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A comparative study of arterial stiffness, flow-mediated vasodilation of the brachial artery, and the thickness of the carotid artery intima?media in patients with systemic autoimmune diseases
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80 Abstract

Patients with autoimmune diseases may have increased vascular risk leading to higher mortality rates. Novel imaging techniques are necessary for the early assessment and management of these patients. In this study, we compared augmentation index (AIx) and pulse wave velocity (PWV), indicators of arterial stiffness, to brachial arterial flow-mediated vasodilation (FMD) and common carotid artery intima–media thickness (ccIMT), standard indicators of endothelial dysfunction and atherosclerosis, respectively. We wished to assess the vascular status of autoimmune patients by using a novel, cheap, and reproducible technique, the arteriograph. Altogether, 101 patients with systemic autoimmune diseases including primary antiphospholipid syndrome, systemic sclerosis, rheumatoid arthritis, and polymyositis, all having various types of vasculopathies, as well as 36 healthy individuals were investigated. Arterial stiffness was assessed by a TensioClinic arteriograph, a recently validated technique. Brachial arterial FMD and ccIMT were determined using high-resolution ultrasonography. Autoimmune patients exerted impaired FMD (3.7 ± 3.8%), increased ccIMT (0.7 ± 0.2 mm), AIx (1.2 ± 32.2%), and PWV (9.7 ± 2.4 m/s) in comparison to control subjects (FMD = 8.4 ± 4.0%; ccIMT = 0.6 ± 0.1 mm; Aix = −41.1 ± 22.5%; PWV = 8.0 ± 1.5 m/s; $p < 0.05$). We found a significant negative correlation of FMD with AIx ($R = -0.64$; $p < 0.0001$) and PWV ($R = -0.37$; $p = 0.00014$). There were significant positive correlations between ccIMT and AIx ($R = 0.34$; $p = 0.0009$), ccIMT and PWV ($R = 0.44$; $p < 0.0001$), as well as AIx and PWV ($R = 0.47$; $p < 0.0001$). AIx, PWV, and ccIMT positively correlated and FMD negatively correlated with the age of the autoimmune patients. Arterial stiffness indicated by increased AIx and PWV may be strongly associated with endothelial dysfunction and overt atherosclerosis in patients with autoimmune diseases. Assessment of arterial stiffness, FMD, and ccIMT are reproducible and reliable noninvasive techniques for the complex assessment of vascular abnormalities in patients at high risk.

81 Keywords separated by ' - ' Antiphospholipid syndrome - Arterial stiffness - Atherosclerosis - Endothelial dysfunction - Polymyositis - Rheumatoid arthritis - Scleroderma

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ORIGINAL ARTICLE

A comparative study of arterial stiffness, flow-mediated vasodilation of the brachial artery, and the thickness of the carotid artery intima–media in patients with systemic autoimmune diseases

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Abstract Patients with autoimmune diseases may have increased vascular risk leading to higher mortality rates. Novel imaging techniques are necessary for the early assessment and management of these patients. In this study, we compared augmentation index (AIx) and pulse wave velocity (PWV), indicators of arterial stiffness, to brachial arterial flow-mediated vasodilation (FMD) and common carotid artery intima–media thickness (ccIMT), standard indicators of endothelial dysfunction and atherosclerosis, respectively. We wished to assess the vascular status of autoimmune patients by using a novel, cheap, and reproducible technique, the arteriograph. Altogether, 101 patients with systemic autoimmune diseases including primary antiphospholipid syndrome, systemic sclerosis, rheumatoid arthritis, and polymyositis, all having various types of vasculopathies, as well as 36 healthy individuals were investigated. Arterial stiffness was assessed by a TensioClinic arteriograph, a recently validated technique. Brachial arterial FMD and ccIMT were determined using high-resolution ultrasonography. Autoimmune patients exerted impaired FMD (3.7±3.8%), increased ccIMT (0.7±0.2 mm), AIx (1.2±32.2%), and PWV (9.7±2.4 m/s) in comparison to control subjects (FMD=8.4±4.0%; ccIMT=0.6±0.1 mm; Aix=−41.1±22.5%; PWV=8.0±1.5 m/s; $p<0.05$). We found a significant negative correlation of FMD with AIx ($R=-0.64$; $p<0.0001$) and PWV ($R=-0.37$; $p=0.00014$). There were significant positive correlations between ccIMT and AIx ($R=0.34$; $p=0.0009$), ccIMT and PWV ($R=0.44$; $p<0.0001$), as well as AIx and PWV ($R=0.47$; $p<0.0001$). AIx, PWV, and ccIMT positively correlated and FMD negatively correlated with the age of the autoimmune patients. Arterial stiffness indicated by increased AIx and PWV may be strongly associated with endothelial dysfunction and overt atherosclerosis in patients with autoimmune diseases. Assessment of arterial stiffness, FMD, and ccIMT are reproducible and reliable noninvasive techniques for the complex assessment of vascular abnormalities in patients at high risk.

