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Parameters of arterial stiffness in patients with Behçet's disease and their relationship with disease duration

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Abstract

The results of investigations of arterial stiffness in Behçet's disease (BD) are contradictory and the reason for this contradictory situation is not clear. The lack of studies in homogenous groups according to the duration of the disease may be the cause of conflicting results. To compare arterial stiffness by assessing pulse wave velocity (PWV) and augmentation index (AIx) measurements in healthy controls (HC) and patients diagnosed with BD with short and long disease duration. This cross-sectional study was conducted between August-November 2017 and 54 patients with BD and 34 HC were included. Patients with BD who were diagnosed within 12 months were included in the group with short disease duration (SDD) and the others in the group with long disease duration (LDD). Parameters of cardiovascular risk of all participants were recorded and PWV and AIx values were measured from the brachial artery. AIx was significantly higher in all patients with BD, patients with BD with SDD and patients with BD with LDD, than in HC ($p=0.005$, $p=0.011$, $p=0.004$, respectively). Pulse wave velocity values were not different from HC in patients with BD. When patients with BD with SDD and LDD were compared with each other, PWV was significantly higher in patients with BD with LDD ($p=0.030$). There was a moderate correlation between PWV and disease duration (Rho = 0.414, $p=0.002$). Augmentation index is higher in patients with BD than HC regardless of disease duration.

Keywords Arterial stiffness · Augmentation index · Behcet's disease · Pulse wave velocity

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Introduction

Behçet's disease is a systemic vasculitis that can cause skin, eye, central nervous system and vascular involvement. Vascular involvement is common in Behcet's disease (BD) and arterial and venous vasculature of all sizes can be involved [1]. Several autoimmune rheumatic conditions are characterized by enhanced atherosclerosis and consequently higher cardiovascular morbidity and mortality rates [2]. Silent myocardial ischemia was described in 25% of BD, which was significantly higher than healthy controls (HC), and there are studies indicating increased premature atherosclerosis in BD compared to healthy controls, but the plaque frequency seen in BD is not as clear as the plaque frequency seen in other connective tissue diseases such as SLE in which accelerated atherosclerosis is well defined [3–7]. There are also studies in the literature that indicate that arterial stiffness does not change in BD [8]. The results of the studies evaluating arterial stiffness in BD are contradictory [4, 8, 9]. Arterial stiffness is an indicator of atherosclerosis and

atherosclerosis is an inflammatory process with immune cell activation, inflammation-driven plaque formation and subsequent rupture [10]. Duration of ongoing inflammation may affect arterial stiffness. Therefore, the length of time after onset of the disease may affect the degree of arterial stiffness. In a study evaluating arterial stiffness in patients with active and inactive BD, the relationship between disease duration and pulse wave velocity (PWV) was evaluated and a significant correlation was found [11]. In the literature, there is no other data on the relationship between disease duration and arterial stiffness in BD. The fact that homogeneous patient groups were not formed according to duration of illness in the studies performed may have been responsible for producing conflicting results. Arterial stiffness can be assessed by invasive and non-invasive methods. Pulse wave velocity and augmentation index (AIx) are highly reproducible and noninvasive methods used to assess arterial stiffness and are used as markers in early cardiovascular risk assessment in inflammatory diseases [12–14]. Pulse wave velocity and AIx are widely considered as independent predictors of cardiovascular events and all cause mortality [15, 16]. In our study, we aimed to investigate arterial stiffness in BD and healthy controls (HC) by grouping BD patients with short disease duration (SDD) and long disease duration (LDD).

Methods

The study was approved by the local ethics committee (2017-13/66) and all patients gave written informed consent. This case–control study was conducted between August and November 2017. 54 patients with BD (F/M: 32/20) who were outpatients and 34 age and gender matched healthy controls (HC) (F/M: 20/14) were included. A flowchart showing how participants were selected for the study is shown in Fig. 1. Participants who were diagnosed with BD within the last 12 months by an experienced rheumatologist fulfilling international study group classification criteria, which requires the presence of oral ulceration plus any two of genital ulceration, typical defined eye lesions, typical defined skin lesions, or a positive pathergy test [17], were defined as BD with SDD, and others as BD with LDD. Healthy controls were those who volunteered to participate in the study from among patient attendants. The Behcet's Syndrome Activity Scale (BSAS) questionnaire was filled out with face-to-face interviews with participants to assess the disease activities of all participants with BD. All participants' height and weight measurements were taken. Venous blood samples were obtained from each participant after an overnight fast for the determination of a routine biochemical profile including total cholesterol, triglycerides and HDL-cholesterol, all determined by standard methods. LDL-cholesterol was calculated by the formula of

