be easily measured in clinical practice by several non-invasive methods. Reference values are available for carotid to femoral pulse wave method, which is currently proposed as the gold standard method to measure arteriosclerosis [12]. Arterial compliance, the inverse of stiffness, describes the ability of the artery to expand and recoil with cardiac systole and diastole [13]. PWV is inversely correlated with arterial elasticity and relative arterial compliance [7].

A number of studies have investigated the effects of the different factors such as age, sex, weight, height, BP, heart rate, and inflammatory markers on PWV [7, 14, 15]. In fact, the most important factor contributing to increased aortic PWV is age, as in our study, because of a decrease in arterial elasticity caused by decrease in elastin fiber, and increase in collagenous material [7]. In addition to the age, PWV also depends on BP level that becomes increased at high BP and decreased at low BP; however, different correlations can be seen [14, 15].

According to the systematic review and meta-analysis that compares the arterial stiffness parameter in subjects diagnosed with BD and normal subjects the PWV, an ideal indicator of arterial stiffness, was increased in patients with BD compared to controls [16]. Arterial stiffness was found to be equally increased in BD when compared to patients with rheumatoid arthritis and systemic lupus erythematosus according to the study of Kocabay et al. [17]. Most of the previous studies [3, 18, 19] found an increased PWV in patients with BD, but the results of a study by Kurum et al. [20] didn't find the similar outcome. The discrepancy in the results of that study could be due to smaller sample size and shorter disease duration. Caldas et al. reported that BD patients with systemic involvement had significantly higher PWV levels than those with only mucocutaneous involvement and carotid intima media thickness (cIMT) was similar between BD and controls [18].

Anti-inflammatory agents reduce severity of inflammation in BD. Anti-inflammatory effect of drugs may decrease arterial compliance [21]. Despite using anti-inflammatory agents, patients in our study have higher PWV than

Table 2. Correlation between PWV and clinical variables in patients with Behcet's disease and control group

Parameters	Behcet's disease (n=50)		Control group (n=49)	
	Correlation coefficient	p	Correlation coefficient	p
Age	0.645	<0.001	0.228	0.115
Weight (kg)	0.071	0.625	0.192	0.185
Height	–0.152	0.291	0.045	0.750
BMI (kg/m2)	0.179	0.214	0.217	0.135
Waist (cm)	0.393	0.005	0.135	0.355
Hip (cm)	0.179	0.213	–0.025	0.864
Waist/hip	0.347	0.013	0.221	0.126
SBP (mmHg)	0.279	0.050	0.118	0.421
DBP (mmHg)	0.376	0.007	0.139	0.339
MBP (mmHg)	0.360	0.010	0.127	0.386
Pulse pressure (mmHg)	–0.042	0.774	0.040	0.783
Heart rate (bpm)	0.315	0.025	–0.174	0.231
Duration (year)	–0.140	0.333	–	–

BMI – body mass index; DBP – diastolic blood pressure; MBP – mean blood pressure; PWV pulse wave velocity; SBP – systolic blood pressure.

control group. Since these patients were already taking these medications, they were not considered to discontinue the medication.

In addition to PWV other non-invasive modalities have been evaluated. Brachial artery flow-mediated dilatation (FMD), which characterizes endothelial function, is also impaired in BD according to a meta-analysis of Merashli et al. [22]. Study of 30 patients showed that PWV measurement might be more useful than cIMT in determination of vascular damage in BD, especially in early stages of disease [23]. Celik et al. measured the arterial stiffness by calculating the augmentation index (AIx), which was positively correlated with the PWV [24]. In another study it was found that cIMT and coronary artery calcium scores were statistically higher and the ankle-brachial pressure index was lower in BD patients than in the control group [25]. Young-Boum Lee et al. hypothesized that the power of pressure wave analysis would be improved if pulse wave pass lengths were not used and they evaluated the power of aorta-to-arm (carotid – femoral to carotid – radial) pulse wave transition time ratio (PWTTR) in the prediction of patients with cardiovascular disease. PWTTR showed a better prediction of the presence of coronary artery disease and stroke than PWV [26]. A trial performed on healthy people demonstrated that age, systolic BP and BMI were the main determinants of arterial stiffness and compliance, whereas age and systolic or diastolic BP had the strongest association with aortic stiffness and compliance [27]. Another non-invasive method, namely FMD, was less sensitive than PWV for detection of vascular dysfunction in patients with rheumatoid arthritis [28].

Conclusion

In conclusion, the present study demonstrated that patients with BD exhibit significantly decreased arterial compliance assessed by carotid-femoral (aortic) PWV, compared to healthy control subjects. However, PWV was found to be positively correlated with age, systolic, diastolic, mean BP, waist, and waist/hip ratio. Longitudinal studies in a large population taking into consideration different imaging modalities are warranted in order to determine the prognostic implications of decreased compliance parameters in the setting of BD.

Study limitations

The primary limitation of the study is that follow-up data were not available at the time of present analysis to compare results of this study with clinical end-points like cardiovascular mortality, morbidity and clinical atherosclerosis. Lack of concurrent evaluation of cIMT and FMD is also a limitation of our study. We didn't include patients with active BD. Therefore large sample size including active patients and long-term studies will be necessary to determine clinical consequences of arterial stiffness in BD.

Abbreviations

BD: Behçet's disease, cIMT: carotis intima media thickness, FMD: flow-mediated dilatation, PWV: pulse wave velocity.

No conflict of interest is reported.

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