

Increased Augmentation Index in Rheumatoid Arthritis and Its Relationship to Coronary Artery Atherosclerosis

INGRID AVALOS, CECILIA P. CHUNG, ANNETTE OESER, TEBEB GEBRETSADIK, AYUMI SHINTANI, DANIEL KURNIK, PAOLO RAGGI, TUULIKKI SOKKA, THEODORE PINCUS, and C. MICHAEL STEIN

ABSTRACT. *Objective.* Arterial stiffness, assessed by the augmentation index and pulse wave velocity, is an independent risk factor for cardiovascular disease. Rheumatoid arthritis (RA) is associated with accelerated atherosclerosis and increased cardiovascular mortality. We examined the hypothesis that augmentation index and pulse wave velocity are increased in RA, and are related to coronary artery atherosclerosis. *Methods.* We measured augmentation index and brachial pulse wave velocity in 117 patients with RA [57 with early (< 6 yrs) and 60 with late disease (> 10 yrs)] and 65 healthy controls. Coronary artery calcification was measured by electron beam computed tomography. Augmentation index and pulse wave velocity were compared in patients with early RA, late RA, and controls, and the association with coronary atherosclerosis was examined. *Results.* Patients with late RA had a higher augmentation index (median 33.8%, interquartile range 27.5%–37.0%) than those with early disease (median 27.5%, IQR 21.0%–34.0%) ($p = 0.008$) and controls (median 27.0%, IQR 20.4%–33.0%) ($p < 0.001$). After adjusting for height and cardiovascular risk factors, the association between late disease and augmentation index remained significant ($p = 0.02$). Augmentation index was associated with coronary calcification score ($r_s = 0.19$, $p = 0.046$), and the association was marginal after adjustment for cardiovascular risk factors, disease status, and disease activity ($p = 0.09$). There was no significant difference in brachial pulse wave velocity among patients with late (9.2 ± 1.7 m/s) and early RA (9.1 ± 1.6 m/s) and controls (8.9 ± 1.5 m/s) ($p = 0.78$). *Conclusion.* Patients with RA have increased augmentation index independent of cardiovascular risk factors. Augmentation index was associated with coronary artery calcification in patients with RA; this was attenuated after adjusting for cardiovascular risk factors. (First Release Nov 15 2007; J Rheumatol 2007;34:2388–94)

Key Indexing Terms:

AUGMENTATION INDEX

RHEUMATOID ARTHRITIS

CORONARY ARTERY ATHEROSCLEROSIS

Rheumatoid arthritis (RA) affects roughly 1% of the population¹ and causes increased cardiovascular risk and mortality^{2,3}. We and others have shown that the prevalence of coronary artery atherosclerosis is increased in patients with RA and that this is not fully accounted for by traditional risk factors^{4,5}.

Atherosclerosis is associated with increased vascular stiffness, and this in turn correlates with endothelial dysfunction,

an early event in the pathogenesis of atherogenesis⁶. There are several ways to measure arterial stiffness. Noninvasive measures that are in wide use include pulse wave velocity (PWV) and augmentation index. PWV measures the velocity at which arterial pressure wave travels, and higher values are associated with established cardiovascular risk factors and with cardiovascular mortality in several populations^{7–10}. Augmentation index, a quantitative index of systemic arterial stiffness, refers to the difference between the first and second systolic peak of the central pressure waveform, expressed as a percentage of the pulse pressure¹¹. Augmentation index is increased in patients with hypercholesterolemia¹², is an independent predictor of decreased survival in patients with end-stage renal disease¹³, and is a risk factor for coronary artery disease in hypertension¹⁴.