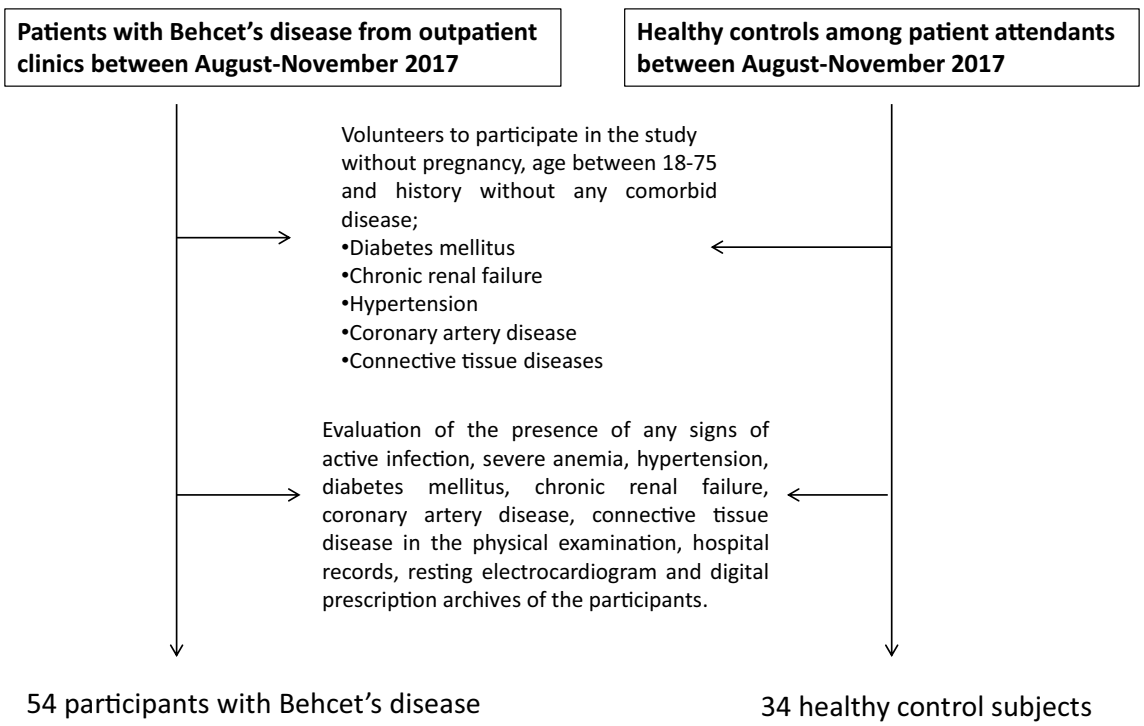

Fig. 1 Flowchart showing how participants were selected

Friedewald for patients with serum triglycerides < 400 mg/dL. All patients with BD underwent ophthalmic examinations, patients with Behcet's disease who had anterior uveitis, posterior uveitis or retinal vasculitis in their ophthalmic examinations were defined as having eye lesions.

Evaluation of arterial stiffness

The patients were asked to refrain from eating and drinking alcohol, coffee or tea for at least 12 h prior to the study. The arterial stiffness test was performed in the supine position in a quiet room. A Mobil-O-Graph 24 h PWA Monitor (IEM GmbH, Stolberg, Germany), which measures brachial PWV and AIx, was used for the vascular evaluation [18]. Because AIx is defined as the percentage ratio of augmentation to the aortic pulse pressure, it also represents the percentage of central pulse pressure. It is important to note that AIx is normalized for a heart rate of 75 beats/min, because the measurement can be influenced by heart rate [19]. The device was supported by the expert software package, Hospital Management System (Hypertension Management System; Client Server Company, Stolberg, Germany; IEM GmbH), in the analysis of all registered measurements. Using the ARC Solver method (Austrian Institute of Technology, Vienna, Austria), the waveforms were recorded with a regular oscillatory brachial cuff suitable for ambulatory measurements. The waveforms were then used to determine the aortic systolic blood pressure and AIx based on the oscillometric blood pressure measurement with a common cuff. Pulse waves at the brachial artery were also assessed [20]. In this study, arterial stiffness measurements were conducted three times in 5-min intervals. The mean value was then calculated for each patient.

