Increased stiffness of the abdominal aorta in women with rheumatoid arthritis

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Objective. To study the distensibility and the diameter of the abdominal aorta and the common carotid artery (CCA) in patients with rheumatoid arthritis (RA), and investigate the relation between mechanical properties of these arteries and disease severity.

Methods. One hundred and one patients with RA (33 consecutive cases with extra-articular manifestations, and 68 subjects with non-extra-articular disease, matched for age, sex and disease duration) were investigated. Echo-tracking ultrasonography was used to measure stiffness and mean diameter of the abdominal aorta and the CCA. The patients were compared with healthy individuals from the corresponding age group (n=74 for measurements of the aorta, n=64 for the CCA). Predicted values for stiffness and mean diameter, based on age and sex, were calculated.

Results. Stiffness of the abdominal aorta was increased in women with RA [mean percentage of predicted value (% predicted) 180; 95% confidence interval (95% CI) 150–211] but not in men (% predicted 99; 95% CI 75–122). CCA stiffness was less markedly increased, and mean diameters of the aorta and the CCA were not different from the expected. In the RA cohort, patients with extra-articular manifestations tended to have greater stiffness of the aorta (P=0.11), and disability, as indicated by a higher Health Assessment Questionnaire score, was associated with increased aortic stiffness (P=0.04).

Conclusion. RA is associated with decreased distensibility of the abdominal aorta in females, and such changes seem to correlate with disease severity. We suggest that arterial stiffness is an important factor in cardiovascular co-morbidity in RA.

Key words: Rheumatoid arthritis, Arterial distensibility, Ultrasound, Aorta, Cardiovascular disease, Extra-articular manifestations, Disease severity.

Rheumatoid arthritis (RA) is associated with an increased mortality compared with the general population [1–4], mainly due to an excess of deaths from cardiovascular disease (CVD) [2, 5]. Disability [6] and severe extra-articular disease manifestations [7, 8] are predictors of poor survival in patients with RA, and persistently high disease activity predicts cardiovascular co-morbidity and mortality [9]. Recent studies indicate that the incidence of CVD events is increased in RA [9–12]. Although some predictors of CVD, in particular smoking [13] and obesity [14], are more frequent in patients with RA than in the general population, available data indicate that the increased incidence of CVD is not explained by excess of traditional risk factors in RA subjects [10, 11]. The increased risk of CVD is mainly due to a higher frequency of myocardial infarctions than expected, whereas the incidence of cerebrovascular events has been found to be closer to that of the background population [11, 12]. It has been postulated that atherosclerotic vascular disease may be regarded as an extra-articular feature of RA, and that vascular pathology is an inherent part of disease expression [15]. Increased thickness of the carotid artery intima-media, a sign of early atherosclerosis [16], has been observed in RA [17, 18]. In addition, in a study of patients with RA aged 50 yr or less, Klocke et al. [19] reported an increased augmentation index, measured by radial pulse wave analysis, indicating increased stiffness of large and medium sized arteries.

Decreased distensibility of central arteries has been proposed as a risk factor for CVD [20]. Arterial stiffness increases central pulse pressure and left ventricular afterload [21]. Surrogate measures of arterial stiffness have been associated with cardiovascular risk and cardiovascular mortality. The aortic pulse wave velocity index is associated with mortality in end-stage renal disease [22], and the augmentation index is associated with known cardiovascular risk factors [23]. Using echo-tracking ultrasonography, it has been demonstrated that stiffness of the abdominal aorta increases markedly with age, in particular in men [24]. In patients with diabetes mellitus type 1, aortic stiffness is increased among women, but not among men, compared with healthy controls. It has been suggested that this may be part of the explanation for the particularly increased risk of CVD complications in diabetic women [25]. The present study was undertaken in order to investigate the distensibility of elastic arteries in patients with RA, and to estimate the impact of disease severity on arterial stiffness.

Patients and methods

Patients with RA seen at the rheumatology out-patient clinics in Malmö were included in a prospective study of extra-articular disease manifestations and vascular co-morbidities in RA.
Thirty-nine consecutive patients with recently diagnosed severe extra-articular disease manifestations according to pre-defined criteria [7] participated. Briefly, the extra-articular manifestations studied were clinically diagnosed pericarditis, pleuritis, Felty’s syndrome, polyneuropathy, mononeuropathy, scleritis, episcleritis, glomerulonephritis, cutaneous vasculitis and vasculitis involving other organs, each supported by objective findings and with other causes unlikely or excluded [7]. Seventy-five patients with non-extra-articular RA, individually matched to extra-articular subjects for age, sex and disease duration, were selected from a community based register of RA patients in the city of Malmö [26], or from a community based early RA inception cohort [27]. These patients had no current or previous evidence for severe extra-articular disease [7] or rheumatoid nodules. All patients fulfilled the 1987 American College of Rheumatology criteria for RA [28]. At inclusion, all patients were seen by the same physician (C.T.) and examined according to a structured protocol. The Swedish validated version of the Stanford Health Assessment Questionnaire (HAQ) [29] was used to estimate the extent of disability.