Keywords Antiphospholipid syndrome · Arterial stiffness · Atherosclerosis · Endothelial dysfunction · Polymyositis · Rheumatoid arthritis · Scleroderma

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Introduction

Vascular endothelial dysfunction is associated with the development and progression of atherosclerosis (reviewed in [1]). Endothelial dysfunction leads to increased vasoconstriction, increased prothrombotic potential, and abundant production of reactive oxygen intermediates (ROI) [1]. Classical cardiovascular risk factors, such as hypertension, dyslipidemia, diabetes mellitus, and smoking, promote oxidative stress and further enhance endothelial dysfunction [1–3]. Atherosclerosis is considered to be an inflammatory condition, as monocyte/macrophages, activated smooth muscle cells, as well as inflammatory cytokines produced by these cells are involved in its pathogenesis [4–6].

Accelerated atherosclerosis and increased cardiovascular mortality have been described in systemic rheumatic diseases, such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), antiphospholipid syndrome (APS), systemic sclerosis (SSc), and dermatopolymyositis (DM/PM) (reviewed in [7, 8]). Numerous epidemiological, clinical, and laboratory investigations suggested that chronic inflammation and immune dysregulation exert a key role in accelerating atherosclerosis in these autoimmune diseases [7–25]. Among pathogenic factors, classical, Framingham, as well as nontraditional, inflammatory risk factors have been implicated in vascular disease underlying autoimmunity [9–18, 21–25].

Different laboratory and imaging methods and novel diagnostic procedures became very valuable for the prediction of early atherosclerotic lesions in these patients [29–36]. In 1992, Celermayer et al. [31] described the assessment of flow-mediated vasodilation (FMD) of the brachial artery. This technique is based on the principle that because of shear forces due to flow increase in the brachial artery, endothelial cells are activated, nitrogen monoxide (NO) synthase and thus NO is abundantly produced by endothelial cells eventually leading to vasodilation. In early atherosclerosis, FMD indicating endothelial dysfunction becomes abnormal first [31, 32]. Therefore, the reduced dilation capability of the arteries can be observed at very early stages [31–35]. By definition, if vasodilation does not reach 5%, there is overt endothelial dysfunction [32]. The assessment of the intima–media thickness of the common carotid artery (ccIMT) is a standard method to assess overt atherosclerosis [10, 18, 36]. Finally, pulse wave velocity (PWV) and augmentation index (AIx) are parameters of arterial stiffness and wave reflection. PWV and AIx may be assessed by the recently validated new oscillometric method, arteriograph [29, 30], as well as broadly accepted tonometric (SphygmoCor) and piezoelectronic (Complior) systems [29].

The major aim of this study was to assess autoimmune patients with cardiovascular abnormalities using arteriograph for the first time. We also wished to compare arterial stiffness assessed by arteriograph to FMD and ccIMT, standard indicators of endothelial dysfunction and overt atherosclerosis, respectively, in patients with systemic autoimmune diseases and healthy control individuals.