In healthy individuals inflammatory markers such as C-reactive protein (CRP) were associated with arterial stiffness measured by PWV¹⁵ and augmentation index¹⁶. These findings suggest that even subclinical inflammation leads to early vascular dysfunction, increased arterial stiffness, and atherosclerosis. Thus, the relationship between inflammation and vascular stiffness in patients with clinical inflammation, such as occurs in RA, is of interest. There is limited information

From the Department of Medicine, Department of Pharmacology, and Department of Biostatistics, Vanderbilt University School of Medicine, Nashville, Tennessee; and Department of Medicine, Division of Cardiology, Emory University School of Medicine, Atlanta, Georgia, USA. Supported by grants HL04012, HL67964, and GM5MO1-RR00095 from the US National Institutes of Health. Dr. Avalos was partly funded by the American College of Rheumatology/REF Lupus Investigator Fellowship Award.

I. Avalos, MD; C.P. Chung, MD, MPH; A. Oeser, BS; T. Sokka, MD; T. Pincus, MD, Department of Medicine; T. Gebretsadik, MPH; A. Shintani, MPH, PhD, Department of Biostatistics; D. Kurnik, MD; C.M. Stein, MD, Departments of Medicine and Pharmacology, Vanderbilt University School of Medicine; P. Raggi, MD, Division of Cardiology, Emory University School of Medicine.

Address reprint requests to Dr. I. Avalos, Division of Rheumatology and Clinical Pharmacology, T-3219 MCN, Vanderbilt University School of Medicine, 1161 21st Ave. South, Nashville, TN 37232-2681.

E-mail: ingrid.avalos@vanderbilt.edu

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comparing arterial stiffness in patients with RA and controls¹⁷⁻²⁰ and no information regarding early disease or the relationship with coronary calcification in RA.

Since augmentation index and PWV may provide information about subclinical atherosclerosis, which is increased in RA²¹, we examined the hypothesis that augmentation index and PWV are increased in patients with RA, and are associated with coronary artery atherosclerosis. Further, since endothelial dysfunction is present among patients with early²² and late RA²³, we studied patients with early and late disease, as this could provide information about the contribution of functional and structural mechanisms involved in atherosclerosis.

MATERIALS AND METHODS

Subjects. We studied 117 patients with RA, 57 with disease duration of 6 years or less (early RA) and 60 with disease duration of 10 years or more (late RA), and 65 control subjects that were frequency-matched for age, sex, and race with the entire cohort of patients with RA. We enrolled consecutive eligible patients older than 18 years of age who met the American College of Rheumatology classification for RA²⁴. Controls did not meet the criteria for RA. Patients and controls have contributed data to ongoing studies of cardiovascular disease in RA²⁵⁻²⁷.

Patients were recruited by advertisements, referred by local rheumatologists, or from a registry of patients with early RA²⁸. Controls were recruited from among the patients' acquaintances, by advertisement, and from a volunteer database maintained by the General Clinical Research Center at Vanderbilt University Medical Center. The study was approved by the Institutional Review Board of Vanderbilt University Hospital, and all subjects provided written informed consent.

Information was obtained through a structured interview, self-report questionnaires, physical examination, laboratory tests, and medical record review. Current and cumulative medication use was determined by combining the information provided by patients and medical records. A family history of coronary artery disease was defined as a first-degree relative having a myocardial infarction or stroke before the age of 55 years in men, and before the age of 65 years in women. Height and weight were measured and body mass index (BMI) was calculated [body weight (kg)/height (m²)]. Blood pressure was determined as the average of 2 measurements obtained 5 minutes apart after subjects had rested in the supine position for at least 10 minutes. Subjects were considered to have hypertension if they were taking antihypertensive agents or if they had systolic blood pressure of at least 140 mm Hg or diastolic blood pressure of at least 90 mm Hg. In patients, disease activity was measured using the Disease Activity Score based on the evaluation of 28 joints (DAS28)²⁹. DAS28 is a validated composite index containing a 28-joint count for tenderness and swelling, the erythrocyte sedimentation rate (ESR), and the patient's overall assessment of well-being. The modified Health Assessment Questionnaire (mHAQ) was used to measure the ability to perform activities of daily living. The total score ranges from 0 to 3, in which a score of 0 represents no impairment of function³⁰.

