Cardiovascular Risk Factors and Disease Characteristics Are Consistently Associated with Arterial Function in Rheumatoid Arthritis

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ABSTRACT. ***Objective.*** Arterial properties influence cardiovascular disease (CVD) risk. We identified potential determinants of arterial function in patients with rheumatoid arthritis (RA).

Methods. Relationships of traditional cardiovascular risk factors and RA characteristics with arterial stiffness (pulse wave velocity), wave reflection (augmentation index, reflected wave pressure, and reflection magnitude), and pressure pulsatility (central systolic and pulse pressure, peripheral pulse pressure, pulse pressure amplification, and forward wave pressure) were identified in multivariable backward regression models among 177 patients without established CVD (118 white, 32 Asian, 22 black, 5 mixed ancestry).

Results. Recorded characteristics explained 37% (pulse wave velocity) to 71% (reflected wave pressure) of the variability in arterial function. These factors were particularly associated with wave reflection and pressure pulsatility: RA duration ($p = 0.04$), rheumatoid factor status ($p = 0.01$ to 0.03), leukocyte counts ($p = 0.02$ to 0.05), and total cholesterol ($p < 0.01$ to 0.03). Body mass index ($p < 0.01$ to 0.02) and insulin resistance ($p < 0.01$ to 0.01) were related to reduced wave reflection and peripheral pulse pressure. Exercise ($p = 0.02$) and alcohol consumption ($p < 0.01$) were associated with increased pulse pressure amplification and decreased peripheral pulse pressure, respectively. Tumor necrosis factor-α inhibition ($p < 0.01$) was related to reduced pulse wave velocity, and tetracycline use ($p = 0.02$) to decreased peripheral pulse pressure.

Conclusion. Traditional cardiovascular risk factors and disease characteristics are consistently associated with vascular hemodynamic alterations in RA. The relative effect of arterial stiffness, wave reflection, and pressure pulsatility on CVD risk in RA needs further study. (First Release June 1 2017; J Rheumatol 2017;44:1125–33; doi:10.3899/jrheum.170029)

Key Indexing Terms:
RHEUMATOID ARTHRITIS   ARTERIAL STIFFNESS
WAVE REFLECTION   PRESSURE PULSATILITY

Aging causes aortic elastin fibers to be replaced by collagen[1,2]. This process results in arteriosclerosis, which is increased by exposure to cardiovascular risk factors but can occur in the absence of atherosclerosis[1,2]. Arteriosclerosis causes arterial stiffness that is most frequently evaluated by pulse wave velocity. Pulse wave velocity represents the velocity at which the pressure wave propagates through arteries. Arterial stiffness increases central systolic blood pressure (BP) and cardiac workload.

The peripheral arterial wall contains mostly muscle fibers and is therefore stiffer than the aorta[1,2,3,4,5]. Consequently, in healthy young persons, the peripheral pulse pressure is substantially larger than that in the aorta[1,2,3,4,5]. This is referred to as (peripheral-to-central) pulse pressure amplifi-

cation, which decreases with vascular aging. The aortic pressure wave comprises the sum of the forward and reflected wave[1,2,3,4,5]. Wave reflection back to the aorta is mediated by changes in blood vessel wall composition and branching points distally along the arterial tree. In normal health, the reflected wave arrives at the heart during early diastole and aids coronary blood flow. Arterial stiffness increases wave reflection. Consequently, the reflected wave returns faster centrally and arrives at the heart during systole. Wave reflection thereby augments central BP and cardiac workload, and reduces diastolic BP and coronary perfusion. Increased wave reflection contributes to increased pulse pressure and reduced pulse pressure amplification.

