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Original research article

The fact not to ignore: Mean blood pressure is the main predictor of increased arterial stiffness in patients with systemic rheumatic diseases

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ABSTRACT

Purpose: We aimed to evaluate the association between carotid-radial pulse wave velocity (PWV), augmentation index (AIx), and flow-mediated dilatation (FMD) of the brachial artery and factors potentially influencing them in patients with rheumatoid arthritis (RA), systemic lupus erythematosus (SLE) and systemic sclerosis (SSc).
Material and methods: 316 patients diagnosed with RA (32%), SLE (20%), SSc (16%) and 156 controls (32%) were included in the study. Parameters of arterial stiffness AIx and PWV were obtained using applanation tonometry. FMD reflecting endothelial function was measured by ultrasound.
Results: AIx was increased in all three diseases ($p < 0.0001$), but no differences were found between rheumatic diseases. In most of the RA cases PWV values were abnormal (on average by 0.52 m/sec higher than in controls), while in SSc patients FMD values were diminished ($p = 0.006$). Mean blood pressure (MBP) was the most consistent predictive factor in all three diseases, influencing both PWV and AIx, although patient age was also important in variation of AIx. The disease activity score (DAS28) was relevant only in RA patients. Furthermore, SLE disease activity index in SLE or Rodnan skin thickness score had no statistical significance in SSc and inflammatory markers.
Conclusions: Both, PWV and AIx are dependent on MBP and age DAS28 may affect AIx in RA patients, while other disease or inflammatory markers are unlikely to have any effect. MBP is one of the main cardiovascular risk factors affecting the arterial stiffness in RA, SLE and SSc patients therefore controlling MBP in systemic rheumatic disease patients is mandatory.

1. Introduction

It has been widely demonstrated that systemic rheumatic diseases are associated with accelerated development of atherosclerosis and increased cardiovascular morbidity and mortality compared to general population [1,2]. They may affect all parts of the vascular system, from small to large arteries. The term 'accelerated atherosclerosis' has been introduced in order to explain the complex interaction between inflammation, enhanced lipid oxidation, antibodies to oxidized low-density lipoprotein, dyslipidaemia, cigarette smoking and concomitant steroid treatment in patients with rheumatic diseases [3]. Although rheumatoid arthritis (RA) has been studied extensively, growing evidence now demonstrate excess cardiovascular risk in other rheumatic diseases, such as systemic lupus erythematosus (SLE) and systemic sclerosis (SSc) [4,5].

Identifying patients at risk of developing cardiovascular disease (CVD) becomes a challenge. Accumulating evidence suggests that vascular stiffness is the early marker of atherosclerosis that can be detected before structural changes in the vessel wall are apparent on angiography or ultrasound [6–8]. Different factors play a role on vascular stiffness in rheumatic diseases: a) increased amounts of pro-atherogenic hormones, decreased amounts of anti-atherogenic hormones and increased insulin resistance in rheumatoid arthritis; b) autoantibodies production in systemic lupus erythematosus; c) smooth muscle cells proliferation, destruction of internal elastic lamina, fibrosis and coagulation and fibrinolytic system dysfunction in systemic sclerosis [9]. There is evidence that RA patients present with more pronounced vascular stiffness and increased subclinical atherosclerosis compared to age-matched

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controls [10,11]. Same as in RA, high prevalence of CVD is also observed in SLE patients [5,12]. It remains unclear whether accelerated atherosclerosis occurs in SSc, as studies aimed to investigate subclinical atherosclerosis risk in SSc patients produced contrasting data [13,14]. However, the level of inflammation in SSc is lower than in RA and SLE. Thus, the atherosclerotic process may not be as aggressive and not as easily detectable in a small number studies [14].

Two major estimates of vascular function, particularly augmentation index (AIx), indicating systemic arterial stiffness, and flow-mediated dilatation (FMD), the parameter of the endothelial function, and to a lesser extent carotid-radial pulse wave velocity (PWV), the parameter of regional arterial stiffness, have been intensively explored in various ways during the last decade in rheumatic patients. The vast majority of these studies reported that endothelial function was significantly impaired in patients with RA compared to healthy controls [15,16]. Similar to RA, endothelial function and arterial stiffness has been widely used as a surrogate endpoint for CVD in patients with SLE. Multiple studies have shown that patients with SLE had a greater extent of endothelial dysfunction and arterial stiffness compared to controls, and increased arterial stiffness was associated with traditional cardiovascular risk factors, as well as SLE related risk factors, such as higher organ damage and activity indices, longer duration of disease and increased inflammatory biochemical markers [17–19]. Recently, the amount of evidence showing that endothelial dysfunction and arterial stiffness are more prevalent among SSc patients than in the general population has been increasing [20,21]. However, the mechanisms of development of endothelial dysfunction and stiffening of arteries in RA, SLE and SSc patients remain unclear, and it continues to be an area of active research. Based on the facts mentioned above the major aim of this study was to evaluate and compare arterial stiffness and endothelial dysfunction in patients with ARD and healthy population.