Materials and methods

Patients

Altogether, 101 patients (77 females, 24 males; mean age= 52.3±13.3 years) with various systemic autoimmune diseases undergoing regular follow-ups in our institution have been selected. This patient cohort included subjects with primary APS (n=50), SSc (n=24), PM (n=13), and RA (n=14). For comparison, 36 healthy individuals matched for sex (26 females, 10 males), age (50.3±10.4 years), and Framingham risk factors served as controls. None of the autoimmune patients or controls smoked, had overt atherosclerosis, cardiovascular, cerebrovascular, or peripheral vascular disease, hypertension, dyslipidemia, or other confounding conditions. None of the autoimmune patients received systemic corticosteroid or non/steroidal anti-inflammatory drug treatment at least 3 months before the study.

Assessment of flow-mediated vasodilation

Measurements were carried out on the patients' right arms by using Hewlett-Packard (HP) Sonos 5500 high-resolution duplex ultrasound instrument (Soma Technology, Bloomfield, CT, USA) using a 10-MHz linear transducer and electrocardiogram gating as described before [10, 21, 31, 34, 35]. Briefly, longitudinal images were taken, based on individual anatomical variability, 4–7 cm proximally from the cubital fossa. Systolic blood pressure was maintained over 50 mmHg for 5 min by inflating the cuff. Subsequently, reactive hyperemia was induced by the quick release of the cuff. We detected and digitally saved the arterial diameter at rest and then the change in the diameter due to increased flow after 60 s. Results were analyzed offline by using the AVITA software (Gtech Information Systems, Oak Brook, IL, USA) [36]. The mean diameter was determined as the mean of three subsequent measurements performed synchronously with the R wave of the heart cycle [34, 35]. Change of FMD is presented as the percentage of increase or decrease in the arterial diameter after flow in comparison to the resting value. All assessments were performed by the same investigator in the morning hours, in an air-conditioned room at 21°C, after overnight fasting of the patient and resting for 30 min. All patients and control subjects were nonsmokers. In the morning of the measurements, participants were not

t1.1 **Table 1** Parameters of endothelial dysfunction, atherosclerosis, and arterial stiffness in autoimmune patients and controls

t1.2		Patients (n=101)	Controls (n=36)	p value
t1.3	FMD (%)	3.66±3.82	8.39±4.03	<0.0001
t1.4	ccIMT (mm)	0.70±0.18	0.58±0.08	0.001
t1.5	AIx (%)	1.22±32.25	−41.15±22.47	<0.0001
t1.6	PWV (m/s)	9.66±2.40	8.00±1.46	0.0002

Values are the mean±standard deviation

FMD flow-mediated vasodilation, *ccIMT* common carotid artery intima–media thickness, *AIx* augmentation index, *PWV* pulse wave velocity

allowed to drink coffee, tea, or to take antioxidant vitamins. No vasoactive drugs were allowed 24 h before the assessments. (The half-life of all vasoactive drugs administered prior to the study was less than 24 h.)

Evaluation of the carotid artery intima–media thickness

ccIMT was determined by high-resolution Duplex ultrasonography using the HP Sonos 5500 instrument described above equipped with 5–10 MHz linear transducer [10, 21, 36]. In brief, longitudinal and transverse section images were taken of the carotid system. If no plaques could be detected applying mediolateral transducer position, longitudinal images were captured of the common carotid arteries, 10 mm proximally from the carotid bulb. Images were captured in the end-diastolic phase and ccIMT data were evaluated offline using the AVITA software [36]. ccIMT was recorded as the distance between the first (lumen–intima border) and the second (media–adventitia border) echogenic lines according to the leading edge method. On both sides, 10 measurements were performed; the mean of the individual values was calculated and results were presented in millimeters.

Assessment of augmentation index and pulse wave velocity

Measurements were carried out by using a TensioClinic arteriograph system (TensioMed Kft., Debrecen, Hungary) [29]. This technique is based on the fact that the contraction of the myocardium initiates pulse waves in the aorta. The first wave becomes reflected from the aortic wall at the bifurcation; therefore, a second, reflected wave appears as a late systolic peak. The morphology of this second, reflected wave depends on the stiffness of the large artery, the reflection time at 35 mmHg suprasystolic pressure of the brachial artery (RT S_{35}) and the peripheral resistance-dependent amplitude.

AIx is calculated from the amplitudes of the first and second waves. AIx is the pressure difference between the late systolic peak pressure and the early systolic peak pressure divided by the late systolic peak pressure. The arteriograph assesses this parameter from the oscillometric data obtained from the 35-mmHg suprasystolic pressure of the brachial artery [29, 33, 37].