Statistical analysis

SPSS Version 22.0 for Windows (SPSS Inc, Chicago, IL, USA) was used to process all data statistically. Variables are presented as mean, median, standard deviation (SD), minimum–maximum or frequency. To compare quantitative variables, Mann–Whitney *U* test was used. For the comparison of qualitative data, χ^2 test or Fischer's exact χ^2 test was used. The correlation between data was analyzed using Spearman's correlation test. All tests were two-tailed, and p values < 0.05 were considered to indicate statistical significance.

Results

This study consisted of 54 patients with BD (27 with SDD and 27 with LDD) and 34 healthy age and sex matched subjects. Clinical features of patients with BD are shown in Table 1. Demographic characteristics, cardiovascular risk factors and parameters of arterial stiffness in patients with BD and in HC are shown in Table 2. Median duration of disease in all patients with BD, patients with BD with SDD and with LDD, were 11.5 (0–424), 0 (0–11) and 120 (12–424) months, respectively. In patients with BD with SDD and LDD, BSAS scores were not statistically different [35.75 (10–88.5), 36 (0–83.0), respectively, $p = 0.729$]. Demographic characteristics, cardiovascular risk factors, disease specific medications and parameters of arterial stiffness in patients with BD with SDD and LDD are shown in Table 3. When HC and patients with BD with LDD were compared; age, gender, BMI, systolic and diastolic blood pressures, heart rates, smoking, total cholesterol, LDL, HDL, and triglyceride levels were not statistically different ($p = 0.282$, $p = 1.000$, $p = 0.131$, $p = 0.214$, $p = 0.657$, $p = 0.621$, $p = 1.000$, $p = 0.428$, $p = 0.850$, $p = 0.123$, $p = 0.273$, respectively). When HC and patients with BD with SDD were compared; age, gender, BMI, systolic and

Table 1 Clinical features in patients with Behçet's disease

Oral ulcerations, *n* (%)	54 (100)
Genital ulcerations, *n* (%)	31 (57.4)
Erythema nodosum, *n* (%)	26 (48.1)
Acneiform lesions, *n* (%)	38 (70.4)
Eye lesions, *n* (%)	19 (35.2)
Arterial disease, *n* (%)	1 (1.9)
Venous disease, *n* (%)	7 (13.0)
Pathergy, *n* (%)	43 (79.6)
HLA B51, (+/−)	44/19

Table 2 Demographic characteristics, cardiovascular risk factors and parameters of arterial stiffness in patients with BD and in HC

	BD ($n = 54$)	HC ($n = 34$)	p
Age (years)	38.0 (21–61)	38.5 (24–60)	0.945
Gender (f/m)	32/20	20/14	1.000
BMI (kg/m^2)	25.7 (17.6–33.3)	26.3 (20.7–36.3)	0.224
Systolic BP (mmHg)	119.5 (89–140)	119.0 (97–138)	0.448
Diastolic BP (mmHg)	78.0 (54–94)	78.00(67–96)	0.764
Heart rate (bpm)	83.0 (54–108)	78.0 (63–112)	0.238
Smoking, *n* (%)	27 (50)	18 (40)	0.788
Total cholesterol	195.0 (126–273)	198.5 (127–266)	0.235
LDL (mg/dl)	121.00 (67–187)	121.0 (56–190)	0.898
HDL (mg/dl)	50.0 (29–85)	52.5 (30–83)	0.177
Triglycerides (mg/dl)	115.00 (18–284)	111.5 (29–288)	0.286
PWV	5.8 (4.6–7.7)	5.75 (4.8–8.8)	0.442
AIx	30.0 (4–52)	22.5 (2–38)	0.005

BD Behcet's disease, *HC* healthy control, *PWV* pulse wave velocity, *AIx* augmentation index

Table 3 Demographic characteristics, cardiovascular risk factors, disease specific medications and parameters of arterial stiffness in patients with BD with SDD and LDD