Blood was collected after an overnight fast for the measurement of a complete blood count and plasma concentrations of creatinine, total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides, Lp(a) lipoprotein by cholesterol content, and homocysteine. In patients with RA, CRP, ESR, and the presence of rheumatoid factor were determined.

Procedures. All subjects underwent noninvasive pulse wave analysis using the commercial SphygmoCor system (AtCor Medical, Sydney, Australia). This system uses a transfer function to calculate central arterial pressure from measurements obtained at the radial artery by a hand-held tonometer (Millar pressure tonometer, PWV Medical, Sydney, Australia). After at least 10 minutes of supine rest, peripheral blood pressure was measured twice by an automated sphygmomanometer (Dinamap Pro 110, GE Healthcare, Milwaukee,

WI, USA) and augmentation index and brachial (carotid to radial) PWV determined by applanation tonometry. The tonometer was held at the point of maximal pulsation and pressed lightly against the radial artery. Measurements were recorded after at least 12 consecutive beats and the quality of the waveforms confirmed by the quality control function provided by the software. After these measurements were obtained, the software generated a corresponding central aortic pressure waveform³¹. Since augmentation index is influenced by heart rate³², values normalized to a heart rate of 75 beats per minute were used^{33,34}. For PWV the arterial pulse wave was recorded at the common carotid and the radial artery sequentially and gated to the peak of the R wave of the electrocardiogram. PWV was calculated as the distance traveled by the arterial pulse wave (meters) divided by the time delay (seconds) between the 2 points.

Subjects underwent imaging with an Imatron C-150 scanner (GE/Imatron, South San Francisco, CA, USA). Imaging was performed with a 100-ms scanning time and a single-slice thickness of 3 mm. Forty slices were obtained during a single breath-holding period starting at the aortic arch and proceeding to the level of the diaphragm. The calculation of coronary calcium score was performed as described by Agatston, *et al*³⁵. In summary, all areas of calcification within the borders of a coronary artery with a minimal attenuation of 130 Hounsfield units (HU) were identified. A calcified coronary plaque was considered present if at least 3 contiguous pixels were detected. The area of each calcified plaque was multiplied by the peak radiologic attenuation inside the area. The sum of the scores for all coronary artery lesions represented the overall Agatston calcium score for each individual. All scans were interpreted by a single expert investigator (PR) who was unaware of the subjects' clinical status.

Statistical analysis. We estimated that for augmentation index a sample size of 60 in each group would provide 90% power to detect a difference in means of 6% (early vs controls and late RA vs controls) using a common standard deviation of 10% and using Student's t-test with a 0.05 two-sided significance level. Data are presented, for continuous variables, as means and standard deviation or median with interquartile range, depending on the distribution. The augmentation index and PWV distributions were compared in patients with early and late RA and controls by Kruskal-Wallis tests. The distributions of age among patients and controls were compared using Wilcoxon rank-sum tests. For categorical variables, frequencies and percentages are presented and chi-square statistics were used to compare proportions by patient status. To assess correlations between continuous variables and augmentation index or PWV, Spearman's rank correlation coefficients (r_s) were calculated.

Covariates were chosen a priori based on clinical relevance while preserving adequate power for the multiple regression, allocating at least 15 subjects per independent variable included in the model³⁶. To prevent overfitting, a first principal component was included for lipid profile variables [HDL, LDL, triglycerides, lipoprotein(a)]. Multiple linear regression models were used to determine if the association between RA and augmentation index and PWV was independent of cardiovascular risk factors (mean arterial pressure, diabetes, smoking, age, race, sex, lipid profile component, BMI, and homocysteine). We calculated the slope (β coefficient) to evaluate the association. Nonlinearity for the effect of systolic blood pressure was assessed and included using a restricted cubic spline. Validity of the multiple linear regression assumptions was assessed by graphically plotting residuals against predicted values, plotting normal Q-Q plots, and using the Shapiro-Wilk test. Within the RA patient group, the relationship between augmentation index, PWV, and coronary artery calcification was examined using proportional-odds logistic regression models by further adjusting for cardiovascular risk factors and disease activity. For all analyses a 2-sided 5% significance level was used for inference. All analyses were performed using R version 2.3.1 (www.r-project.org) and SAS version 8.2 (SAS Institute, Cary, NC, USA).

