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Concise report

Pulmonary arterial wall thickness increased in Behçet's disease patients with major organ involvement: Is it a sign of severity?

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Abstract

Objectives. Behçet's disease (BD) is a unique systemic vasculitis mainly involving veins, in contrast to other vasculitides. Prior studies have shown that pulmonary arteries (PAs) have a similar structure to systemic veins. In this study we aimed to assess PA wall thickness by transthoracic echocardiography (TTE) in BD patients compared with healthy controls (HCs) and patients with non-inflammatory pulmonary embolism (NIPE).

Methods. Patients with BD ($n = 77$) and NIPE ($n = 33$) and HCs ($n = 57$) were studied. PA wall thickness was measured from the mid-portion of the main PA with TTE by two cardiologists blinded to cases.

Results. PA wall thickness was significantly lower in HCs [3.6 mm (S.D. 0.3)] compared with NIPE [4.4 mm (S.D. 0.5)] and BD [4.4 mm (S.D. 0.6)] ($P < 0.001$ for both). PA wall thickness was similar between BD and NIPE ($P = 0.6$). Among patients with BD, PA wall thickness was significantly higher in patients with major organ involvement compared with mucocutaneous limited disease [4.7 mm (S.D. 0.4) *vs* 3.7 (0.4), $P < 0.001$], HCs and NIPE ($P < 0.001$ and $P = 0.006$, respectively). PA wall thickness was comparable between patients with vascular and non-vascular major organ involvement [4.6 mm (S.D. 0.5) *vs* 4.7 (0.3), $P = 0.3$].

Conclusion. We observed that PA wall thickness was significantly higher in BD with major organ involvement compared with patients with only mucocutaneous limited disease, HCs and NIPE. These results suggest that increased PA wall thickness may be a sign of severe disease with major organ involvement in BD.

Key words: Behçet's disease, pulmonary artery wall thickness, echocardiography

CLINICAL SCIENCE

Rheumatology key messages

- Pulmonary artery (PA) wall thickness is increased in patients with BD compared with healthy controls and patients with thrombotic pulmonary disease.
- Increased PA wall thickness is mainly observed in patients with major organ involvement.
- Increased PA wall thickness may be a sign of a more severe disease spectrum in patients with BD.

Introduction

Behçet's disease (BD) is an inflammatory disease characterized by mucocutaneous and systemic involvement. Vascular involvement (VBD) is observed in up to 40% of patients and is the major cause of mortality and morbidity [1]. Inflammation of vessel walls is seen in both arterial and venous systems. Venous wall inflammation manifests mainly as thrombosis, and deep venous thrombosis (DVT) of lower extremities is the most common form of VBD (up to 80%) [2]. However, data assessing the veins are limited [3–5].

We recently published the first controlled Doppler US study showing increased vein wall thickness (VWT) of

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lower extremity veins in male BD patients [6]. Increased common femoral VWT was observed as a distinctive feature of BD, therefore measurement of common femoral vein thickness with Doppler US can be a diagnostic test for BD [7].

In a subgroup of BD patients, arterial inflammation, mostly in the pulmonary artery (PA), can manifest as thrombosis and aneurysms [2]. In a historic cadaver study, mean PA wall thickness was measured 430 microns (0.43 mm) histologically [8]. The wall thickness of small diameter PA measured by optical coherence tomography and intravascular ultrasonography was suggested as 'increased' at measurements >0.2 mm [9, 10]. Prior studies showed that PAs have a structure similar to veins in terms of wideness and thin walls, increased compliance, low resistance and pressure [11].

When these unique features are considered, we aimed to investigate whether PA wall thickness increases in response to systemic inflammation in BD. PA wall thickness is assessed by transthoracic echocardiography (TTE), which is a reliable and practical diagnostic modality in cardiology and was compared with healthy controls (HCs) and patients with non-inflammatory pulmonary embolism (NIPE).

