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Arterial stiffness in a muscular artery in women with longstanding rheumatoid arthritis compared with healthy controls and patients with traditional cardiovascular risk factors

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Abstract Pulse wave velocity (PWV), a marker of arterial stiffness, reflects vascular dysfunction and is associated with cardiovascular risk. Rheumatoid arthritis (RA) is associated with profound changes in vascular function and premature death, mainly caused by cardiovascular diseases. The aim of this study was to investigate arterial stiffness in the brachial artery (a muscular type of artery) as measured by PWV in women with longstanding RA and to compare the results with healthy controls and to patients with traditional cardiovascular risk factors without RA. A total of 80 female participants underwent non-invasive measurement of PWV. Participants were allocated to one of three groups: patients with longstanding RA (disease duration >5 years) without traditional cardiovascular risk factors ($n = 30$), patients with traditional cardiovascular risk factors ($n = 20$) and healthy controls ($n = 30$). Patients and controls were matched for age. PWV was significantly higher in RA patients (8.6 ± 0.9 m/s) as compared with healthy controls (8.1 ± 0.7 m/s; $P = 0.02$). PWV was virtually the same in RA patients and patients who had traditional cardiovascular risk factors (8.6 ± 1.5 m/s; NS). PWV was also higher in this group as compared with healthy controls, but this difference did not reach statistical significance (NS). RA is associated with a higher PWV as compared with healthy controls and is comparable to patients with known traditional risk factors. This reflects vascular dysfunction in patients with RA.

Keywords Rheumatoid arthritis · Pulse wave velocity · Cardiovascular risk factors · Arterial stiffness

Introduction

In recent years, it has become clear that there is a considerable relationship between rheumatoid arthritis (RA) and premature atherosclerosis [1]. It could be demonstrated that the life span of RA patients is shortened by approximately 3–18 years [2]. Most cases of death are of cardiovascular origin [3–7]. It is believed that accelerated atherosclerosis and vascular damage in RA, as well as in other inflammatory rheumatic diseases, are due to high- or low-grade inflammation [8, 9]. Arterial stiffness is a marker of vascular dysfunction. It is a predictor of cardiovascular disease and mortality [10–13]. The mechanical properties of the arteries have been recognized as important components of the vascular system [14]. The stiffness of the arterial vessels can be measured by pulse wave velocity (PWV) [15]. However, segments of the arterial tree are not uniform. According to the Windkessel theory, large, elastic arteries act as a reservoir, from which the blood flows further to the peripheral arteries, which work as non-elastic conduits [16]. While the aorta consists of more elastic elements [17], the arteries of the upper limb for instance are of a muscular type [18]. One of the main differences is that the stiffness of elastic arteries is strongly linked to age when the elastic fibers break down. In contrast to that, age has only minimal influence on muscular arteries [17–19].

Using different methods, higher arterial stiffness could be found in RA patients as compared to controls in previous studies [20, 21]. However, little is known of arterial stiffness in a predominately muscular segment of the arterial tree. The aim of the present study was, thus, to investigate arterial

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stiffness in the brachial artery (a muscular type of artery) as measured by non-invasive PWV in women with longstanding RA. To eliminate the influence of traditional cardiovascular risk factors, only patients without such factors were included in the study. The results were compared to age-matched healthy female controls. In addition, we included a second control group, which consisted of patients with traditional cardiovascular risk factors. This should allow to better interpret the results measured in RA patients.

Materials and methods

Patients

A total of 80 female participants were included in this cross-sectional analysis (30 RA patients without traditional cardiovascular risk factors, 30 healthy controls, 20 non-RA patients with traditional cardiovascular risk factors). The study was approved by the local ethics committee and is in accordance with the Helsinki Declaration. All participants gave informed consent.