PWV is the quotient of the jugular fossa–symphysis distance and RT S_{35} in meters per second. The jugular fossa–symphysis distance is anatomically identical with the distance between the aortic trunk and the bifurcation. In order to have reproducible results, the patient needs a rest for at least 5 min before the assessment. In addition, the investigation room should be quiet [29, 33, 37].

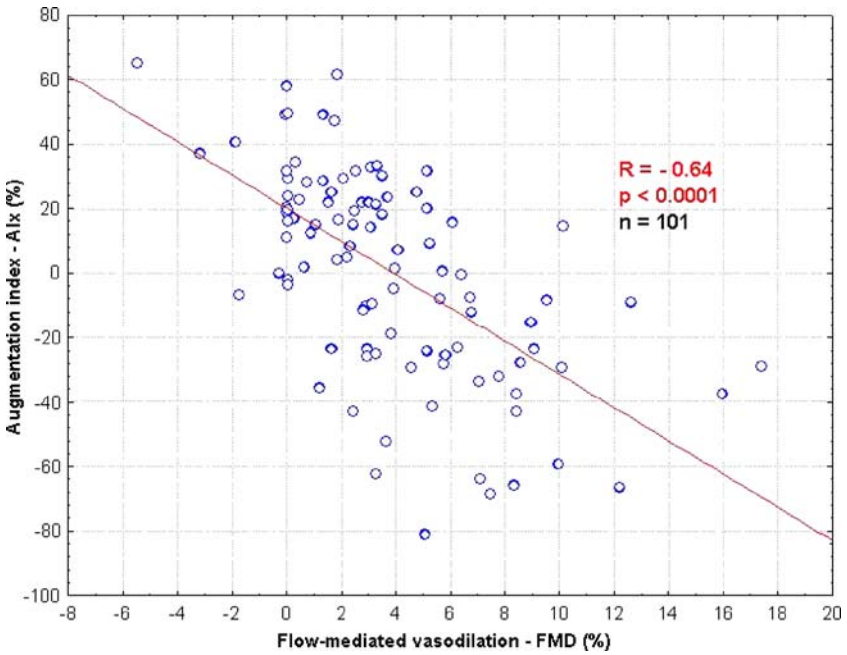

Fig. 1 Relationship of AIx and FMD in autoimmune patients. A significant negative correlation is indicated between the measured parameters. *R* regression coefficient, *p* level of statistical significance

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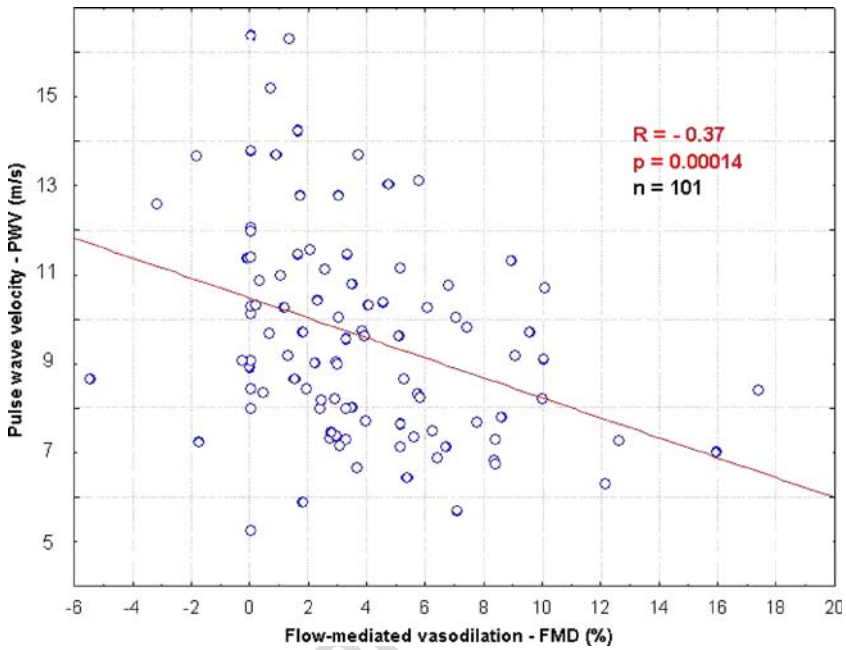