Methods

Patients with BD fulfilling International Study Group for Behçet's Disease Criteria [12] ($n = 77$) and patients with NIPE ($n = 33$) were recruited from the Vasculitis Clinic of the Rheumatology and Pulmonology Departments of Marmara University Hospital. As HCs, 57 age- and gender-matched individuals from the hospital staff and medical students were included. Although one HC had hypertension, two had hyperlipidaemia and hypertension and one had hypothyroidism, none of them experienced a thrombotic event.

Data on demographics, disease characteristics and immunosuppression (IS) use were collected from patient charts and activity status was assessed by the Behçet's Disease Current Activity Form [13]. TTE was performed by two experienced (>12 years) cardiologists (>1000 TTE/year) blinded to the clinical data of all patients and HCs with a Philips Epiq 7 echocardiography device and an S5-1 transducer (3.5 MHz; both from Philips Medical Systems, Andover, MA, USA). Greyscale images were acquired at a rate of 44–82 frames/sec. Patients were positioned in a left lateral decubitus position. Two-dimensional (2D) parasternal aortic short-axis images were obtained during a breath-hold, stored in cine loop format from three consecutive beats and transferred to a workstation for further offline analysis. PA wall thickness was calculated from the mid-portion of the main PA (~1–2 cm distal to the pulmonary valve) (Supplementary Fig. S1, available at *Rheumatology* online).

The study protocol was approved by the Marmara University Local Ethics Committee (2021-870) and written informed consent was obtained from each patient. The study was performed according to the Declaration of Helsinki.

Statistical analysis

Data were analysed using SPSS 26.0 software (IBM, Armonk, NY, USA). Categorical variables were reported as frequencies and percentages, which were compared with chi-squared and Fisher's exact tests. Continuous variables were summarized as mean (S.D.). The distribution of continuous variables was analysed with the Kolmogorov–Smirnov/Shapiro–Wilk test. Independent-sample *t*-test, one-way analysis of variance and Mann–Whitney *U* test were used for the analysis of quantitative variables. The correlation between non-parametric variables was evaluated by Spearman's correlation analysis. A correlation coefficient (r) of <0.20 was considered as negligible, 0.20–0.40 as fair, 0.41–0.60 as moderate, 0.61–0.80 as good and >0.80 as excellent agreement. Receiver operating characteristics (ROC) analysis was used to determine the cut-off value. *P*-values <0.05 were considered statistically significant.

Results

The mean age was similar among the BD, HC and NIPE groups [39.4 years (S.D. 8.8), 35.5 (10.1) and 38.7 (8.3), respectively]. There was a female dominance in the NIPE group [52.6% ($n = 19$)] compared with the BD group [39% ($n = 30$)] and HCs [33.3% ($n = 19$)]. Among patients with BD, 53 (68.8%) had major organ involvement, with 36 (46.8%) having vascular, 24 (31.8%) ocular and 14 (18.2%) neurologic manifestations. The ongoing treatments of BD patients are presented in Table 1. Measurements >4 mm have been accepted as increased wall thickness according to ROC analysis [area under the curve 0.71 (95% CI 0.640, 0.798), $P < 0.001$] (Supplementary Fig. S2, available at *Rheumatology* online).

In the NIPE group, 24 (72.7%) patients had pulmonary emboli in both PAs. While pulmonary embolism was detected after postoperative DVT in two patients, emboli in other patients were non-provoked and DVT could not be detected. Pulmonary emboli were observed in the main PA in 2 (6.1%) patients and the lobar, segmental and subsegmental branches in 9 (27.3%), 16 (48.5%) and 6 (18.2%) patients, respectively. Only one of these patients (3%) had cardiac chamber dilatation and none had pulmonary hypertension.