RESULTS

Demographic data for 117 patients and 65 controls are shown in Table 1. There was a predominance of female Caucasian subjects in both patient and control groups. The median age of

Table 1. Demographic characteristics of patients with RA and control subjects. Data are presented as median (interquartile range) or percentage.

Characteristics	Controls, n = 65	Early RA, n = 57	Late RA, n = 60	p*
Age, yrs	54 (48–60)	51 (42–60)	59.5 (52–67.8)	0.001
Female, %	66	58	72	0.29
Caucasian, %	85	93	85	0.30
Disease duration, yrs	0	2 (1.0–3.0)	19 (14.0–24.0)	< 0.001
Current smoking, %	11	19	30	0.03
Pack/yrs of smoking	0.0 (0.0–11)	0.0 (0.0–17)	0.0 (0.0–19.8)	0.55
Hypertension, %	45	40	65	0.02
Systolic blood pressure, mmHg	130 (119.0–138.0)	124 (115.5–139.5)	137.5 (124.4–150.2)	0.007
Diastolic blood pressure, mmHg	73.0 (68.0–78.0)	73.0 (69.0–81.0)	76.3 (68.0–82.8)	0.34
Body mass index, kg/m ²	26.8 (23.9–30.2)	28.3 (23.8–33.5)	26.9 (23.6–31.4)	0.37
Family history of early coronary-artery disease, %	32	30	28	0.89
Total cholesterol, mmol/l	5.1 (4.3–5.6)	4.8 (4.1–5.4)	4.8 (4.0–5.5)	0.46
Low-density lipoprotein, mmol/l	3.2 (2.6–3.8)	3.0 (2.4–3.6)	2.9 (2.2–3.5)	0.20
High-density lipoprotein, mmol/l	1.2 (1.0–1.4)	1.0 (0.9–1.3)	1.2 (1.0–1.4)	0.03
Homocysteine, μ mol/l	8.2 (7.2–10.2)	9.9 (8.2–11.5)	11 (8.3–13.5)	< 0.001
Rheumatoid factor, %	NA	65	74	0.31 [†]
Erythrocyte sedimentation rate, mm/h	NA	15.0 (7.5–25.8)	27.5 (7.8–42.3)	0.06 [†]
C-reactive protein, mg/l	NA	3.0 (3.0–10.0)	4.0 (2.5–15.0)	0.94 [†]
Disease activity VAS score (0–100 mm)	NA	25 (12–49)	35 (17–54)	0.14 [†]
Pain VAS score (0–100 mm)	NA	30 (16–55)	42 (24–57)	0.22 [†]
DAS28	NA	3.2 (2.1–4.0)	3.2 (2.5–4.2)	0.51 [†]
mHAQ score (0–3)	NA	0.25 (0.0–0.63)	0.5 (0.13–1.0)	0.02 [†]
Corticosteroids cumulative dose, mg	NA	1825 (365–3650)	10332 (2168–22202)	< 0.001 [†]

* Wilcoxon rank-sum test for continuous variables, chi-square tests for categorical variables. [†] p values correspond to comparison between early and late RA groups, Wilcoxon rank-sum test. VAS: visual analog scale, DAS28: disease activity score, mHAQ: modified Health Assessment Questionnaire. NA: not applicable.