The adverse effects of wave reflection on end-organ circulatory systems cannot be detected by brachial BP measurements[6]. Wave reflection has been mostly estimated by the aortic augmentation index[7,8,9]. However, the augmentation index incorporates a large proportion of the forward wave along with the reflected wave because of their overlap in time[7,8,9,10]. In 2015, the American Heart Association recommended the use of wave separation analysis rather than augmentation index in investigations focused on the role of wave reflection as an exposure for a cardiovascular outcome or a target for intervention[10]. Upon using this approach, the adverse effect of wave reflection on cardiovascular disease (CVD) risk has been increasingly recognized[7,8,9,10,11]. Enhanced wave reflection is a novel mechanical biomarker for heart failure[8].

Arterial stiffness as assessed by increased pulse wave velocity augments the risk of CVD independent of major traditional risk factors in non-RA persons[5]. Ikdahl and colleagues recently reported that pulse wave velocity but not augmentation index is also associated with incident cardiovascular events in RA[12]. In 2010, Vlachopoulos and colleagues reported that a 1 SD increase in pulse wave velocity was associated with a 47%, 47%, and 42% enhanced risk of cardiovascular events, mortality, and all-cause mortality, respectively[13]. However, among arterial function markers, not only pulse wave velocity but also a long list of factors are each independently associated with CVD risk in the general population[1,2,3,4,5,6,7,8,9,10-17]: wave reflection assessed by the augmentation index, reflected wave pressure, and reflection magnitude defined as the reflected-forward wave pressure ratio, as well as pressure pulsatility evaluated by central systolic and pulse pressure, peripheral pulse pressure, pulse pressure augmentation, and forward wave pressure[14]. The latter hemodynamic measures are the result of several different factors, including but not limited to arterial stiffness[10].

Rheumatoid arthritis (RA) increases cardiovascular event and mortality rates by about 50%[18,19]. Disease characteristics including particularly high-grade inflammation, unfavorable traditional cardiovascular risk factor profiles, and genetic factors associate with CVD in RA[20]. The mechanisms involved in the increased cardiovascular risk in patients with RA are currently under investigation[20]. In this regard, a metaanalysis of 25 studies by Ambrosino and colleagues[21] documented a significant increase in pulse wave analysis and augmentation index in patients with RA. The aim of the present study was to identify potential determinants of comprehensively assessed arterial function in a relatively large group of ethnically diverse patients with RA.

MATERIALS AND METHODS

Patients. We initially enrolled 186 consecutive patients who met the 1987 American College of Rheumatology (ACR) and 2010 ACR/European League Against Rheumatism criteria for RA[22,23] at the Milpark Hospital, Johannesburg, South Africa. Nine had established CVD and were excluded. The remaining 177 patients comprised 118 white, 32 Asian, 22 black, and 5 mixed ancestry participants. This study was performed in line with the principles of the Helsinki declaration and approval was obtained from the University of Witwatersrand Human (Medical) Research Ethics Committee (approval number: M06-07-33; protocol number: M120562) in Johannesburg, South Africa. All participants gave written informed consent.

Baseline characteristics. Baseline characteristics including cardiovascular risk factors were recorded using previously reported methods[24] and are given in the Supplementary File, available from the authors on request.

Arterial function. Central arterial function measurements were evaluated using radial applanation tonometry and SphygmoCor software, as previously reported[9]. Pulse wave velocity, central aortic BP, and its determinants (reflected and forward wave pressures) were measured using a high-fidelity SPC-301 micromanometer (Millar Instrument Inc.), interfaced with a computer using SphygmoCor software version 9.0 (AtCor Medical Pty. Ltd.). After resting for 15 min in the supine position, arterial waveforms at the radial (dominant arm), carotid, and femoral artery pulses were recorded for a period of 10 consecutive waveforms (heartbeats). The pulse wave was calibrated by manual measurement (auscultation) of brachial BP taken immediately before the recordings. Using a validated generalized transfer function incorporated in the SphygmoCor software, the peripheral pressure wave form was converted into a central aortic waveform. When systolic or diastolic variability of consecutive waveforms exceeded 5% or the amplitude of the pulse wave signal was < 80 mV, the recorded results were discarded. The aortic pulse wave velocity was calculated as distance in meters divided by transit time in seconds. The magnitude of the forward and reflected wave components of the aortic pressure waveform was determined by the SphygmoCor software that separates the aortic waveform by using a modified triangular waveform. Augmentation index was calculated as (second systolic peak/first systolic peak) × 100, reflection magnitude as (reflected wave amplitude/forward wave amplitude) × 100, and pulse pressure amplification as radial pulse pressure/aortic pulse pressure. All measurements were made by a single experienced technician who was unaware of the cardiovascular risk factor profiles of the patients. Brachial BP was recorded in all patients. Technically sound measurements of the central pressure wave and pulse wave velocity were obtained in 169 and 160 patients, respectively. Further details on arterial function measurements are given in the Supplementary File, available from the authors on request.