Women with a diagnosis of RA according to the 1987 ACR criteria [22] and a disease duration of >5 years were included in this study. Efforts were made to study an RA population in which traditional cardiovascular risk factors were absent. RA patients were excluded if one of the following traditional cardiovascular risk factors was present: smoking; hypercholesterolemia (total cholesterol >6.5 mmol/l) or use of lipid-lowering drugs; history of former cardiovascular event; history of diabetes, anti-hyperglycemic treatment or elevated fasting blood glucose (>5.6 mmol/l); elevated blood pressure (>150/90 mmHg); positive family history of premature coronary heart disease (CHD) (in male first-degree relative <55 years of age or female first-degree relative <65 years of age). Furthermore, we excluded patients who had chronic kidney disease or who had inflammatory diseases other than RA. An upper age limit was set at 60 years. Finally, 31 patients were eligible for the analysis (these composed the RA-positive and traditional cardiovascular risk factors-negative group: RA+/CV-). For one patient only inadequate PWV measurements were obtained and so the patient was excluded from the study. Thus, this gave a total of 30 patients who entered the final analysis. For comparison of the results, 30 healthy age-matched female controls were recruited (RA-/CV- group). In a second control group, 20 female non-RA patients were included, who did have at least one traditional cardiovascular risk factor (RA-/CV+ group), such as smoking ($n = 14$), diabetes ($n = 7$) and/or (treated) hypertension ($n = 7$) (13 patients with one, five patients with two, and two patients with three risk factors). Overt cardiovascular disease was absent in these patients.

We evaluated disease duration, present treatment with disease modifying antirheumatic drugs (DMARD) and previously failed DMARD therapy as well as the presence of rheumatoid factor (RF) (measured on at least two occasions several weeks apart). Erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), duration of morning stiffness and patient global assessment (PGA; 100 mm visual analog scale) were measured. In addition, tender joint count (TJC), swollen joint count (SJC) and the disease activity score 28 (DAS28) were investigated [23].

Pulse wave velocity

Pulse wave velocity was assessed at the upper limb with the use of the Spymocor instrument (AtCor Medical, version 6.31, Sydney, Australia) as previously described [24]. A high-fidelity micro-manometer (SPC-301, Millar Instruments, Houston, TX, USA) was used to continuously record the pulse on the common carotid artery as well as (in a second step) the radial artery on the same side for 20 s. The transit distance of the pulse wave was assessed as follows: the distance from the suprasternal notch to the appplanation point of the radial artery was measured with a tape. In the same way the distance from the appplanation point at the common carotid artery to the suprasternal notch was measured and subtracted from the distance suprasternal notch → radial artery. The calculated distance gave the transit distance of the pulse wave, which was used for assessment of the PWV. An ECG tracing was recorded simultaneously. The Spymocor instrument calculated the mean delay from the R peak of the ECG to the rise of the pulse at the measure point at the common carotid artery and at the radial artery. With the averaged delay between the two sites and the known transit distance, the PWV of the upper limb could be calculated. Each measurement was taken three times and the mean was used for statistical analysis.

Statistical analysis

Continuous variables were compared between two groups by using the independent, two-tailed t test. To test for correlation for continuous variables, the Pearson correlation was used. In the case of non-parametric variables, the Spearman r correlation was used. Parameters with a markedly skewed distribution were \log_{10} -transformed. A P value of <0.05 was accepted as statistically significant.

Results

Participant characteristics are summarized in Table 1. Upper limb PWV was significantly higher in RA patients

Table 1 Participant characteristics of RA patients (RA+/CV−), healthy controls (RA−/CV−) and patients with traditional cardiovascular risk factors (RA−/CV+)

	RA+/CV− (n = 30)	RA−/CV− (n = 30)	RA−/CV+ (n = 20)
Age (years)	45.6 ± 8.0	44.4 ± 6.3	48.2 ± 7.2
Systolic blood pressure (mmHg)	123 ± 17	122 ± 13	138 ± 31
Diastolic blood pressure (mmHg)	76 ± 9	73 ± 11	81 ± 145
Heart rate (bpm)	70 ± 12	69 ± 12	73 ± 13
Disease duration (years)	15.1 ± 6.2		
ESR (mm/h)	29.7 ± 30.2		
CRP (mg/dl)	2.6 ± 5.0		
DAS28	3.7 ± 1.6		
Prednisolone (no/yes, mean dose)	18/12 (mean 7.7 g/day)		
NSAIDs (no/yes)	13/17		
TNF α blocker (no/yes)	16/14		
Number of current DMARDs (n, %)			
0	1 (3.3)		
1	7 (23.3)		
2	21 (70.0)		
3	1 (3.3)		
Number of previously failed DMARD (n)	3.4 ± 1.6		

