Evaluation of pulse wave velocity in systemic lupus erythematosus, rheumatoid arthritis and Behçet’s disease

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Keywords
Arterial dilatation; Systemic lupus erythematosus; Rheumatoid arthritis; Behçet’s disease

Summary
Objectives: Connective tissue diseases involve characteristic inflammatory lesions in the cardiovascular system, in addition to other systems. The involvement of the cardiovascular system in the course of connective tissue diseases may result in serious morbidity and mortality.

Pulse wave velocity which is an indicator of arterial dilatation capacity may predict cardiovascular risk of patients. Pulse wave velocity is inversely proportional to arterial dilatation capacity. Decreased dilatation capacity leads to a reduction in arterial blood pressure and flow dynamics and impairment in coronary perfusion.

Methods: In our study, we examined pulse wave velocity in frequent chronic inflammatory rheumatologic diseases: rheumatoid arthritis, systemic lupus erythematosus, and Behçet’s disease. A total of 98 subjects participated in our study including 24 patients with newly diagnosed rheumatoid arthritis (4 males, 20 females; mean age 42.5 ± 11.5 years), 22 patients with newly diagnosed systemic lupus erythematosus (1 male, 21 females; mean age 35.8 ± 11.1 years), 33 patients with newly diagnosed Behçet’s disease (26 males, 7 females; mean age 32.7 ± 8.0 years), and 19 healthy subjects in the control group (10 males, 9 females; mean age 36.2 ± 15.0 years). Aorta pulse wave velocity was determined by Compilior Colson (Cratech Industrie, Garges les Gonesses, France) device which allowed for pulse wave recording and automated measurement.

Results: Pulse wave velocity was higher in rheumatoid arthritis, systemic lupus erythematosus, and Behçet’s disease groups compared to the control group. When all variables were included in the regression analysis only age was found to affect pulse wave velocity independently.

Conclusion: Pulse wave velocity was found to be high in chronic inflammatory connective tissue diseases compared to the control group. However, no difference was found between groups. Age was determined as the most important independent variable in the regression analysis.

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Introduction

Connective tissue diseases involve characteristic inflammatory lesions in the cardiovascular system, in addition to other systems. The involvement of the cardiovascular system in the course of connective tissue diseases may result in serious morbidity and mortality [1–3].

Atherosclerosis develops in the process of cardiovascular aging while several rheumatologic diseases accelerate this process [4].

Invasive or non-invasive methods are used for atherosclerosis. Non-invasive methods which are preferred for being simple and their ease of use include hysteresis of pressure—diameter curves, arterial diameter waveform, arterial pressure waveform, arterial wall thickness, viscoelastic parameters, relative arterial compliance calculated by classical formula of Bramwell and Hill [volume change (dV) ratio induced by the change in transmural tension pressure (dP) (dV/dP)] and pulse wave velocity (PWV) measurement [5–7].

Arterial stiffness is increasingly recognized as a surrogate end point for cardiovascular disease. The measurement of aortic PWV, which is considered the gold standard method for assessing aortic stiffness, is a tool for assessment of subclinical organ damage [8]. Measurement of PWV is one of the major methods to determine the elasticity of large vessels and is based on the measurement principal using two ultrasound or pressure sensitive transducers placed on the skin above traces of two arteries in a specific distance (carotid–femoral arteries are used in our study) [5]. Measured PWV is an indicator of arterial wall stiffness and also inversely proportional to arterial dilatation capacity or arterial compliance [2]. Similar to arterial elasticity, PWV and arterial dilatation capacity index are also affected by heart rate and blood pressure [6]. Pulse pressure and PWV are supported in studies in which they are predictors of cardiovascular diseases in the general population and in patients with hypertension, diabetes, advanced age, and end stage renal failure [7–14].