Data analysis. Results are presented as mean (SD), median [interquartile range (IQR)], or proportions as appropriate. Non-normally distributed characteristics were logarithmically transformed prior to statistical analysis.

Mean values of arterial function measures among patients from different population groups were compared by the ANOVA test. Correlations among arterial function measures were assessed by the Pearson's correlation coefficient test.

Age, sex, race, heart rate, body height, and brachial BP are major confounders in the present context. We assessed the association of traditional risk factors and RA characteristics with arterial function in multivariable linear regression models with adjustment for the respective features. This

revealed a large number of patient characteristics that were associated with arterial function. These characteristics were therefore consistently entered in stepwise backward regression models to identify independent relationships.

Statistical computations were made using SPSS software, version 21 (SPSS). Significance was set at $p < 0.05$.

RESULTS

The recorded patient characteristics are given in Table 1. Mean (SD) age at time of the study was 58.0 years (12.1) and median (IQR) RA duration 14.5 years (9.0–21.7). Dyslipidemia, hypertension (HTN), current smoking, and diabetes were recorded in 47.5%, 40.7%, 10.2%, and 5.6% of the patients, respectively. Lipid-lowering medications and antihypertensive agents were each used in 40% of the study population.

Rheumatoid factor (RF) and anticitrullinated protein antibody positivity were present in 75.1% and 69.5% of the participants, respectively. Disease activity was overall well controlled with a median (IQR) Clinical Disease Activity Index (CDAI) score of 5 (1–13) and a mean (SD) 28-joint Disease Activity Score (DAS28) of 2.8 (1.7); 67.8% and 61.7% of patients had mild disease activity or experienced remission according to recommended CDAI and DAS28 score cutoff values, respectively. One or more synthetic disease-modifying agents were taken by 90.3% of participants, whereas 11.3% took biologic agents. The mean (SD) central systolic pressure was 126 (16) mmHg and median (IQR) pulse wave velocity was 8.0 (6.1–9.3) m/sec.

Table 1. Recorded characteristics in 177 patients with rheumatoid arthritis. Dichotomous variables are expressed as proportions or percentages and continuous variables as mean (SD) or median (interquartile range).