Fig. 2 Correlation between FMD and PWV in autoimmune patients. A significant negative correlation was found between FMD and FWV. *R* regression coefficient, *p* level of statistical significance

Statistical analysis

For the analysis of endothelial dysfunction, AIx, and PWV, Kolmogorov–Smirnov and Lilliefors tests were used. Subsequently, we performed correlation analyses. In cases of normal distribution (parametric), Pearson's test was performed; while in cases of non-normal distribution (nonparametric) Spearman's test was performed. When significant correlation was found, the two independent variables were plotted in a coordinate system, indicating the type of correlation, the level of significance, and the value of the regression coefficient. *p* values less than 0.05 were considered statistically significant.

Results

Differences in FMD, ccIMT, AIx, and PWV in autoimmune patients and controls

At baseline, there were no differences in the patients vs controls in the mean diameter of the brachial artery at rest

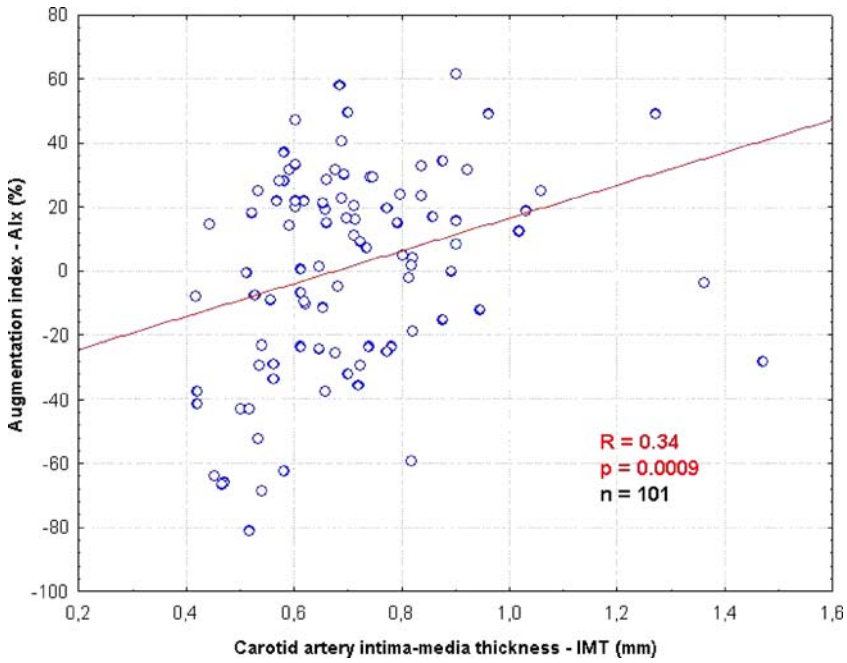

Fig. 3 Correlation between ccIMT and AIx in autoimmune patients. A significant positive correlation was detected between ccIMT and AIx. *R* regression coefficient, *p* level of statistical significance