the control group [54 (48–60) yrs] was similar to that of the overall RA group [55 (47–65) yrs]; but patients with early RA [age 51 (42–60) yrs] were younger than those with late disease [60 (52–68)] years. The median duration of disease among patients with early RA was 2 years (IQR 1–3) and in those with late disease, 19 years (IQR 14–24). Patients with RA were more likely to smoke and be hypertensive and had higher homocysteine concentrations ($p < 0.001$) and Agatston coronary calcification scores than controls ($p < 0.001$). There was no significant difference in the frequency of diabetes among controls and patients with RA ($p = 0.51$). As expected, patients with late RA had higher cumulative doses of corticosteroids than those with early RA, but disease activity measured by the DAS28 was similar (Table 1).

Patients with late RA had a higher augmentation index

(33.8%, IQR 27.5–37.0%) than those with early disease (27.5%, IQR 21.0–34.0%) ($p = 0.008$) and controls (27.0%, IQR 20.4–33.0%) ($p < 0.001$; Figure 1, Table 2). Among patients with RA, augmentation index was higher in female patients and correlated with age, family history of early coronary artery disease, systolic blood pressure, Agatston score, total cholesterol concentration, disease duration, disease activity score by visual analog scale, and mHAQ score. PWV was higher in men and correlated with diastolic blood pressure, BMI, augmentation index, and height (Table 3).

After adjusting for height, which is known to influence augmentation index, and cardiovascular risk factors, the relationship between late RA and augmentation index remained statistically significant ($p = 0.02$) and was of borderline significance in patients with early RA ($p = 0.08$; Table 4). The

Table 2. Measures of arterial stiffness and coronary calcification among control and RA subjects. Data are median (interquartile range).

Characteristic	Controls, n = 65	Early RA, n = 57	Late RA, n = 60	p
Augmentation index*, %	27.0 (20.4–33.0)	27.5 (21.0–34.0)	33.8 (27.5–53.7)	< 0.001
Pulse wave velocity, m/s	8.8 (8.0–10.1)	9.0 (8.2–10.2)	9.1 (8.4–10.0)	0.78
Total Agatston score	0 (0–16.4)	0 (0–33.8)	65.5 (0–400.5)	< 0.001

* Augmentation index is normalized to a heart rate of 75 beats/minute.