The mechanical properties of the abdominal aorta and the common carotid artery (CCA) were investigated in 101 of these patients (33 with extra-articular disease, 68 with non-extra-articular RA). Current extra-articular manifestations in those examined included major cutaneous vasculitis (n = 8), pleuritis (n = 8), pericarditis (n = 7), Felty’s syndrome (n = 6), mononeuropathy (n = 2) and polyneuropathy (n = 2). To obtain age- and gender-matched reference values for aortic and carotid artery diameter and distensibility indices, a control group of 145 healthy subjects was used [30, 31]. The study was approved by the research ethics committee of the Medical Faculty, Lund University, and all subjects gave informed consent according to the Declaration of Helsinki.

Arterial stiffness and diameters were investigated using echo-tracking sonography and blood pressure measurements, as previously described [25]. Briefly, the pulsatile changes in vessel diameter were registered with an ultrasound echo-tracking system (Diamove, Teltec AB, Lund, Sweden) [32], interfaced with a 3.5 and a 5 MHz B-mode real-time linear scanner (EUB 240, Hitachi, Tokyo, Japan), capable of detecting vessel wall movements of less than 10 mm and with a time resolution of 1.2 ms [32, 33]. In combination with blood pressure measurements, the pulsatile changes in diameter form the basis for calculation of vessel wall distensibility. All measurements were performed in a quiet room with the subject in the supine position after at least 15 min rest. From the real-time picture, the vessel wall was insonated in a longitudinal section, the echoes from the vessel walls were optimized and the pulsatile diameters were then recorded. Measurements from the right CCA were performed approximately 2 cm proximal to the bifurcation, and the recording of the abdominal aorta was conducted distal to the renal arteries, approximately 3.5 cm proximal to the bifurcation. Vessel diameters and diameter changes were calculated, and indirect blood pressure measurements performed immediately after measurements of the pulsatile vessel diameter with a sphygmanometer and a standard cuff on the left arm.

The distensibility of the arterial wall was expressed as stiffness [30]:

\[
\text{stiffness} = \frac{\ln(P_{\text{systolic}}/P_{\text{diastolic}})}{(D_{\text{systolic}} - D_{\text{diastolic}})/D_{\text{diastolic}}}
\]

where \(P_{\text{systolic}}\) and \(P_{\text{diastolic}}\) are the systolic and diastolic blood pressure levels in mmHg, and \(D_{\text{systolic}}\) and \(D_{\text{diastolic}}\) are the corresponding diameters in mm. We also calculated the distensibility coefficient (DC) and the compliance coefficient (CC) [35].

Each subject was examined three times at each location, with calculation of stiffness from the corresponding diameter, pulsatile diameter change and blood pressures obtained by the auscultatory method. The mean arterial blood pressure (MABP) was taken as the diastolic blood pressure plus one-third of the pulse pressure. Using this technique, the intra-observer variability for repeated measurements have previously been shown at this laboratory to be 15% for the pulsatile diameter change, 5% for the mean diameter and 18% for stiffness [36]. The measurements in the present study were performed by the same technicians as in the previously reported investigation [36], and recent evaluations have shown similar variability.

Seventy-four healthy subjects (39 women, 35 men) examined at the abdominal aorta, and 64 (34 women, 30 men) examined at the CCA were within the same age range as the RA patients (42 to 88 yr). The controls were assessed within the same time period as the RA patients, and by the same technicians. The subjects assessed at the CCA constituted a subgroup of those examined at the abdominal aorta. Stiffness and diameters in these subjects were compared with patients with RA. As both age and gender influence diameter and stiffness [31, 37], women and men were analysed separately. Individually predicted values for RA patients, based on sex and age, were calculated as previously described [25], and results were expressed as the percentage of predicted values (% predicted). As the unadjusted stiffness values of the abdominal aorta and the CCA had a non-normal distribution, the Mann-Whitney U-test was used for comparison of patients and controls. The mean diameters, the % predicted values of diameters, and stiffness of the aorta and the CCA were normally distributed, and results were expressed as mean values with 95% confidence intervals. Patients with RA and healthy subjects, as well as analysis of cases with extra-articular RA and matched non-extra-articular patients, was performed using the Student’s t-test. Multivariate linear regression models were used to estimate the effect of age, sex and RA on the natural logarithm of unadjusted stiffness and diameter values in all subjects combined, as well as the effect of age and blood pressure on stiffness and DC and CC values in men and women separately. We also examined associations between HAQ scores and rheumatoid factor and % predicted values in the RA cohort in linear regression models. Analysis of variance was used to estimate differences in % predicted aortic stiffness by quartile of HAQ-score.