All values are given as mean \pm SD if not otherwise stated; $P < 0.05$ for systolic and diastolic blood pressure healthy controls versus positive controls

CRP C-reactive protein, DMARD disease-modifying antirheumatic drug, ESR erythrocyte sedimentation rate, NSAID non-steroidal anti-inflammatory drug, TNF tumor necrosis factor

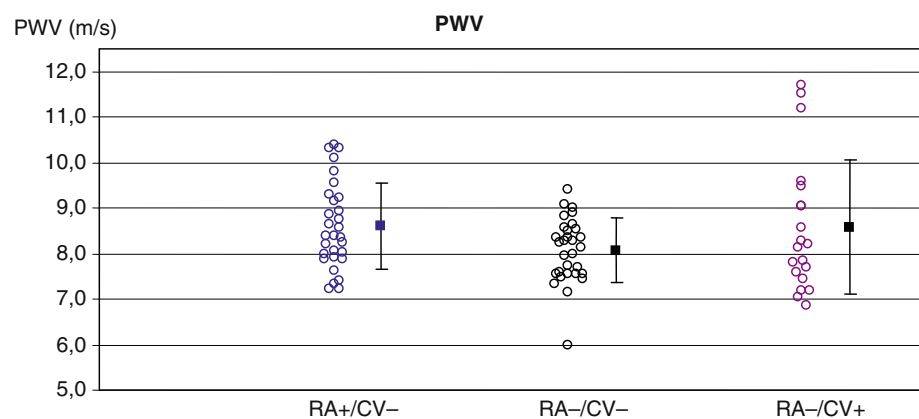
(8.6 \pm 0.9 m/s) as compared with healthy controls (8.1 \pm 0.7 m/s; $P = 0.02$). PWV was virtually the same in RA patients and patients who had traditional cardiovascular risk factors (8.6 \pm 1.5 m/s; $P > 0.05$). PWV was also higher in this group as compared with healthy controls, but this difference did not reach statistical significance ($P > 0.05$). The results of PWV are presented in Fig. 1.

Pulse wave velocity correlated significantly with pulse rate ($r = 0.41$; $P = 0.03$) and diastolic blood pressure ($r = 0.40$; $P = 0.03$). However, there was no correlation with duration of the disease or number of previously failed DMARDs ($P > 0.05$). In addition, there was no significant

correlation of PWV with biochemical parameters of inflammation (logESR and logCRP; $P > 0.05$ for both) or the DAS28 ($P > 0.05$).

There was no difference between RA patients taking NSAIDs ($n = 17$; PWV = 8.5 \pm 0.9 m/s) compared to patients who did not take NSAIDs ($n = 13$; PWV = 8.7 \pm 1.0 m/s; $P > 0.05$). The same was true for tumor necrosis factor (TNF)- α -blockers (14 users: PWV = 8.4 \pm 0.8 m/s vs. 16 non-users: PWV = 8.8 \pm 0.9 m/s; $P > 0.05$). Patients who used corticosteroids tended to have a lower PWV as compared with those without that treatment (12 users: PWV = 8.2 \pm 1.1 m/s vs. 18 not-users: PWV = 8.8 \pm 1.1 m/s; $P = 0.07$).

Fig. 1 PWV in RA patients (RA+/CV−; 8.6 \pm 0.9 m/s), healthy controls (RA−/CV−; 8.1 \pm 0.7 m/s) and patients with traditional cardiovascular risk factors (RA−/CV+; 8.6 \pm 1.5 m/s). The mark and lines to the right side of all single measurements reflect the mean and SD



Discussion

In this study, PWV of the upper limb (a predominantly muscular conduit vessel part of the arterial tree) in female RA patients without traditional cardiovascular risk factors turned out to be higher than compared to healthy controls. The PWV in RA patients was virtually the same as in non-RA patients with known traditional cardiovascular risk factors such as diabetes, hypertension or smoking. Healthy controls had a lower PWV as compared to non-RA patients with known traditional cardiovascular risk factors; however, this difference did not reach statistical significance. This fact is most likely due to the smaller number of participants in the latter group as well as the high SD in this group.