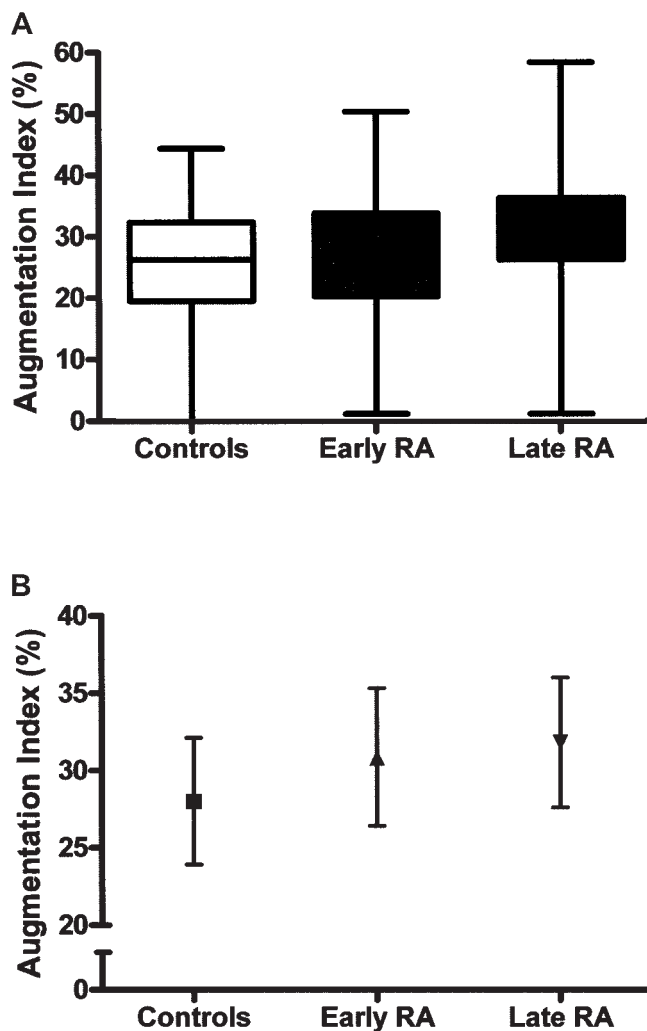


Figure 1. Augmentation index among patients with early RA and late RA and control subjects. A. Disease status was significantly associated with distribution of augmentation index, overall p value < 0.001. Box represents 25th to 75th percentile; median is shown as a line across the box. Whiskers represent the lower quartile minus 1.5 times IQR, or the upper quartile plus 1.5 times IQR. B. Mean and 95% confidence interval values for augmentation index (%) by disease status adjusted for age, sex, race, height, mean arterial blood pressure, diabetes, smoking, BMI, homocysteine, lipid profile [HDL, LDL, triglycerides, lipoprotein(a)].

association between augmentation index and coronary calcification ($r_s = 0.19$, $p = 0.046$) was attenuated after adjustment for cardiovascular risk factors and disease status and activity (OR 1.65, 95% CI 0.93–2.95; $p = 0.09$). Neither the univariate ($r_s = -0.03$, $p = 0.73$) nor the multivariate (OR 0.77, 95% CI 0.47–1.27, $p = 0.31$) analyses showed a significant association between PWV and coronary calcification.

DISCUSSION

The important findings of this study are that the augmentation index, a marker of vascular dysfunction, is significantly higher in patients with RA than in control subjects. In addition, our

data suggest an association between augmentation index and coronary artery calcification in patients with RA.

There is some information about arterial stiffness in RA, and various methods have been used to study it. In a small study, 14 patients had a higher augmentation index than 14 control subjects³⁷, and in a larger cross-sectional study, arterial stiffness was increased in patients with systemic lupus erythematosus and RA, independent of traditional cardiovascular risk factors³⁸. Wong, *et al* have also reported decreased small and large artery elasticity in patients with RA compared to controls³⁹. There is little information in report of a large group of patients with RA about augmentation index⁴⁰ and its relationship with cardiovascular risk markers and inflammation.

A recent study⁴¹ of 77 patients with RA and disease duration of 13 ± 10 years reported increased aortic and to a lesser degree brachial PWV, and no difference in augmentation index, compared to controls. In contrast, we found increased augmentation index and no difference in brachial PWV in patients with RA compared to controls. There were differences in the study populations that are relevant. Maki-Petaja and colleagues⁴¹ excluded subjects with cardiovascular risk factors such as current smoking or increased cholesterol. We specifically did not exclude such subjects since there is substantial evidence that traditional cardiovascular risk factors are increased in patients with RA⁴², and that smoking in particular interacts with RA in a deleterious fashion^{43,44}. Nevertheless, it is interesting that the association between augmentation index and RA in our study population remained significant after statistical adjustment for cardiovascular risk factors. In addition to excluding patients with cardiovascular risk factors, their population appeared to have more severe inflammation as evidenced by a higher CRP concentration than in our study. A subgroup analysis performed by Maki-Petaja, showing that PWV did not differ among patients who had CRP concentrations < 10 mg/l and controls, supports this notion⁴¹.

Inflammation may affect vascular stiffness in other populations. In patients with untreated essential hypertension there was an independent association between augmentation index and CRP, suggesting a role for subclinical inflammation in alterations in wave reflection⁴⁵. In our study, augmentation index was not significantly associated with CRP or ESR, but was associated with duration of disease and functional capacity measured by the mHAQ score, suggesting that the chronic effects of inflammation may be more important than current inflammation in RA-related changes in augmentation index.