Systemic lupus erythematosus (SLE) is a disease characterized by generalized inflammation of connective tissues and vessel structures particularly in young women. This systemic disease is associated with hypertension [15], myocardial infarction [15,16], and risk of stroke. While the pathogenesis of vascular disease in SLE is not clearly understood, it is considered to be multifactorial and that atherosclerotic factors have a role [17].

Behçet’s disease (BD) is a diffuse vasculitic disease characterized by repeated genital and oral ulcerations and uveitis. Dilatation developed in proximal aorta as a result of diffuse aortitis may cause severe aorta failure requiring valve replacement [18]. Deep vein and arterial thrombosis, and aortic and arterial aneurysm may occur in the course of disease.

Rheumatoid arthritis (RA) is a systemic inflammatory disease associated with accelerated atherosclerosis and consequently increased cardiovascular mortality and morbidity [19]. This inflammation results in endothelial dysfunction. The changes in arterial compliance and elasticity have an important role in the initiation and progression of atherosclerosis.

Arterial pulse wave velocity

Currently, cardiovascular diseases are important causes of mortality. It is not clearly understood how atherosclerosis begins and progresses in large arteries. Because the atherosclerosis process and most cardiovascular risk factors are insidious, the early diagnosis of arterial changes and functional and/or structural lesions will be useful in identifying individuals under high risk for clinical events. Conducting dynamic studies on large arteries is difficult because blood flow is pulsatile in nature; vessel wall has a complex structure and the tonus of the smooth muscle component differs continuously [20]. PWV was developed to evaluate the viscoelasticity of large vessels in human.

The measurement of PWV is one of the important methods to identify the elasticity properties of arteries. It is based on the measurement principal using two ultrasound or pressure sensitive transducers placed on the skin above the traces of two arteries in a specific distance (such as carotid–femoral, brachial–radial arteries) [5]. Measured PWV is an indicator of arterial wall stiffness and also inversely proportional to arterial dilatation capacity (dilatation capacity) or relative arterial elasticity (elasticity) [6]. Additionally, aortic PWV is a strong predictor of future cardiovascular events and all-cause mortality [8].

Age and atherosclerosis show more significant impact on central and elastic arteries. In both genders, the velocity levels of aorta pulse wave (carotid–femoral or body PWV) increase with age. The studies using non-interventional techniques based on pressure waves or blood flow rate showed that advancing age increases the aorta or carotid–femoral PWV [21,22]. A study was conducted in a Chinese population who are known to have a low prevalence of atherosclerosis, to analyze the effect of age on arterial stiffness [21]. According to this study, the values for central PWV were lower than the values of peripheral PWV.

The objective of this study was to evaluate arterial dilatation capacity by carotid–femoral PWV in newly diagnosed SLE, RA, and BD and to determine the relationship between them for arterial dilatation capacity.

Materials and methods

A total of 98 subjects participated in our study including 24 patients with newly diagnosed RA (4 males, 20 females; mean age 42.5 ± 11.5 years), 22 patients with newly diagnosed SLE (1 male, 21 females; mean age 35.8 ± 11.1 years), 33 patients with newly diagnosed BD (26 males, 7 females; mean age 32.7 ± 8.0 years), and 19 healthy subjects in the control group (10 males, 9 females; mean age 36.2 ± 15.0 years). Written consent was obtained from all participants.

Patients with secondary or treatment-resistant hypertension, diabetes, hyperlipidemia (total cholesterol levels ≥200 mg/dL), heart failure, renal failure (plasma creatinine >1.5 mg/dL), hepatic failure, heart valve disease, peripheral vessel disease, cerebrovascular disease, and previous myocardial infarction anamnesis, identified to have atrial fibrillation and/or previous myocardial infarction findings in 12-lead surface electrocardiography, smokers, and in the case of affecting measurement results for technical
reasons patients having body mass index of $\geq 35$ kg/m$^2$ and waist to hip ratio of $\geq 1$ were excluded from the study. Patients having active diseases and using immunosuppressant agents (steroid, azathioprine, methotrexate, and cyclophosphamide) were not included in the study.