Arterial stiffness is a marker of vascular dysfunction and is associated with cardiovascular risk. Some studies evaluated arterial stiffness of elastic arteries in RA patients. While most of these studies included patients with known traditional cardiovascular risk factors, such patients were not allowed in our study. In addition, we not only compared our results with healthy women, but also with women with traditional cardiovascular risk factors to better interpret the impact of RA on PWV.

Roman et al. [20] assessed arterial stiffness at the common carotid artery (an elastic artery) and found that arterial stiffness was increased in RA patients (mean age 45 years). Patients with traditional cardiovascular risk factors (e.g., hypertension, smokers) were allowed to participate in the study. Mäki-Petäjä et al. [21] analyzed PWV of the aorta and the upper limb in 77 RA patients (mean age 57 years) and found an increased PWV for both sites as compared with controls. Patients with treated hypertension were included in the study. Turesson et al. [25], who measured the distensibility of the aorta found it to be reduced in RA patients. However, this was not true for male patients (and not in the carotid artery). The study included 27% of smokers. Additional cardiovascular risk factors were not mentioned. Arosio et al. [26] measured brachio-radial PWV (a muscular segment of the arterial tree) with an alternative method (piezoelectric plethysmography) in RA patients without traditional cardiovascular risk factors and found it to be increased as compared to controls. All these results are in line with our data. To eliminate possible confounders, we excluded RA patients with traditional cardiovascular risk factors and found a higher PWV in this group as compared with healthy controls. In addition, PWV in RA patients was comparable to PWV in patients with such traditional risk factors, but without RA. The results found in RA patients are in line with the increased cardiovascular risk in this population.

An important determinant of PWV is blood pressure. The higher the intravascular pressure, the greater the

recruitment of relatively inelastic collagen fibers, which in turn leads to a reduction in elasticity [16]. In our study, blood pressure was comparable between the RA and both control groups (blood pressure was higher in patients with traditional cardiovascular risk factors as compared with healthy controls). A number of factors have an influence on arterial stiffness, e.g., smooth muscle tone in the arterial wall, composition of the vessel wall, presence of traditional cardiovascular risk factors, drugs and also genetic determinants [16, 27]. In recent years, it has become clear that different inflammatory rheumatic diseases are associated with profound changes in the function and structure of the cardiovascular system [2, 28–30] and that, vice versa, inflammation plays a major role in the initiation and progression of atherosclerosis [31, 32]. It seems very likely that the chronic inflammatory state in RA accounts for the differences we have found in PWV in this study. Low-grade inflammation also could have increased arterial stiffness in the control group with traditional cardiovascular risk factors. However, we could not demonstrate any correlation of markers of inflammation and PWV. A possible explanation for this finding might be the fact that actual parameters of inflammation are not very closely linked to the total “cumulative” burden of inflammation in a chronic and longstanding disease as RA. A further point that should be considered is that in the studied RA population, the disease activity was rather low. Only a few patients had a high disease activity. This could make it difficult to find a correlation with actual parameters of inflammation. Additionally, we cannot rule out that in a much larger sample size, such a correlation could have been found. In an alternative hypothesis, we also need to consider additional influences on the arterial system. For instance, in theory, specific treatment of the disease could also have caused the differences we have found in PWV.

As mentioned above, a variety of factors significantly influence arterial stiffness and, therefore, it is difficult to exactly determine each single effect. In RA, vascular function may be influenced, in addition to inflammation and antirheumatic treatment as mentioned above, by disease duration (not in this study) or disease-specific factors such as RF or shared epitope [33]. Finally, a comparison of PWV in populations with different levels of inflammation as well as other autoimmune diseases could help to more specifically determine the effect of inflammation on arterial stiffness [34].

In conclusion, RA is associated with a higher PWV of the upper limb arteries as compared with healthy controls. PWV in RA patients without traditional cardiovascular risk factors is comparable to non-RA patients with known traditional cardiovascular risk factors. This difference is most likely due to the chronic inflammatory state in RA patients.

Conflict of interest statement None of the authors has any conflict of interest.

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