Increased vascular stiffness may occur as a result of structural changes in vessels, for example atherosclerosis, or as a result of functional changes, for example endothelial dysfunction, or a combination of them. Our finding of increased augmentation index in patients with late RA suggests that chronic inflammation may increase arterial stiffness, independent of age and other cardiovascular risk factors. A study by Roman, *et al*⁴⁶ supports these findings; they found increased arterial

Table 3. Association between clinical variables and augmentation index and PWV among patients with RA.

Categorical Variables	No.	Augmentation Index, median (IQR), %	Pulse Wave Velocity, median (IQR), m/s
Sex			
Male	41	26.0 (21.8–34.0)*	9.8 (8.2–10.6)*
Female	76	35.5 (25.6–36.5)	8.9 (8.1–9.6)
Race			
Caucasian	104	30.0 (22.5–36.0)	9.1 (8.1–10.1)
Others	13	34.0 (29.0–36.5)	9.0 (8.6–10.8)
Current smoking			
No	88	31.8 (23.4–36.5)	9.0 (8.1–10.5)
Yes	29	28.0 (22.5–34.0)	9.1 (8.5–9.8)
Hypertension			
No	55	32.0 (25.8–36.6)	9.0 (8.1–10.0)
Yes	62	26.5 (21.0–34.0)	9.1 (8.2–10.3)
Continuous Variables	Median (IQR)	Augmentation Index, Spearman (r_s), %	Pulse Wave Velocity, m/s, Spearman (r_s)
Age, yrs	55 (47–65)	0.35 [†]	0.04
Cholesterol, mmol/l	4.9 (4.0–5.4)	0.21*	–0.08
Homocysteine, μ mol/l	10.5 (8.2–12.3)	0.03	0.12
Pack-years of smoking	0 (0–18)	–0.03	0.07
Agatston score	4.8 (0–209.8)	0.19*	–0.03
Pulse wave velocity, m/s	9.1 (8.2–10.1)	0.18*	1.0
Height, m	1.7 (1.6–1.8)	–0.26*	0.21*
Systolic blood pressure, mmHg	134.5 (119–146)	0.41 [†]	0.08
Diastolic blood pressure, mmHg	75 (68.5–82)	0.12	0.25*
Disease duration, yrs	10 (2–19)	0.27*	0.06
Disease Activity Score VAS (0–100 mm)	30 (14–50)	0.21*	–0.04
DAS28	3.2 (2.3–4.1)	0.13	–0.16
mHAQ score (0–3)	0.4 (0–0.8)	0.19*	0.07
Erythrocyte sedimentation rate, mm/h	16 (7.8–38)	0.14	–0.08
C-reactive protein, mg/l	4 (3–10.2)	0.08	–0.09
Corticosteroids, cumulative dose, mg	3477 (840–10950)	0.18*	0.05

The association between augmentation index and PWV with categorical variables was examined with the use of Wilcoxon rank-sum test. Spearman correlations were used for continuous variables. * $p < 0.05$; [†] $p < 0.001$.

Table 4. Association between augmentation index and pulse wave velocity and RA.

	Augmentation Index [†] β (95% CI)*	P value	β (95% CI)	p
Early RA	2.65 (–0.46–5.75)	0.09	2.79 (–0.29–5.87)	0.08
Late RA	4.15 (1.07–7.24)	0.01	3.79 (0.74–6.84)	0.02
Pulse wave velocity ^{††}				
Early RA	0.15 (–0.42–0.72)	0.61	0.13 (–0.42–0.69)	0.64
Late RA	0.16 (–0.40–0.73)	0.57	0.03 (–0.52–0.58)	0.91