**Measurements**

The weight and height of participants with light clothing and bare feet were measured using standard scales with mobile ruler marker and an arm capable of weight measurement. Body mass index (kg/m$^2$) was calculated by dividing weight in kg to height in m.$^2$.

Waist circumference (cm) was measured at the middle line between last rib and crista iliaca after ensuring the participant was standing straight, relaxed abdomen with arms down and feet closed. Hip circumference (cm) was measured at the line of trochanter major. Waist–hip ratio was calculated by dividing waist circumference to hip circumference.

Arterial blood pressure was measured with a standard mercury monomer (ERKA, Bad Tölz, Germany) in the lying position after 30 min of rest. Systolic blood pressure was considered as the point in which Korotkoff sounds were first heard; diastolic blood pressure was considered as the point that the sounds disappear (phase 5).

The following formulations were used:

- **Pulse pressure**
  
  \[ \text{Pulse pressure} = \text{systolic blood pressure} - \text{diastolic blood pressure} \]

- **Mean blood pressure**
  
  \[ \text{Mean blood pressure} = \frac{\text{systolic blood pressure} + 2 \times \text{diastolic blood pressure}}{3} \]

- Heart rate was determined by counting for 1 min after the blood pressure measurement from radial artery.

**Measurement of carotid–femoral pulse wave velocity**

Aorta PWV was calculated as mentioned above, using Complior device (Createch Industrie, Garges les Gonesse, France) which allows for automated pulse wave recording and automated calculation of PWV [23]. The correlation coefficient of automated measurement method for interobserver measurements and for measurements between different time points by one observer was $>0.9$. Carotid communis and femoral arterial pressure waveforms were measured non-invasively by using TY-306 Fukuda (Fukuda, Tokyo, Japan) pressure sensitive transducer. Measurements were repeated in cardiac cycle for more than 10 phases and mean value was used for analyses of results. PWV was calculated automatically by the following formula:

\[ \text{PWV} = \frac{\Delta D}{\Delta t} \]

$\Delta D$ is the distance between two recording points taken by pulse wave on body surface (m) and $\Delta t$ the pulse wave transition time automatically determined by Complier device (s).

**Statistical evaluation**

Statistical analysis was conducted by using IBM SPSS version 13.0 ready to use statistical program (IBM, Armonk, NY, USA). Inter-group comparisons were conducted by using one-way ANOVA and post hoc Tukey test. Regression analysis method was used for independent variables that may affect PWV. Results were expressed as mean $\pm$ standard deviation. Statistical significance was $p < 0.05$.

**Results**

A total of 98 subjects participated in our study including 24 patients with newly diagnosed RA, 22 patients with newly diagnosed SLE, 33 patients with newly diagnosed BD, and 19 healthy subjects in the control group.

The mean values of connective tissue diseases of SLE, RA, BD, and the control group are presented in Table 1. The inter-group analyses with one-way ANOVA and post hoc Tukey test showed statistical significance only between age ($p = 0.01$) and PWV ($p = 0.007$). No significance was determined in the inter-group analyses for body mass index, waist–hip ratio, systolic blood pressure, diastolic blood pressure, mean blood pressure and pulse pressure, and heart rate ($p > 0.05$).

According to age groups in which significance was determined, age was higher in the RA group compared to the BD group ($p = 0.009$). There was no significant difference for age between the control group and connective tissue diseases ($p > 0.05$).

PWV was higher in SLE, BD, and RA groups compared to the control group (respectively, $p = 0.019$; $p = 0.012$; $p = 0.018$).

**Regression analysis**

When all variables were included in the regression analysis ($R = 0.51$; $R^2 = 0.26$; $p = 0.001$; $F = 3.563$) only age was found to affect PWV independently ($p < 0.001$; $t = 3.903$). No significance was determined for gender ($p = 0.86$). The correlation of PWV as an independent variable with other parameters is given in Table 2.