Variables	Values	Variables	Values
Demographic characteristics		RF-positive	75.1
Age at study time, yrs	58.0 (12.1)	ACPA-positive	69.5
Age at disease onset, yrs	42.1 (13.8)	Clinical Disease Activity Index	5 (1–13)
Female sex	82.5	Disease Activity Score in 28 joints	2.8 (1.7)
White	66.7	ESR, mm/h	12 (4–26)
Asian	18.1	C-reactive protein, mg/l	3.2 (1.2–7.9)
Black	12.4	Leukocytes, n/nl	5.5 (4.5–7.0)
Mixed	2.8	Deformed joints, n	0 (0–10)
Lifestyle factors		Extraarticular manifestations	22
Exercise	32.2	Stanford HAQ-DI	0.375 (0.000–0.875)
Alcohol use	31.6	Synthetic disease-modifying agents	
Current smoking	10.2	Methotrexate	75.7
Anthropometry		Chloroquine	50.3
Body mass index, kg/m^2	26.8 (5.5)	Leflunomide	40.1
Waist circumference, cm	92 (14)	Sulfasalazine	16.4
Waist-to-hip ratio	0.88 (0.09)	Tetracycline	15.3
Metabolic risk factors		Azathioprine	6.8
Hypertension	40.7	Current DMARD, n	2.1 (1.1)
Systolic BP, mmHg	128 (15)	Biological disease-modifying agents	
Diastolic BP, mmHg	81 (8)	TNF-α inhibitors	8.5
Total cholesterol, mmol/l	4.5 (1.0)	Abatacept	2.8
HDL cholesterol, mmol/l	1.66 (0.46)	Nonsteroidal antiinflammatory drugs	34.5
LDL cholesterol, mmol/l	2.4 (0.9)	Prednisone use	2.3
Triglycerides, mmol/l	1.0 (0.7–1.3)	CKD-EPI, ml/min/1.73 m^2	99.3 (87.3–107.6)
Cholesterol–HDL cholesterol ratio	2.7 (2.3-3.2)	Heart rate, bpm	72 (12)
Cholesterol–HDL cholesterol ratio > 4, %	9.0	Framingham score	2.9 (5.4)
Dyslipidemia	47.5	Arterial function	
Diabetes	5.6	Central systolic BP, mmHg	126 (16)
Glucose, mmol/l	4.9 (4.5–5.1)	Central diastolic BP, mmHg	84 (9)
HOMA-IR	1.4 (1.0–1.9)	Central pulse pressure, mmHg	42 (14)
Cardiovascular agents		Aortic-femoral pulse wave velocity, m/sec	8.0 (6.1–9.3)
Antihypertensives	40.1	Aortic augmentation index, %	31 (11)
Statins	40.1	Forward wave pressure, mmHg	28 (9)
Ezetimibe	10.7	Reflected wave pressure, mmHg	21 (8)
Oral glucose-lowering agents	2.3	Reflection magnitude, %	75 (23)
Insulin	1.7	Pulse pressure amplification	1.22 (1.16–1.31)
RA characteristics		Peripheral pulse pressure, mmHg	47 (13)
RA duration, yrs	14.5 (9.0–21.7)		

HDL: high-density lipoprotein; LDL: low-density lipoprotein; BP: blood pressure; HOMA-IR: homeostatic model assessment of insulin resistance; RA: rheumatoid arthritis; RF: rheumatoid factor; ACPA: anticitrullinated protein antibodies; ESR: erythrocyte sedimentation rate; Stanford HAQ-DI: Stanford Health Assessment Questionnaire–Disability Index; DMARD: disease-modifying antirheumatic drugs; TNF: tumor necrosis factor; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration.

Disparities in arterial function measures among patients with RA with a different population origin are given in Table 2. Significant differences in mean values (logarithmic transformation was applied for data with non-normal distribution) across groups were observed for central pulse pressure and the forward and reflected wave pressure.

Table 3 shows the bivariate relations between the evaluated arterial function measures. Reflected wave pressure, central systolic pressure, and central and peripheral pulse pressure were each related to all other measurements. Pulse wave velocity was associated with other measurements except for the augmentation index and reflection magnitude, and a borderline significant relationship (p = 0.06) to pulse pressure amplification.

Associations of patient characteristics with arterial function. Table 4 shows the age, sex, race, heart rate, body height, and systolic and diastolic adjusted significant associations of other patient characteristics with arterial function; apart from race, these potential confounders were indeed each associated with 1 to 5 of the evaluated arterial function measures as reported in non-RA populations[1,2,3,4,5,6,7,8,9,10–14].