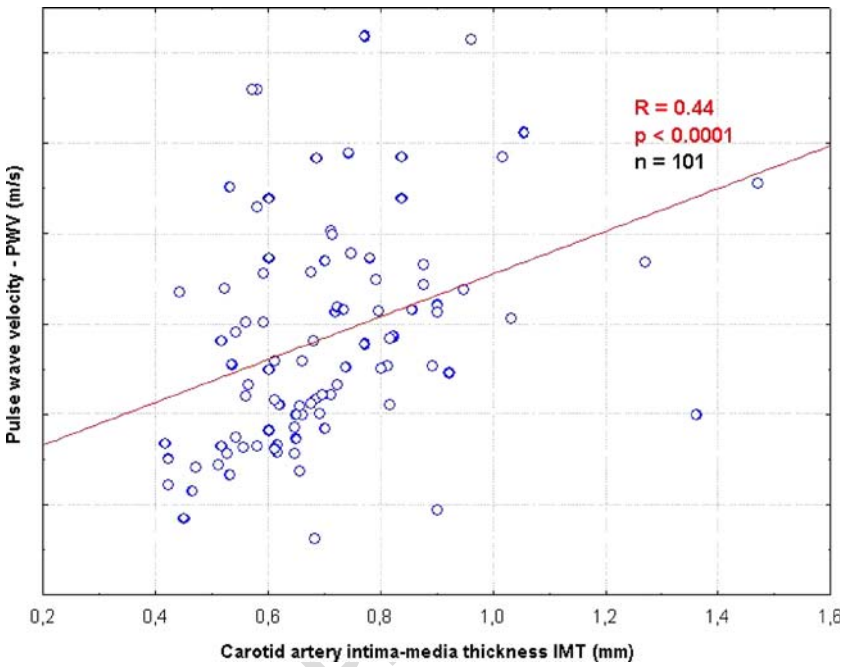

Fig. 4 Correlation between ccIMT and PWV in autoimmune patients. A significant positive correlation was found between ccIMT and PWV. *R* regression coefficient, *p* level of statistical significance

(both 4.02 mm) and after provocation (4.17 vs 4.36 mm). The mean value of FMD indicating endothelium-dependent vasodilation was significantly decreased in the autoimmune patients compared to healthy controls (3.66±3.82% vs 8.39 ±4.03%; $p<0.0001$). In contrast, ccIMT (0.70±0.18 vs 0.58±0.08 mm; $p=0.001$), AIx (1.22±32.25%. vs −41.15± 22.47%; $p<0.0001$), and PWV (9.66±2.40 vs 8.00± 1.46 m/s; $p=0.0002$) were significantly increased in autoimmune patients vs controls (Table 1).

Correlations between parameters of endothelial dysfunction, atherosclerosis, and arterial stiffness in autoimmune patients

When correlation analysis was performed, FMD, a marker of endothelium-dependent vasodilation, exerted significant negative correlations with either AIx ($R=-0.64$; $p<0.0001$) (Fig. 1) or with PWV ($R=-0.37$; $p=0.00014$) (Fig. 2). We could also confirm the negative correlation between FMD

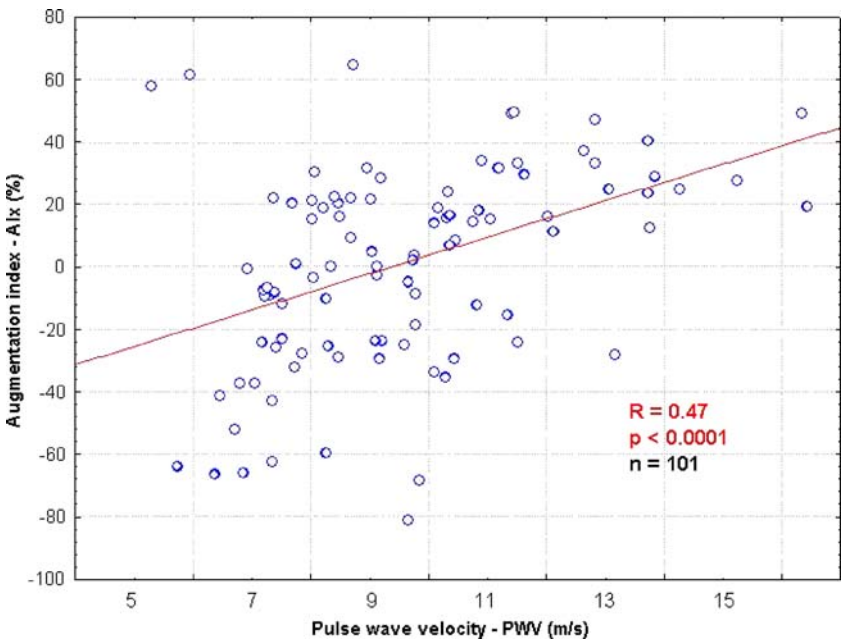

Fig. 5 Correlation between AIx and PWV in autoimmune patients. A significant positive correlation was found between AIx and PWV. *R* regression coefficient, *p* level of statistical significance

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and ccIMT (R=−0.48; p<0.0001) (data not shown). Moreover, positive correlations were found between ccIMT and AIx (R=0.34; p=0.0009) (Fig. 3), ccIMT and PWV (R=0.44; p<0.0001) (Fig. 4), as well as between the two stiffness parameters, AIx and PWV (R=0.47, p<0.0001) (Fig. 5). Among the four assessed parameters, AIx (R=0.42; p<0.0001), PWV (R=0.34; p=0.0006), and ccIMT (R=0.72; p<0.0001) positively correlated and FMD (R=−0.43; p<0.0001) negatively correlated with the age of the patients (data not shown).