**Results**

The RA cohort consisted of 101 patients (59 females, 42 males). Thirty-three patients had extra-articular disease manifestations according to pre-defined criteria [7], and 68 patients had non-extra-articular RA. The clinical characteristics of the studied patients are listed in Table 1. Data on arterial stiffness and arterial diameter were compared with those of 74 healthy controls (39 females, 35 males) for the abdominal aorta examined in parallel with the RA patients. A subgroup of 64 healthy controls (34 females, 30 males) were examined at the common carotid artery (CCA) and compared with the RA cohort.

**Stiffness and diameter of the abdominal aorta**

Stiffness of the abdominal aorta was increased among patients with RA compared with the expected values, based on their age and sex distribution. The aortic stiffness among patients with RA was on average 147% of that predicted, based on age and sex [95% confidence interval (95% CI) 125–169]. In a multivariate linear regression model examining the combined cohort of patients with RA and healthy controls, adjusted for each of the included variables, age (\(P < 0.0001\)), male sex (\(P < 0.01\)) and RA (\(P = 0.02\)) were all significantly associated with an increased stiffness. This indicates that each of these factors had independent effects on aortic stiffness in the combined sample.
TABLE 1. Characteristics of the RA cohort. All values are mean±SEM unless otherwise indicated

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>RA Cohort</th>
<th>Controls, aorta</th>
<th>Controls, CCA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>66±1</td>
<td>62±2</td>
<td>62±2</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>42/59</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Disease duration (yr)</td>
<td>12±1</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Extra-articular manifestations</td>
<td>33%</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>RF positive (%)</td>
<td>63%</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>HAQ score</td>
<td>0.9±0.1</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>CRP (mg/l)</td>
<td>20±3</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Current smokers (%)</td>
<td>27%</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>139±2</td>
<td>134±2</td>
<td>137±3</td>
</tr>
<tr>
<td>MABP (mmHg)</td>
<td>99±1</td>
<td>99±2</td>
<td>102±2</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>78±1</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Stiffness, aorta (% predicted)</td>
<td>147±11</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Mean diameter, aorta (% predicted)</td>
<td>96±2</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Stiffness, CCA (% predicted)</td>
<td>119±5</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Mean diameter, CCA (% predicted)</td>
<td>102±2</td>
<td>ND</td>
<td>ND</td>
</tr>
</tbody>
</table>

Abbreviations: RF, rheumatoid factor; HAQ, Health Assessment Questionnaire; SBP, systolic blood pressure; MABP, mean arterial blood pressure; DBP, diastolic blood pressure; % predicted, percentage of predicted value (based on age and sex); CCA, common carotid artery.

TABLE 2. Clinical and vascular data in female patients with RA and female controls. All values are mean±SEM unless otherwise indicated

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>RA Cohort</th>
<th>Controls, aorta</th>
<th>Controls, CCA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>66*±1</td>
<td>64±2</td>
<td>62±2</td>
</tr>
<tr>
<td>RF positive (%)</td>
<td>58</td>
<td>ND</td>
<td>ND</td>
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<tr>
<td>HAQ score</td>
<td>1.1±0.1</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>CRP (mg/l)</td>
<td>20±4</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>141**±3</td>
<td>131±3</td>
<td>131±3</td>
</tr>
<tr>
<td>MABP (mmHg)</td>
<td>98±2</td>
<td>96±2</td>
<td>94±2</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>77±1</td>
<td>81±1</td>
<td>78±1</td>
</tr>
<tr>
<td>Stiffness, aorta</td>
<td>18**±2</td>
<td>9±1</td>
<td>NA</td>
</tr>
<tr>
<td>Mean diameter, aorta (mm)</td>
<td>16±0</td>
<td>16±0</td>
<td>NA</td>
</tr>
<tr>
<td>Stiffness, CCA</td>
<td>12±1</td>
<td>NA</td>
<td>9±1</td>
</tr>
</tbody>
</table>

***P<0.001 vs CCA controls,
**P<0.001 vs controls.
*P<0.02 vs controls.
NA, not applicable; ND, not done. Other abbreviations as Table 1.