The analysis revealed that a further 20 patient character-istics were, to a variable extent, significantly related to arterial function. These features were lifestyle factors (exercise and alcohol consumption), anthropometric measures [body mass index (BMI), waist circumference and waist-to-hip ratio], metabolic risk factors [total and high-density lipoprotein (HDL) cholesterol concentrations and homeostatic model assessment for insulin resistance (HOMA-IR)], cardiovascular drug use (statins and insulin), Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) estimated glomerular filtration rate, RA characteristics [disease duration, deformed joint count, RF status, C-reactive protein (CRP) levels and leukocyte count], and RA treatment with methotrexate (MTX), chloroquine, tetracycline, and tumor necrosis factor (TNF)-α inhibition. Among anthropometric measures, BMI was associated with 3 arterial function measures whereas waist circumference and waist-to-hip ratio related to only 1 of the respective variables. Also, among markers of cumulative inflammation, disease duration was associated with 6 arterial function measures whereas deformed joint count related to only 1 of the respective measures. Recorded characteristics that were not associated with arterial function are given in Supplementary Table 1, available from the authors on request.

Table 2. Arterial function among patients with rheumatoid arthritis from different population groups. Results are expressed as mean (SD) and median (interquartile range) for normally and non-normally distributed characteristics, respectively.

Measurement	White, n = 118	Asian, n = 32	Black, n = 22	Mixed, n = 5	p
Central systolic BP, mmHg	127 (16)	123 (15)	125 (15)	131 (17)	0.5
Central pulse pressure, mmHg	**44 (14)**	**37 (11)**	**39 (13)**	**46 (11)**	**0.02**
Pulse wave velocity, m/s	7.3 (5.9–10.0)	7.2 (6.3–8.3)	7.3 (6.2–8.5)	7.5 (3.3–15.0)	0.7
Augmentation index, %	30 (11)	32 (12)	37 (11)	31 (7)	0.08
Forward wave pressure, mmHg	**29 (8)**	**25 (8)**	**24 (9)**	**32 (13)**	**0.01**
Reflected wave pressure, mmHg	**22 (8)**	**17 (5)**	**19 (7)**	**22 (4)**	**0.02**
Reflection magnitude, %	75 (24)	70 (19)	81 (26)	74 (16)	0.4
Pulse pressure amplification	1.22 (1.15–1.32)	1.24 (1.17–1.32)	1.22 (1.16–1.28)	1.21 (1.12–1.42)	0.9
Peripheral pulse pressure, mmHg	48 (13)	42 (10)	44 (17)	49 (19)	0.07

Intergroup comparisons were made by the ANOVA test with logarithmic transformation of pulse wave velocity and pulse pressure amplification. Significant disparities are shown in bold. BP: blood pressure.

Table 3. Bivariate relations among arterial function measurements in 177 patients with rheumatoid arthritis. Results are expressed as Pearson correlation coefficients (p).

	Pulse Wave Velocity	Augmentation Index	Reflected Wave Pressure	Reflection Magnitude	Central Systolic BP	Central Pulse Pressure	Peripheral Pulse Pressure	Pulse Pressure Amplification	Forward Wave Pressure
Pulse wave velocity	**1**								
Augmentation index	0.10 (0.2)	**1**							
Reflected wave pressure	**0.27 (< 0.01)**	**0.54 (< 0.01)**	**1**						
Reflection magnitude	0.07 (0.4)	**0.78 (< 0.01)**	**0.62 (< 0.01)**	**1**					
Central systolic BP	**0.39 (< 0.01)**	**0.35 (< 0.01)**	**0.76 (< 0.01)**	**0.30 (< 0.01)**	**1**				
Central pulse pressure	**0.28 (< 0.01)**	**0.42 (< 0.01)**	**0.96 (< 0.01)**	**0.42 (< 0.01)**	**0.80 (< 0.01)**	**1**			
Peripheral pulse pressure	**0.29 (< 0.01)**	**0.21 (0.01)**	**0.66 (< 0.01)**	**0.25 (< 0.01)**	**0.64 (< 0.01)**	**0.68 (< 0.01)**	**1**		
Pulse pressure amplification	–0.15 (0.06)	**–0.76 (< 0.01)**	**–0.59 (< 0.01)**	**–0.70 (< 0.01)**	**–0.37 (< 0.01)**	**–0.48 (< 0.01)**	**–0.18 (0.02)**	**1**	
Forward wave pressure	**0.28 (< 0.01)**	–0.04 (0.6)	**–0.16 (0.03)**	**–0.16 (0.03)**	**0.66 (< 0.01)**	**0.80 (< 0.01)**	**0.57 (< 0.01)**	–0.06 (0.4)	**1**