**Discussion**

We evaluated the PWV by using carotid–femoral PWV in connective tissue diseases concurrent with chronic inflammatory processes such as RA, SLE, and BD in our study. An increase in carotid–femoral PWV was determined in all patients who participated in our study compared to the control group.

Connective tissue diseases are mainly considered as diseases of the musculoskeletal system, while they can involve the cardiovascular system, characterized by inflammatory lesions. Generally, the most important cause of mortality and morbidity in connective tissue diseases is cardiovascular involvement [1,4,19].
The importance of cardiovascular diseases in rheumatologic diseases became significant as a result of prolonged life time with the improvements in the treatment of rheumatologic diseases, the recognition of the importance of inflammation, the better understanding of the impact of the immune system on atherosclerosis, and the usage of improved non-invasive diagnostic methods for cardiovascular diseases.

Inflammation causes endothelial dysfunction and atherosclerosis. Endothelial dysfunction characterized by decreased nitric oxide bioavailability comprises the early stage of atherosclerosis [22]. Inflammation, which is the basis for atherosclerosis, and the damage in vessel walls lead to an increase in arterial stiffness. Atherosclerosis and its impacts on vessels can be identified by non-invasive techniques [23]. One of these techniques is the measurement of PWV which is an indicator for arterial dilatation capacity and defined as the velocity of arterial wave through the vessel [22,23]. The patients who have an increased cardiovascular and cerebrovascular risk can be determined by PWV [23]. PWV is an indicator of arterial wall stiffness and also inversely proportional to arterial dilatation capacity (dilatation) or relative arterial elasticity (elasticity) [6].

Several biochemical markers have been used to examine different aspects of endothelial cell functions such asymmetrical dimethylarginine, soluble intercellular adhesion molecule-1, soluble vascular cell adhesion molecule, plasminogen activator inhibitor-1, and tissue plasminogen activator. Although the ability of these parameters to detect endothelial dysfunction before overt cardiovascular disease make them attractive tools, determination of these parameters is not easy and cost-effective [24].

### Rheumatoid arthritis

We found that carotid–femoral PWV was increased in the RA group, the prototype of systemic inflammatory diseases in which accelerated atherosclerosis and increased cardiovascular mortality and morbidity is present, compared to the control group (9.26±2.16 m/s vs. 7.53±0.80 m/s, p=0.018). This finding is consistent with other studies [22,25,26]. The inflammation produced in the course of RA impairs endothelial function and plays an important role in the initiation and progression of atherosclerosis. Carotid–femoral PWV, which is an important indicator of inflammation, is increased during this process. Arterial stiffness is associated with the duration of the disease and inflammatory mediators [27]. In this study, the increased PWV of patients with newly diagnosed RA shows that inflammation has previously affected endothelium.

Endothelial dysfunction has been implicated as an important event in the pathogenesis of arteriosclerosis, coronary vasoconstriction, hypertension, and myocardial ischemia especially during connective tissue diseases. Ghelani et al. [28] reported that during Kawasaki disease without overt coronary artery involvement, there are significant differences for the percent flow mediated dilatation and carotid artery stiffness index between children with Kawasaki disease and controls. Another report from Hamako et al. [29] showed that fluvastatin treatment changed the PWV. There was a significant decrease after 12 months of treatment.