Stiffness was significantly increased among women (mean 18 vs 9: *P<0.001; Table 2), but not among men (mean 17 vs 16; Table 3), with RA compared with controls. The mean percentage of the predicted stiffness value (% predicted) was 180.3 in female patients with RA (95% CI 149.7–210.9) and 98.5 (95% CI 75.2–121.8) in male RA patients (Fig. 1). In linear regression models, adjusted for age and mean arterial blood pressure, RA was significantly associated with increased aortic stiffness among women (*P<0.0001), but not among men.

Comparisons of the distensibility coefficient (DC) and the compliance coefficient (CC) according to van Bortel et al. [35] gave similar results, with reduced distensibility [DC mean 0.0015/mmHg, IQR 0.0009–0.0023 vs mean 0.0024/mmHg, inter-quartile range (IQR) 0.0019–0.0033, *P<0.0001] and compliance (CC; mean 0.33 mm²/mmHg, IQR 0.18–0.42 vs mean 0.48, IQR 0.40–0.59, *P<0.0001) among women with RA compared with controls. These differences remained significant when controlling for age and mean arterial blood pressure (*P<0.0001 in these models for the association between RA and lower DC and CC).

Adjusting for the systolic blood pressure in these models and in the models for the association between RA and lower DC and CC.

There was no major difference in the mean diameter of the aorta between RA patients and controls (Table 1), and this was not influenced by gender or the presence of extra-articular no difference for DC and CC between male patients with RA and controls (data not shown).

Patients with extra-articular RA tended to have higher stiffness than non-extra-articular RA patients (% predicted 167, 95% CI 125–209 vs % predicted 137, 95% CI 112–162), but the difference was not significant (*P=0.11). In linear regression models, with the percentage of the predicted value of the stiffness index in patients with RA as the dependent variable, a higher disability index, measured by the HAQ (*P=0.04), but not positive rheumatoid factor (*P=0.69), was associated with increased aortic stiffness. For analytical purposes, HAQ scores were split into quartiles as follows: HAQ1, range 0–0.125; HAQ2, range 0.25–0.675; HAQ3, range 0.75–1.375; HAQ4, range 1.375–2.875. Subjects with a higher HAQ score within quartiles 3–4 (i.e. HAQ-score ≥0.75) were more likely to have an increased stiffness of the aorta compared with the expected (Fig. 2). There was no significant correlation between aortic stiffness and RA disease duration (*P=0.30) or between stiffness and current C-reactive protein (CRP) levels (*P=0.51). In the RA group, 27% were smokers and 29% (34% of extra-articular cases; 27% in the non-extra-articular subset) were currently on corticosteroid treatment, whereas the controls were all non-smokers and not on corticosteroids currently. However, smoking and steroid treatment had no significant impact on arterial stiffness in the RA group (data not shown).
manifestations (Tables 2–4). Only two patients (one with extra-articular RA, one without) had a mean diameter in excess of 30 mm, indicating the presence of an aortic aneurysm. Stiffness and diameter of the aorta in patients with RA were not different in smokers vs non-smokers (data not shown).

Stiffness and diameter of the common carotid artery

The stiffness index of the CCA in patients with RA was on average 118.7% of that predicted, based on age and sex (95% CI 109–128). CCA stiffness was slightly increased compared to the predicted in women (mean % predicted 120; 95% CI 109–131), as well as in men (mean % predicted 117; 95% CI 104–133). However, when examining the effects of RA on CCA stiffness in linear regression models, adjusted for age, there was no significant association between RA and increased stiffness in women (P = 0.13) or in men (P = 0.21). This indicates that the minor differences in CCA stiffness between RA patients and controls were in part due to differences in the age distribution within the groups.

CCA stiffness was not different in patients with RA with and without extra-articular disease (Table 4). The mean diameter of the CCA did not differ from the expected in patients with RA, and was similar in patients with vs without extra-articular manifestations (Table 4). Stiffness and diameter of the CCA in patients with RA were not different in smokers vs non-smokers (data not shown).