Significant associations are shown in bold. [1]Logarithmically transformed. BP: blood pressure.

Table 4. Associations of baseline characteristics with arterial function in 177 patients with rheumatoid arthritis.

Characteristic	Arterial Stiffness		Wave Reflection										Pressure Pulsatility							
	Pulse wave velocity		Augmentation index		Reflected wave pressure		Reflection magnitude		Central systolic BP		Central pulse pressure		Peripheral pulse pressure[1]		Pulse pressure amplification		Forward wave pressure	
	Partial r	p	Partial r	p	Partial r	p	Partial r	p	Partial r	p	Partial r	p	Partial r	p	Partial r	p	Partial r	p
Age	**0.37**	**< 0.01**	0.03	0.7	**0.30**	**< 0.01**	0.10	0.2	**0.20**	**0.01**	**0.31**	**< 0.01**	**0.38**	**< 0.01**	–0.13	0.1	**0.22**	**0.01**
Female	–0.09	0.3	**0.22**	**0.01**	0.14	0.08	**0.19**	**0.01**	0.01	0.9	0.09	0.2	0.07	0.4	**–0.17**	**0.03**	–0.05	0.5
Heart rate	0.05	0.6	**–0.42**	**< 0.01**	**–0.54**	**< 0.01**	**–0.56**	**< 0.01**	**–0.24**	**< 0.01**	**–0.41**	**< 0.01**	0.04	0.6	**0.70**	**< 0.01**	0.08	0.3
Body height	0.02	0.8	**–0.19**	**0.02**	**–0.17**	**0.03**	**–0.17**	**0.03**	–0.06	0.5	–0.14	0.08	–0.04	0.6	**0.19**	**0.01**	–0.05	0.5
SBP	0.15	0.06	**0.20**	**0.01**	**0.64**	**< 0.01**	**0.23**	**< 0.01**	**0.66**	**< 0.01**	**0.63**	**< 0.01**	—	—	**–0.16**	**0.04**	**0.47**	**< 0.01**
DBP	0.06	0.5	0.03	0.7	**–0.36**	**< 0.01**	–0.06	0.5	0.07	0.4	**–0.37**	**< 0.01**	—	—	–0.05	0.5	**–0.28**	**< 0.01**
Exercise	–0.01	0.9	–0.11	0.2	–0.10	0.2	–0.06	0.5	**–0.15**	**0.05**	–0.11	0.2	–0.12	0.1	0.10	0.2	–0.07	0.4
Alcohol	0.06	0.5	0.09	0.2	–0.01	0.9	0.11	0.1	–0.04	0.7	–0.04	0.6	**–0.16**	**0.02**	–0.13	0.1	–0.10	0.2
BMI[2]	–0.11	0.2	**–0.22**	**< 0.01**	**–0.19**	**0.02**	–0.13	0.09	–0.14	0.08	–0.13	0.1	0.01	0.9	**0.23**	**< 0.01**	–0.02	0.8
Waist	–0.06	0.5	–0.15	0.07	–0.12	0.1	–0.09	0.3	–0.03	0.7	–0.07	0.4	0.02	0.8	**0.19**	**0.02**	–0.02	0.8