### Systemic lupus erythematosus

Inflammation was shown to be positively correlated with atherosclerosis in SLE, which is a chronic inflammatory disease characterized with increased atherosclerosis.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Mean values of the parameters of systemic lupus erythematosus (SLE), Behçet’s disease (BD), and rheumatoid arthritis (RA) and control group.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control group</td>
</tr>
<tr>
<td>Age</td>
<td>36.2 ± 15.0</td>
</tr>
<tr>
<td>Waist–hip ratio</td>
<td>0.86 ± 0.0</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>111.05 ± 11.50</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td>71.05 ± 7.37</td>
</tr>
<tr>
<td>Heart rate</td>
<td>74.53 ± 9.01</td>
</tr>
<tr>
<td>Pulse wave velocity</td>
<td>7.53 ± 0.80</td>
</tr>
<tr>
<td>Body mass index</td>
<td>25.89 ± 3.88</td>
</tr>
<tr>
<td>Pulse pressure</td>
<td>41.57 ± 11.18</td>
</tr>
<tr>
<td>Mean blood pressure</td>
<td>84.89 ± 7.47</td>
</tr>
</tbody>
</table>

* The inter-group analyses with one-way ANOVA and post hoc Tukey test showed: age was higher in RA group compared to BD group (p = 0.009).

** The inter-group analyses with one-way ANOVA and post hoc Tukey test showed: pulse wave velocity was higher in SLE, BD, and RA groups compared to control group (respectively, p = 0.019; p = 0.012; p = 0.018).

<table>
<thead>
<tr>
<th>Table 2</th>
<th>The correlation of pulse wave velocity with other parameters.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulse wave velocity</td>
<td>ρ</td>
</tr>
<tr>
<td>Age</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Waist–hip ratio</td>
<td>0.46</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>0.05</td>
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<tr>
<td>Diastolic blood pressure</td>
<td>0.57</td>
</tr>
<tr>
<td>Heart rate</td>
<td>0.94</td>
</tr>
<tr>
<td>Body mass index</td>
<td>0.48</td>
</tr>
<tr>
<td>Pulse pressure</td>
<td>0.86</td>
</tr>
<tr>
<td>Mean blood pressure</td>
<td>0.44</td>
</tr>
</tbody>
</table>
particularly in young women [30]. We found that carotid–femoral PWV was increased in the 22 patients with SLE who participated in our study, compared to 19 control subjects (9.29 ± 2.46 m/s vs. 7.53 ± 0.80 m/s, p = 0.019). The study conducted by Yildiz et al. [31] showed that arterial dilatation capacity was decreased in female post-menopausal patients with SLE. In our study, the increased PWV of patients with newly diagnosed SLE shows that inflammation has affected endothelium before musculoskeletal system, similar to RA.

Behçet’s disease

The reason for vascular involvement in BD, which appears with oral aphthous and genital ulcers, skin lesions, and uveitis, is considered to be vasculitis. We compared 33 patients with BD with a control group including 19 healthy subjects in our study. Carotid–femoral PWV increased significantly in the BD group compared to the control group (9.23 ± 1.64 m/s vs. 7.53 ± 0.80 m/s, p = 0.012). This finding is supported with the results of the study by Chang et al. [32], but in another study, it was reported that there was no difference between BD and control group for PWV [33]. A study conducted by Kurum et al. [33] included 14 patients with BD and showed no difference with healthy control group for PWV. This may be due to the small number of patients who participated in the study. Our study supports the hypothesis that inflammation seen in the course of BD impairs vascular function and increases arterial stiffness.

Although PWV was found to be higher in connective tissue diseases compared to the control group, no difference between disease groups was determined. Therefore, it may be concluded that arterial stiffness is increased equally in chronic inflammatory rheumatologic diseases.

Relation with age

In elder individuals, arteries are less elastic and velocity of pulse wave is high; reflected wave can be observed in ascending arm of systolic pressure. The typical changes in the pattern of pulse wave with age are attributed to increased aorta stiffness and PWV [23,33,34]. Several studies also showed that aorta PWV levels (carotid–femoral or body PWV) were increased with age [21,35]. In our study, although there was a significant difference only between patients with BD and RA for age, no difference was found when control groups were compared with other groups. In the regression analysis of all variables, age was found to be the most important independent variable. The detection of increase of PWV parallel to advanced age is supported by other studies [36].

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References

Evaluation of arterial dilatation capacity