Controls have been used as the reference value. * Multiple linear regression age and sex-adjusted, with β representing regression coefficients. ** Multiple linear regression adjusted for age, sex, race, height, mean arterial pressure, diabetes, smoking, BMI, homocysteine, lipid profile [HDL, LDL, triglycerides, lipoprotein(a)]. [†] Global test for overall association between disease status and augmentation index ($p = 0.04$). ^{††} Global test for overall association between disease status and PWV ($p = 0.89$).

stiffness in the patients with RA compared to controls, and an association between arterial stiffness and duration of RA. They also found increased arterial stiffness in patients with RA that had no detectable carotid plaque. Thus, increased vascular stiffness may precede structural changes within the vasculature. In patients with early RA in our study, augmentation index was slightly higher than in controls, and this was of borderline statistical significance only after adjustment for cardiovascular risk factors; nevertheless, it is compatible with the notion that the onset of arterial stiffness may occur early in the course of RA. This is concordant with the observation that endothelial dysfunction occurs early in patients with RA⁴⁷ and, in experimental human studies, that acute inflammation rapidly results in endothelial dysfunction^{48,49}.

PWV did not differ among patients with RA and controls.

PWV and augmentation index, although related, provide measures of different variables. Thus, PWV is predominantly a measure of arterial stiffness of large vessels, and is determined in part by the elasticity of the artery⁵⁰. As the arterial tree extends to the periphery, the arterial wall changes and becomes less elastic and more muscular. The augmentation index takes into account resistance at the level of smaller muscular vessels, where wave reflection occurs. Therefore, a possible explanation for an increase in augmentation index, but no change in PWV, is that in patients with chronic inflammation such as RA, the changes in vascular response may occur predominantly in small and medium-size vessels. Van Doornum, *et al*⁵¹ described abnormal pulse wave analysis findings in patients with RA. There was a significant inverse correlation between small artery compliance and the modified Sharp score ($r_s = -0.69$, $p = 0.009$), in keeping with the suggestion that small vessels are involved in the setting of chronic inflammation. Further, brachial PWV may not reflect early stiffening due to atherosclerosis since the vessel is relatively resistant to atherosclerosis.

We found a significant association between augmentation index and coronary calcium score among patients with RA, which is consistent with what has been described in the general population⁵². However, in the multivariate analysis, this association was not independent of other cardiovascular risk factors. Thus, although inflammation-related vascular stiffness and coronary calcification are 2 separate processes, the same cardiovascular risk factors that drive the presence and severity of coronary artery calcification in RA also influence the degree of arterial stiffness. Although augmentation index represents both structure and function, there is evidence that it can be altered by therapy. For example, treatment with atorvastatin for 12 weeks decreased augmentation index in patients with RA⁵³. On the other hand, in keeping with the modest associations found between augmentation index and measures of inflammation, anti-tumor necrosis factor therapy improved RA disease activity but did not alter the augmentation index significantly⁵⁴. These findings suggest that endothelial dysfunction and increased vascular stiffness are present in patients with RA and they may respond to targeted therapy, and this, in turn, may prevent development of structural changes such as atherosclerosis.

Our study should be interpreted with potential limitations in mind. First, the majority of the patient population had moderate disease activity as determined by the DAS28 score, thus these findings may not apply to patients with greater disease activity. Second, as with all cross-sectional studies, the results demonstrate association but not necessarily causation; hence, longitudinal data to further evaluate causality would be of interest. Third, we measured only carotid-radial (brachial) PWV; the relationship between carotid-femoral (aortic) PWV and coronary calcification would also be of interest, since recent studies suggest that aortic PWV is more strongly associated with atherosclerotic burden⁵⁵. Fourth, blood pressure

was taken with subjects in the supine position. However, differences in values attributed to posture are small, with no difference in systolic and a mean difference of 5 mm Hg in diastolic blood pressure (higher in patients sitting)⁵⁶.

Patients with RA have increased augmentation index, which is associated with higher coronary calcium scores. These findings support the notion that increased vascular stiffness may be associated with cardiovascular disease in patients with RA.

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