WHR	0.05	0.6	–0.06	0.4	–0.06	0.5	–0.03	0.7	0.06	0.5	–0.06	0.5	0.03	0.7	**0.18**	**0.02**	–0.06	0.5
Statin	0.06	0.5	–0.04	0.6	0.04	0.6	–0.08	0.3	**0.21**	**0.01**	0.10	0.2	0.05	0.5	0.09	0.2	0.10	0.2
Insulin treatment	–0.07	0.4	0.10	0.2	0.00	1.0	0.10	0.2	**–0.16**	**0.04**	–0.01	0.9	**0.16**	**0.04**	–0.12	0.1	–0.06	0.4
RA duration[3]	**0.18**	**0.03**	0.09	0.3	**0.29**	**< 0.01**	0.14	0.07	**0.20**	**0.01**	**0.28**	**< 0.01**	**0.21**	**0.01**	–0.12	0.1	**0.17**	**0.03**
CRP	–0.13	0.1	–0.07	0.4	–0.10	0.2	0.08	0.3	–0.12	0.1	**–0.16**	**0.04**	**0.17**	**0.03**	0.08	0.3	**–0.16**	**0.05**
Deformed joint	0.01	0.9	0.07	0.4	0.14	0.08	0.06	0.5	**0.19**	**0.01**	0.15	0.06	–0.00	1.0	–0.02	0.8	0.13	0.1
RF-positive	0.02	0.9	0.09	0.3	**0.17**	**0.03**	0.10	0.22	0.06	0.4	0.14	0.07	0.07	0.4	**–0.17**	**0.03**	0.08	0.3
WCC	0.00	1.0	0.10	0.1	0.15	0.07	**0.17**	**0.03**	0.09	0.3	0.11	0.2	0.10	0.2	–0.12	0.1	–0.01	0.9
Methotrexate	**0.16**	**0.05**	–0.05	0.6	0.03	0.7	–0.06	0.5	0.04	0.6	0.08	0.3	0.50	0.6	–0.01	0.9	0.11	0.2
Chloroquine	0.02	0.8	0.01	0.9	–0.03	0.7	0.03	0.7	–0.08	0.3	–0.04	0.6	**–0.17**	**0.03**	–0.02	0.8	–0.04	0.6
Tetracycline	0.07	0.4	–0.02	0.8	0.03	0.7	–0.07	0.4	0.05	0.5	0.06	0.5	**–0.18**	**0.02**	0.01	0.9	0.10	0.2
TNF-α inhibitor	**–0.19**	**0.02**	–0.14	0.08	–0.06	0.5	–0.09	0.3	–0.04	0.6	–0.01	0.9	0.05	0.5	**0.16**	**0.04**	0.04	0.6
CKD-EPI[4]	**–0.28**	**< 0.01**	0.16	0.07	–0.05	0.6	0.07	0.4	–0.03	0.7	–0.09	0.3	**–0.25**	**< 0.01**	–0.10	0.2	–0.13	0.1
Total cholesterol	0.02	0.8	**0.20**	**0.01**	0.03	0.7	**0.21**	**0.01**	0.01	0.9	–0.04	0.6	0.07	0.4	**–0.20**	**0.01**	–0.13	0.09
HDL cholesterol	0.09	0.3	**0.20**	**0.01**	0.14	0.08	**0.22**	**< 0.01**	–0.07	0.4	0.05	0.6	0.04	0.6	**–0.22**	**< 0.01**	–0.08	0.3
HOMA-IR	–0.03	0.8	**–0.20**	**0.02**	–0.07	0.4	–0.07	0.4	–0.03	0.7	–0.02	0.8	0.11	0.2	0.09	0.3	–0.00	1.0