	Patients with BD		*p*
	SDD ($n=27$)	LDD ($n=27$)	
Age (years)	35.0 (24–55)	42.0 (21–61)	0.080
Gender (f/m)	17/10	15/12	0.782
BMI (kg/m^2)	25.82 (19.5–33.3)	25.10 (17.6–31.2)	0.291
BSAS	35.75 (10-88.5)	36.0 (0–83.0)	0.729
Systolic BP (mmHg)	118.0 (104–140)	124.00 (89–139)	0.311
Diastolic BP (mmHg)	76.00 (60–85)	82 (54–94)	0.102
Heart rate (bpm)	84 (54–99)	81 (59–108)	0.478
Smoking, *n* (%)	13 (48.1)	14 (51.9)	0.785
Total cholesterol	194.00 (126–273)	195.00 (139–266)	0.510
LDL (mg/dl)	121.00 (72–162)	121.00 (67–187)	0.522
HDL (mg/dl)	51.00 (35–85)	50.0 (29–68)	0.340
Triglycerides (mg/dl)	115.00 (37–275)	115.00 (18–284)	0.539
Drugs, *n* (%)			
Colchicine	10 (37.0)	18 (66.7)	0.056
Azathioprine	2 (7.4)	8 (29.6)	0.076
Cyclosporin	0 (0)	3 (11.1)	0.236
Corticosteroid	4 (14.8)	6 (22.2)	0.728
Infliximab	0 (0)	2 (7.4)	0.491
PWV	5.6 (4.6–7.5)	6.40 (5.1–7.7)	0.030
AIx	29.00 (7–42)	33.00 (4–52)	0.264

SDD Short disease duration, *LDD* long disease duration, *BD* Behcet's disease, *HC* healthy control, *PWV* pulse wave velocity, *AIx* augmentation index

diastolic blood pressures, heart rates, smoking, total cholesterol, LDL, HDL and triglyceride levels were also not statistically different ($p=0.337$, $p=0.796$, $p=0.642$, $p=0.965$, $p=0.340$, $p=0.132$, $p=0.799$, $p=0.222$, $p=0.684$, $p=0.454$, $p=0.476$, respectively). Augmentation index was significantly higher in all patients with BD, patients with BD with SDD and in patients with BD with LDD than in the healthy controls ($p=0.005$, $p=0.011$, $p=0.004$, respectively). PWV was not different in patients with BD with SDD and in patients with BD with LDD than in the healthy controls ($p=0.527$, $p=0.053$, respectively). There was a moderate correlation (Fig. 2) between PWV and disease duration (Rho = 0.414, $p=0.002$) and there was no correlation (Fig. 3) between AIx and disease duration (Rho = 0.111, $p=0.423$).

Discussion

To the best of our knowledge this study is the first study evaluating arterial stiffness by grouping patients according to disease duration in BD. We found that in patients with BD, AIx values were significantly higher than the HC group

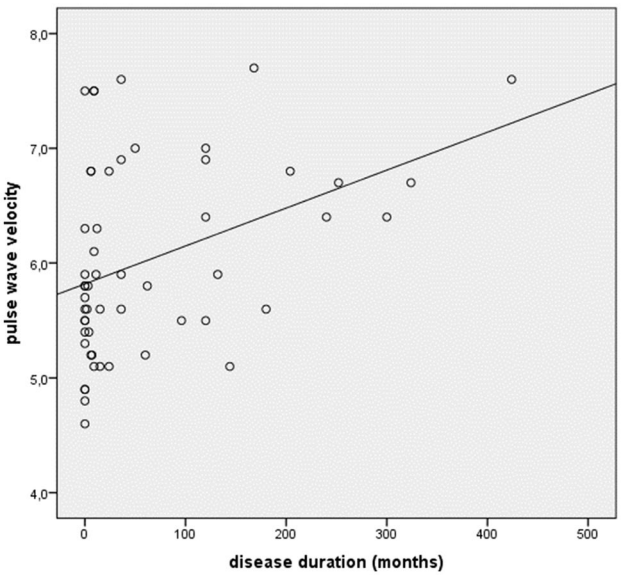

Fig. 2 Scatter-dot graph indicating the correlation between pulse wave velocity and duration of disease in patients with Behçet's disease

($p=0.005$). When patients with BD were grouped according to the time elapsed after diagnosis, we found that AIx levels were higher than HC in both patient groups, those diagnosed within 1 year or for a longer time ($p=0.011$, $p=0.004$). However, since patients with BD diagnosed within 1 year or for more than 1 year were compared with each other, AIx was not different between the groups ($p=0.264$) and there was no significant correlation of AIx with disease duration.