Vasculopathy in different autoimmune diseases

Subsequently, subgroup analysis was performed in the different autoimmune diseases. Although the number of patients in each group was relatively small for statistical analysis, and therefore, it is hard to draw definite conclusions, in general, patients with APS, RA, SSc, or PM had lower FMD and higher AIx in comparison to controls (data not shown). In addition, although most assessed parameters were not different in the various disease subgroups, AIx was higher in RA (3.36±28.67%) and SSc (11.4±27.2%) than in PM (−15.97±19.87%) (p=0.0327 and p=0.0346, respectively) (data not shown).

Discussion

The pathogenesis of atherosclerosis involves numerous autoimmune–inflammatory mechanisms [38], which may explain the existence of accelerated atherosclerosis and increased vascular morbidity in autoimmune rheumatic diseases [7–25]. There is a need for novel diagnostic techniques that can predict early endothelial dysfunction, as well as overt atherosclerosis preclinically. These diagnostic tools need to be fast, reproducible, and applicable on a relatively large cohort of patients and should be able to easily and cost-effectively identify patients at high risk for cardiovascular morbidity and mortality. Although the evaluation of ccIMT and FMD are suitable and reliable techniques to assess carotid atherosclerosis and endothelial dysfunction, respectively [10, 18, 31, 34–36, 39, 40], both methods are relatively expensive and require special expertise. In contrast, oscillometric arteriography used for the determination of arterial stiffness is a simple and relatively cheap technique performed in a simple automated system, which has recently been validated by its comparison to two standard tonometric (SphygmoCor) and piezoelectronic (Complior) systems [29, 30, 33]. Autoimmune patients have not been previously tested for arterial stiffness using the arteriograph system.

Therefore, in the present study, we detected impaired FMD, as well as increased ccIMT, AIx, and PWV in 101 autoimmune patients in comparison to 36 healthy control subjects. Impaired endothelium-dependent vasodilation and increased stiffness were observed in all patient subgroups including APS, RA, SSc, and PM. In addition, by studying arterial stiffness using arteriograph for the first time, both stiffness parameters, AIx and PWV, exerted negative correlation with FMD and positive correlation with ccIMT in the patient population. AIx and PWV also positively correlated with each other. Previously, various investigators reported accelerated atherosclerosis indicated by increased ccIMT in APS, RA, and SSc [7, 10, 13, 18, 21, 22, 34]. Thus, while endothelial dysfunction (FMD) and accelerated atherosclerosis (ccIMT) have previously been described by us and others, we introduced arteriograph, a novel tool to assess arterial stiffness in autoimmune diseases. Arterial stiffness is closely associated with autoimmune inflammation as we have recently reported in APS.

In conclusion, the major aim of this study was to assess arterial stiffness of autoimmune patients for the first time using the arteriograph and to compare this method to other techniques used to assess endothelial dysfunction and atherosclerosis. Novel imaging methods are necessary for the early diagnosis and effective management of accelerated atherosclerosis seen in high-risk autoimmune patients. The arteriograph technique gives us a simple and cheap opportunity to assess the vasculature in these patients. Our data, as well as reports from other investigators, suggest that increasing arterial stiffness may be related to early endothelial dysfunction and overt atherosclerosis. As FMD and ccIMT assessments require special expertise and are relatively expensive and as arterial stiffness correlates with both FMD and ccIMT, the simple arteriograph technique may be used to screen patients at high risk for cardiovascular disease early. Thus, effective vasoprotective therapy can be initiated in order to prevent further cerebrovascular and cardiovascular complications.

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