2. Materials and methods

2.1. Patient data

In this cross sectional study we examined 316 consecutive patients with an established RA (149 patients), SLE (93 patients), SSc (74 patients) diagnosis and 156 controls between 2006 and 2014 at Vilnius University hospital Santariskiu Klinikos. Demographic, clinical and laboratory data including fasting lipid profile and inflammation markers were obtained from patients and control subjects a day before taking the arterial measurements. Ethical approval for this research was granted in 2010-12-08 by the regional ethical committee for biomedical research (no. 158200-12-268-61). The mean age of patients was 48.88 (±13.52) years, 89.6% of the patients were women. The median disease duration was 11 years, ranging from 0 to 42 years. All patients presented their written informed consent to participate in the study.

The comparison of available characteristics of patients and control group is presented in Table 1. There were significant differences between patient and control groups with respect to their baseline characteristics. The patient population was older, there were more female patients, furthermore, mean blood pressure (MBP), total cholesterol, triglyceride and C reactive protein (CRP) values were significantly higher in this group. Treatment received during the last 6 months was also recorded and is presented in detail in Table 2. Treatment received by different patient groups can be summarized as follows: 89.3% in RA group, 80.7% in SLE group and 54% in SS group received disease modifying medications including biologicals. Antihypertensive medications were used by the majority of SSc patients–87.8%, and to a lesser extent in SLE and RA groups, 43% and 26.8%, respectively. Almost all of the patients in RA and SLE groups received steroids.

2.2. Non-invasive assessment of arterial stiffness

Subjects refrained from eating and drinking alcohol, coffee or tea for 12 hours prior to the study. Patients continued to take their medications for disease control. The test of arterial stiffness was performed in the supine position in a quiet, temperature controlled room (22–24 °C) in the morning. PWV was determined by measuring the carotid-to-radial pulse wave transit time. Carotid and radial pulse waves, MBP were obtained non-invasively by applanation tonometry using high-fidelity micromanometer (Sphygmocor v.7.01 AtCor Medical Pty. Ltd). AIx was calculated from radial pulse waves of the non-dominant arm as previously described in detail [22]. Blood pressure was recorded using an automatic BP monitor (HEM-757; Omron Corporation, Japan).

2.3. Non-invasive assessment of endothelial function

An endothelium-dependent FMD test in the brachial artery was performed according to the method described by Celermajer et al.

Table 1
The comparison of demographic and clinical characteristics between rheumatic patients and healthy population.

	Patients (n = 316)				Healthy (n = 156)	P**
	Total	Rheumatoid arthritis (n = 149)	Systemic lupus erythematosus (n = 93)	Systemic sclerosis (n = 74)		
Age, yr*	48.88 (13.52)	51.67 (13.44)	40.72 (11.53)	53.32 (11.14)	42.84 (11.05)	<0.0001
Disease duration, yr	11.02 (0-42)	11.39 (8.91)	9.20 (0–31)	5.42 (0.5–42)	–	–
Female, n (%)	283 (89.6)	131 (87.3)	92 (92.9)	73 (90.1)	114 (73.1)	<0.0001
Body mass index, kg/m^2	24.973 (4.91)	25.28 (4.63)	24.60 (5.50)	24.59 (4.65)	24.752 (3.76)	0.590
Mean blood pressure, mmHg	97.35 (12.00)	98.36 (11.69)	97.43 (11.83)	95.80 (13.51)	92.19 (9.91)	<0.0001
Total cholesterol, mmol/l	5.59 (1.32)	5.52 (1.28)	5.69 (1.33)	5.54 (1.33)	5.26 (1.13)	0.009
Low density lipoprotein cholesterol, mmol/l	3.41 (1.10)	3.41 (1.11)	3.36 (0.95)	3.44 (1.21)	3.32 (0.98)	0.407
High density lipoprotein cholesterol, mmol/l	1.47 (0.48)	1.52 (0.40)	1.89 (1.62)	1.36 (0.63)	1.49 (0.35)	0.654
Triglycerides, mmol/l	1.53 (1.05)	1.27 (0.56)	1.89 (1.62)	1.58 (0.63)	0.97 (0.51)	<0.0001
Erythrocyte sedimentation rate, mm/hr	35.32 (26.02)	41.62 (28.27)	28.38 (2–27)	30.79 (2–120)	–	–
C reactive protein, mmol/l	4.61 (0.06-185)	13.10 (0.06-185)	4.48 (0.10–49.30)	8.25 (0.20-83.60)	1.51 (0.07–21.60)	<0.0001

* For continuous variables – mean (SD) or median (min-max).
** p value presents the statistical significance between total patients group and healthy persons.