The mean PA wall thickness was significantly higher in patients with BD [4.4 mm (S.D. 0.6)] and NIPE [4.4 mm (S.D. 0.5)] compared with HCs [3.6 mm (S.D. 0.3)] ($P < 0.001$ for both). The mean PA wall thickness was similar between BD and NIPE ($P = 0.6$). The mean PA wall thickness was significantly higher in patients with major organ involvement compared with mucocutaneous limited disease [4.7 mm (S.D. 0.4) *vs* 3.7 (0.4), $P < 0.001$], whereas it was similar between patients with only mucocutaneous involvement and in HCs [3.7 mm (S.D. 0.4) *vs*

Table 1 Baseline characteristics of patients with BD

Characteristics	Values
Age, years, mean (S.D.)	39.4 (8.8)
Sex, *n* (%)	
Male	47 (61)
Female	30 (39)
Duration of disease, years, mean (S.D.)	10.0 (6.5)
Family history, *n* (%)	22 (28.6)
Pathergy, *n* (%)	
Positive	22 (28.6)
Negative	24 (31.2)
Unknown	15 (19.5)
Follow-up period, months, mean (S.D.)	79.7 (51.1)
BDCAF, median (IQR)	2 (1–2)
Mucocutaneous involvement, *n* (%)	24 (31.2)
Patients with oral ulcers, *n* (%)	76 (98.7)
Patients with genital ulcers, *n* (%)	56 (72.7)
Major organ involvement, *n* (%)	53 (68.8)
Vascular involvement, *n* (%)	36 (46.8)
DVT	13 (16.9)
Pulmonary thrombus	12 (15.6)
DVT + pulmonary thrombus	6 (7.8)
Other[a]	5 (6.5)
Ocular involvement, *n* (%)	24 (31.2)
Neurological involvement, *n* (%)	14 (18.2)
Dural sinus thrombosis, *n* (%)	6 (7.8)
Parenchymal involvement, *n* (%)	8 (10.4)
Gastrointestinal involvement, *n* (%)	2 (2.6)
Articular involvement, *n* (%)	25 (32.5)
Patients receiving colchicine, *n* (%)	51 (66.2)
Patients receiving IS therapy, *n* (%)	50 (64.9)
Azathioprine	42 (54.5)
Mycophenolate mofetil	3 (3.9)
Ciclosporin A	1 (1.3
Other[b]	13 (16.9)
Patients receiving biologic therapy, *n* (%)	11 (14.3)
Infliximab	6 (7.8)
Adalimumab	4 (5.2)
Ustekinumab	1 (1.3)

[a]Other vascular involvements: 1 patient (1.3%) had DVT and intracardiac thrombus, 1 (1.3%) had vena cava superior syndrome and DVT, 1 (1.3%) had a pulmonary artery aneurysm, 1 (1.3%) had superficial thrombophlebitis and 1 (1.3%) had pulmonary thrombus and coronary artery aneurysm. [b]Other ongoing treatments: sulphasalazine, 8 (10.4%); methotrexate, 2 (2.6%); pulse cyclophosphamide, 3 (3.9%).

3.6 (0.3), $P = 0.3$]. In BD patients with major organ involvement, the mean PA wall thickness was also significantly higher than in NIPE and HCs [4.7 mm (S.D. 0.4) *vs* 4.4 (0.5), $P = 0.006$ and 4.7 mm (S.D. 0.4) *vs* 3.6 (0.3), $P < 0.001$, respectively] (Fig. 1).

Among BD patients with major organ involvement, mean PA wall thickness was comparable between patients with vascular and non-vascular major organ involvement [4.6 mm (S.D. 0.5) *vs* 4.7 (0.3), $P = 0.3$]. These patients also had significantly higher mean PA wall measurements compared with NIPE patients ($P = 0.04$ and $P = 0.02$, respectively). The mean PA wall thickness was also significantly higher for patients under IS compared with patients without IS [4.7 mm (S.D. 0.4) *vs* 3.8 (0.4), $P < 0.001$]. In analysis performed by excluding BD patients with pulmonary thrombus from the entire BD cohort, the mean PA wall thickness was 4.3 mm (S.D. 0.6), which was also significantly higher compared with HCs ($P < 0.001$). Intra-observer ($r = 0.9$, $P < 0.01$) and interobserver reliability ($r = 0.9$, $P = 0.01$) was very good in our assessments. There was a positive correlation between age and mean PA wall thickness ($r = 0.24$, $P = 0.02$), however, no relationship was determined between disease duration, disease activity and mean PA wall thickness.