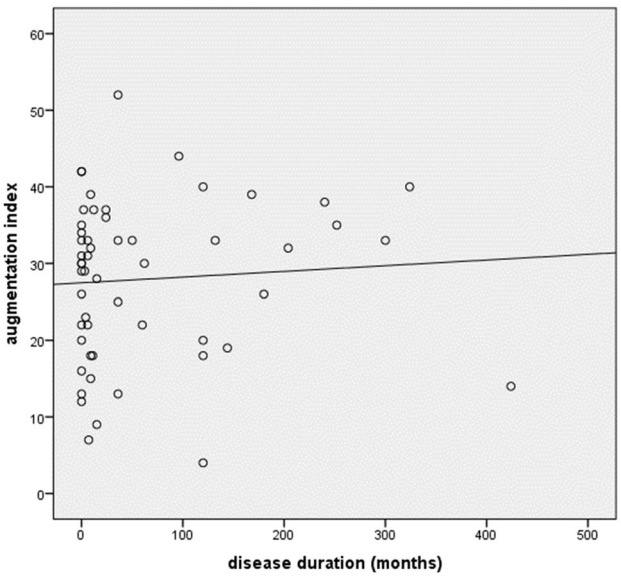

Fig. 3 Scatter-dot graph showing the correlation between augmentation index and duration of disease in patients with Behçet's disease

When PWV was evaluated, it was seen that PWV values in patients with BD were not different from HC ($p=0.442$), but PWV values were higher in patients with a disease duration of more than 1 year compared to those with shorter duration ($p=0.030$). However, when evaluating these results, it should not be ignored that SDD and LDD groups were not homogeneous when evaluated for cardiovascular risk factors. Although the differences were not statistically significant, it should be seen that the LDD group was older but had lower BMI values ($p=0.080$, $p=0.291$). Although PWV values were not statistically different ($p=0.527$) between healthy controls and the group with a disease duration of less than 1 year, PWV was higher in HC. However, BD patients with a duration of disease longer than 1 year were found to have higher PWV levels compared to HC, although this was not significant ($p=0.053$). We also found that PWV values correlated moderately with disease duration (Rho = 0.414, $p=0.002$). According to the data obtained from this study, AIx was higher in patients with BD regardless of disease duration, whereas PWV values were not different in patients with BD and HC but tended to increase with increasing disease duration in patients with BD. There is little data about the relationship between parameters of arterial stiffness and disease duration in patients with BD. Similar to the present study, in the study of Yilmaz et al., the duration of the disease was correlated with PWV values ($\beta=0.449$, $p=0.001$) [11].