Discussion

We report an increased stiffness of the abdominal aorta associated with RA in women, but not in men. In the general population, the distensibility of the aorta decreases more rapidly in men than in women. A contrasting pattern has been observed in women with type 1 diabetes, who have a markedly increased aortic stiffness compared with controls [25]. In the present study, women with RA had stiffness indices comparable to men of the same age, and significantly higher than age-matched female controls. The magnitude of the increased stiffness in women with RA (mean 180% of the predicted value) was even slightly greater than that previously reported in diabetic women (mean 164% of the predicted value) [25].

In contrast, the distensibility of the carotid artery was only slightly different in patients from normal controls. The particular variation in aortic stiffness may have an impact on cardiovascular morbidity in RA. Increased left ventricular afterload may contribute to the risk of sudden cardiac death, and explain the higher risk of coronary events, but not of strokes, in patients with RA compared to the general population [11, 12]. The effect of aortic stiffness on cardiovascular morbidity and mortality should be investigated in longitudinal studies.

Sex-related differences in vascular pathology associated with systemic inflammatory diseases are of major interest, as a preferential increase of mortality in female patients with RA has been suggested [4]. Gabriel et al. [4] found life expectancy in a community-based RA cohort to be reduced compared with the general population by 4 yr in a 50-yr-old woman, but only by 1 yr in a 50-yr-old man. The impact of aortic stiffness and other vascular abnormalities on prognosis in women with RA should be investigated in longitudinal studies, and the mechanisms associated with such sex-related differences should be further studied.

Stiffness of the aorta tended to be higher in patients with recently diagnosed severe extra-articular manifestations, and there was a significant association between disability, as measured by the HAQ score, and aortic stiffness. This indicates that disease severity may have an impact on arterial wall abnormalities in patients with RA. It is known that increased CRP levels predict cardiovascular morbidity in early inflammatory polyarthritis [38], and that severe extra-articular RA is a strong predictor of cardiovascular mortality [7]. Increased CRP and erythrocyte sedimentation rate (ESR) are associated with greater thickness of the carotid artery intima-media in RA and also in healthy subjects [39]. Others have found CRP levels to be associated with aortic pulse wave velocity in healthy individuals [40] and in patients with systemic vasculitis [41], but we did not find any association between current CRP levels and aortic stiffness. In a study of histopathological findings in aortic aneurysms, inflammatory cell infiltrates were more prominent in women, and HLA-DRB1 genotypes were suggested to influence the risk of aneurysm formation as well as the presence of signs of inflammation [42]. This indicates that the process of ageing of the wall of the abdominal aorta may be influenced by sex and also by immunogenetic factors. The association found between stiffness and disability suggests that long-standing inflammation is important in this context. This is in accordance with the findings by Van Doornum et al. [43], who observed a reduced arterial compliance in patients with RA, and an inverse correlation between joint damage and small arterial compliance. However, there was no significant correlation between stiffness and RA disease duration in our study. Alternatively, the increased HAQ scores in a subset of the patients in the present study, who had on average long disease duration, may reflect reduced physical activity, a cardiovascular risk factor in its own right, causing aortic stiffness.
In attempting to measure indices of arterial distensibility, the arterial diameter change and the intra-arterial blood pressure ideally should be measured simultaneously at the same location, since it is well known that the arterial pressure waves undergo transformation in the arterial tree. Though widely used, the method of using the auscultatory blood pressure in the upper arm when calculating distensibility indices for the abdominal aorta may be questioned. Comparison between intra-arterial pressure in the abdominal aorta and the brachial blood pressure obtained by the auscultatory method in healthy subjects has, however, clearly shown that the pulse pressure is systematically underestimated when the auscultatory method is used without obvious differences between gender or between the young and the elderly [44]. Hence, our use of auscultatory blood pressure cannot explain our findings.

The strengths of the current study include the comparison with a control group from an appropriate age group, which enabled computations of expected stiffness and diameter values. We used a validated method to study vascular distensibility and diameters in our patients. The use of pre-defined criteria for severe extra-articular disease and the standardized assessment of the patients are important for the estimate of the impact of disease severity on arterial stiffness. One limitation is due to the sample size, which limits the power to evaluate an effect of disease-associated factors and other factors on vascular abnormalities.

In conclusion, we demonstrate a marked increase of stiffness of the abdominal aorta in women, but not in men, with RA compared with healthy controls. Furthermore, our findings suggest that aortic stiffness is associated with disease severity in RA. We suggest that arterial stiffness is an important factor in cardiovascular co-morbidity in female patients with RA. The underlying mechanisms and the clinical implications of this phenomenon should be studied further.

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References