Discussion

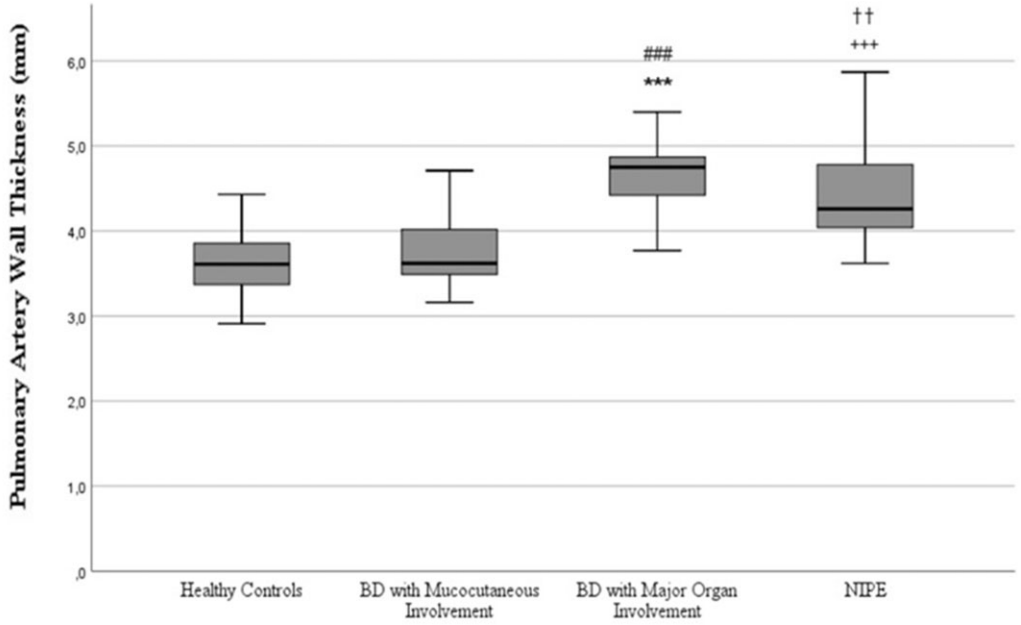
As a disease with venous thromboses as the major vascular event, recent attention in BD has focused on finding evidence of venous wall inflammation by non-invasive imaging methods. In this study, we present for the first time, increased PA wall thickness in BD—similar to vein walls.

The increased PA thickness was limited to patients with major organ involvement, regardless of organ involvement type. However, in a subset of patients with high PA wall thickness in the mucocutaneous group, we observed that they were older, time from the beginning of symptoms to diagnosis was longer and duration of colchicine use was shorter. It can be assumed that these patients may have been exposed to more intense and prolonged inflammation during their disease course. As a supportive observation, Hamuryudan *et al.* [14] reported that the use of colchicine is protective against long-term IS therapy in patients diagnosed with mucocutaneous involvement at an advanced age. In contrast, there are some patients with low PA wall thickness in the major organ group. Since life-threatening major organ involvement developed simultaneously with the diagnosis of these patients, they have used effective IS, therefore early and intensive IS may have rapidly suppressed inflammation in the vessel wall. However, further prospective studies are needed to clarify the effects of colchicine and the type and duration of IS on PA wall thickness.