Arterial stiffness is an indicator of atherosclerosis and atherosclerosis is a progressive inflammatory process that can result in fatal vascular events. The initial mechanism of the atherosclerotic process is endothelial dysfunction, which is a characteristic finding in BD [21]. There are many studies in the literature that show endothelial dysfunction in BD. Increased plasma malondialdehyde, reduced glutathione:oxidized glutathione ratio, reduced superoxide dismutase, and elevated catalase levels have been observed and were findings indicating increased oxidative stress in BD [22, 23]. Endothelium-dependent flow-mediated dilation is reduced in patients with BD [23, 24]. Elevated levels of symmetric dimethylarginine (ADMA), an endogenous inhibitor of NO synthase, have been observed in Behçet's syndrome [25]. Although there is much data on endothelial dysfunction, there is less evidence for an increased incidence of cardiovascular events in BD [3–7]. The etiological factors responsible for the onset of atherosclerosis in BD are well defined. However, there is insufficient data about the occurrence of atherosclerosis and its progression over time. Increased arterial stiffness is one of the earliest stages of the atherosclerotic process and PWV is widely accepted as an accurate and non-invasive method for assessing arterial stiffness [26, 27]. Although PWV is a parameter of direct arterial distension, augmentation index is a more complex parameter depending on vascular elasticity and peripheral resistance [28]. Pulse wave velocity and AIx are widely considered as independent predictors of cardiovascular events and all cause mortality [15, 16]. There are studies showing that arterial stiffness does not change, as well as studies showing that arterial stiffness increases in BD compared to HC [8, 9, 11, 29]. This may be related to the fact that patient populations in studies were not similar in disease duration. In the study conducted by Kurum et al. [9] the mean duration of disease in patients with BD was 6.64 ± 4.5 years and PWV was not different in BD than in HC (8.4 ± 1.4, 8.5 ± 1.1 m/s respectively). However, in the study of Caldas et al. [29] the mean duration of the disease in patients with Behcet's disease was 8.9 ± 5.6 years and PWV was higher in BD than in HC (8.7 ± 1.2, 7.8 ± 0.7 m/s respectively), and in the study of Balta et al. [30] the duration of the disease in patients with Behcet's disease was 9.87 ± 7.32 years and PWV was higher in BD than in HC (7.28 ± 1.42, 6.64 ± 0.87 m/s, respectively). Caldas et al and Balta et al. found increased PWV in patients with BD, however, the results of the study by Kurum et al. did not support this finding. Perhaps discrepancies in the findings were due to Kurum's patient group having a shorter disease duration. In the present study, the mean disease duration of patients with BD was 63.54 ± 97.40 months. The absence of increased PWV values in patients with BD in this study may be due to the short duration of disease. Mean disease duration of patients with BD with LDD in our study was 124.07 ± 108.18 months and mean PWV values in this patient group was higher than the control group, with the difference being close to statistical significance. For assessing arterial stiffness in patients with BD, AIx has been less well studied. In the study of Yılmaz at al. [11] AIx measurements were evaluated and were not different in active BD patients, inactive BD patients and HC. In another study conducted by Celik et al. [31] AIx was not different from healthy controls in patients with BD. However, in the study of Ikonomidis et al. [32] AIx measurements were found to be higher in BD than HC. In the present study, AIx was found to be higher in patients with BD than in the HC, even in the newly diagnosed group of patients. In patients with BD, AIx may allow us to predict cardiovascular risk earlier. There is a need for further evaluation of these data. PWV may not change significantly in the early atherosclerotic artery because the artery may still remain elastic, and in an elastic artery, AIx is more likely to be related to the intensity of the reflected wave rather than to its velocity [33]. This may explain why PWV values were not increased at the onset of BD. However, further research is needed to explain this issue. Another important result we found in this study was that AIx was not correlated with duration of disease in BD. In the literature, there is no data on the relationship between

AIx and disease duration in BD. Perhaps the structural changes in the artery from the early stage of the disease affect AIx, but maybe augmentation of the artery is not affected by the progression of arterial stiffness. Further studies are needed to explain the independence of AIx from disease duration in BD. The data in the literature suggest that atherosclerosis may be seen more in patients with BD than healthy subjects, but this expectation has not been met sufficiently in the studies investigating arterial stiffness. In most of these studies, arterial stiffness was assessed by PWV. In the present study, arterial stiffness was assessed by both PWV and AIx in patients with BD and AIx was found to be significantly higher in both early and late periods of BD compared to healthy controls. To evaluate arterial stiffness particularly in patients newly diagnosed with BD, AIx can be used. There is no evidence in the literature on this subject. Further studies are needed to clarify this issue.

There are some limitations to this study. This study was conducted with a limited number of patients and for the confirmation of our findings studies with more participants are needed. In this study, the disease duration of patients with BD was determined by the clinician from the time of diagnosis of BD, but since some patients may have delayed diagnosis, the duration of the disease may not reflect the actual disease duration of the patients. In our study, although the frequency of drug use among SDD and LDD groups was not statistically significant, it is one of the limiting conditions of the study that the frequency of drug use in patients with BD grouped by the duration of disease is not homogeneous and this may affect the results of PWV and AIX. In this study, arterial stiffness was evaluated cross-sectionally. The main shortcoming is the fact that the progression of arterial stiffness was not evaluated prospectively.

Conclusions

On the basis of these results, AIx is higher in patients with BD than HC regardless of disease duration. Although PWV was not different in patients with BD compared to HC, it seemed to be higher when disease duration was extended.

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Compliance with ethical standards

Conflict of interest The authors have no conflicts of interest to declare.

Ethical approval Ethics committee approval was obtained from Uludag University Faculty of MedicineClinical Research Ethics Committee (2017-13/66). The study was carried out inaccordance with ethical standards.

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