We did not find a correlation between wall thickness and other clinical parameters except a weak correlation with age. This implies that increased PA thickness may also be an underlying process of pathogenetic vascular mechanisms unassociated with current disease activity.

However, higher PA wall thickness in BD patients with major organ involvement may be a sign of more severe disease. The majority of BD patients in our study were receiving IS for major organ involvement and the PA wall thickness of these patients was higher compared with the patients who did not receive IS, mostly with mucocutaneous involvement with a mild disease course. These findings may confirm the association between higher PA wall thickness and more severe disease course. However, our previous studies demonstrated that the VWTs of BD patients with and without major organ involvement were comparable [7, 15], suggesting that

FIG. 1 Comparison of PA wall thickness of HCs and NIPE and BD patients with major organ and mucocutaneous involvement



***$P < 0.001$ compared with HCs, ###$P < 0.001$ compared with BD with mucocutaneous involvement; ††$P = 0.006$ compared with BD with major organ involvement, +++$P < 0.001$ compared with HCs.

there may be differences in effects of inflammation among different vessel types in BD.

Increased PA wall thickness was also observed in NIPE in our study. The thrombotic process triggered by endothelial damage may be the cause of wall thickening in NIPE [16]. Since 'remodelling' of the vessel wall is thought to have a direct effect on thickness, we made a subgroup analysis after we excluded the BD patients with a history of pulmonary thrombus. It is interesting to note that the mean wall thickness was also higher in this subgroup compared with HCs. In addition, patients with non-vascular major organ involvement had higher wall thickness compared with other study groups. Therefore, increased PA thickness in BD cannot be completely explained by the same mechanisms in NIPE. The cumulative evidence suggests that the pathogenesis of thrombosis in BD is probably not due to a hypercoagulable state, but rather to the vascular damage induced by inflammation or intrinsic endothelial dysfunction resulting in '*in situ* thrombosis'. Also, current limited data support that different layers of arterial wall are affected in BD and NIPE. In BD, inflammatory infiltrates in large arteries are mostly observed in adventitia and media and a concentric wall thickness is demonstrated by imaging [17]. In contrast, increased eccentric wall thickness determined by imaging is accompanied by intimal hyperplasia and medial hypertrophy in NIPE [9]. However, TTE may be insufficient to differentiate which layers are more affected.

TTE may be used as an imaging modality to measure PA wall thickness. Narin *et al.* [18] measured the mean PA wall thickness of paediatric HCs as 3.8 mm and echocardiographic properties were similar to our protocol. Since we aimed to visualize a deep structure such as PA, we preferred a low-frequency transducer, used in routine TTE practice, so depth penetration would not be impaired. The lateral resolution of the transducer ranges from 1.2 to 2.8 mm [19], therefore it is acceptable for the measurements. In terms of ensuring reliability, measurements were made by two different cardiologists, and both had excellent agreement.

Our PA measurements were higher compared with Mackay *et al.*'s [8] histopathologic study. This contradictory result may be due to formalin fixation, which underestimates original thickness. Moreover, the aforementioned technical properties of the transducer, increased dispersion of the sonographic beam towards the deep tissues and high light reflectivity of the elastic fibres of PA may cause distortion of image resolution, resulting in higher measurements [19, 20].

The most important limitation of our study is its cross-sectional design, which limits the interpretation of our results for disease course and prognosis. Also, there is a male predominance in the HC and BD groups, while more female patients are included in NIPE group. The main reason for this is the unwillingness of the patients to participate in the study due to the coronavirus disease 2019 pandemic.

In conclusion, our study showed that PA wall thickness increased in BD patients, mainly with major organ involvement, suggesting that not only veins, but PAs have signs of inflammation in BD. Further longitudinal studies

are planned to investigate the course of PA wall thickness during the follow-up of BD patients.

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Data availability statement

The data underlying this article will be shared upon reasonable request to the corresponding author.

Supplementary data

Supplementary data are available at *Rheumatology* online.

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