Associations were assessed in age, sex, race, body height, heart rate, and systolic and diastolic BP adjusted linear regression models with exceptions as stated below. Non-normally distributed variables were log transformed prior to being entered in the models. Significant associations are shown in bold. [1]Systolic and diastolic BP were not included in the models because these characteristics form part of brachial BP measurements. [2]Body height was not entered into the models because this characteristic is included in BMI calculation. [3]Age at time of the study was replaced by age at disease onset, to avoid duplication. [4]Age, sex, and race were not entered into the models because these characteristics are included in CKD-EPI calculation. SBP: systolic blood pressure; DBP: diastolic blood pressure; BMI: body mass index; RA: rheumatoid arthritis; WHR: waist-hip ratio; CRP: C-reactive protein; RF: rheumatoid factor; WCC: white cell (leukocyte) count; TNF: tumor necrosis factor; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration; HDL: high-density lipoprotein; HOMA-IR: homeostatic model assessment for insulin resistance.

Independent relationships of patient characteristics with arterial function. In view of the large number of associations between recorded characteristics and arterial function measures in the previous analysis, patient characteristic–arterial function relationships were further evaluated in stepwise backward regression models. These results are given in Table 5. Except for waist circumference, waist-to-hip ratio, and deformed joint count, each patient characteristic shown in Table 3 was entered consistently into the models; race was additionally forced into the models. The CKD-EPI was rejected by the analysis owing to co-linearity with age.

Besides HDL cholesterol concentrations and chloroquine, all analyzed characteristics were independently associated with at least 1 and up to 8 of the 9 evaluated arterial function measures. Age and brachial systolic or mean BP related to large, and body height and diastolic BP to low measures of arterial function, as reported in non-RA populations. Race was also directly associated with augmentation index and inversely to peripheral pulse pressure. In this regard, the mean (SD) augmentation index values were lower in whites [130 (11)] compared to patients from other population groups [131 (7) to 137 (11); Table 2] whereas peripheral BP was larger in white [48 (13)] than in Asian [42 (10)] and black [44 (17)] RA participants. Exercise, alcohol consumption, and insulin therapy were associated with favorable, and total cholesterol concentrations with unfavorable arterial function measures. Statin therapy was paradoxically associated with increased central systolic BP (partial r = 0.28, p < 0.01). The mean (SD) Framingham score was 4.1 (6.4) and 2.1 (4.5) in patients taking statins compared to patients not taking them (p < 0.01), respectively. BMI (partial r = –0.19, p = 0.02) and HOMA-IR (partial r = –0.20, p = 0.01) were each paradoxically related to low augmentation index values. BMI was further paradoxically associated with a large pulse pressure

Table 5. Independent relationships of baseline characteristics with arterial function in 177 patients with rheumatoid arthritis.

| Characteristic | Arterial Stiffness | | Wave Reflection | | | | | | | | Pressure Pulsatility | | | | | | | | |
| | Pulse wave velocity | | Augmentation index | | Reflected wave pressure | | Reflection magnitude | | Central systolic BP | | Central pulse pressure | | Peripheral pulse pressure[1] | | Pulse pressure amplification | | Forward wave pressure | |
	Partial r	p	Partial r	p	Partial r	p	Partial r	p	Partial r	p	Partial r	p	Partial r	p	Partial r	p	Partial r	p
Age	**0.27**	**< 0.01**	—	—	**0.29**	**< 0.01**	—	—	—	—	**0.33**	**< 0.01**	**0.24**	**< 0.01**	—	—	**0.31**	**< 0.01**
Female	**–0.22**	**0.01**	**0.16**	**0.05**	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Race[2]	—	—	**0.21**	**0.01**	—	—	—	—	—	—	—	—	**–0.28**	**< 0.01**	—	—	—	—
Body height	—	—	**–0.27**	**< 0.01**	**–0.39**	**< 0.01**	**–0.43**	**< 0.01**	—	—	**–0.32**	**< 0.01**	—	—	**0.42**	**< 0.01**	—	—
Heart rate	—	—	**–0.43**	**< 0.01**	**–0.56**	**< 0.01**	**–0.62**	**< 0.01**	**–0.27**	**< 0.01**	**–0.41**	**< 0.01**	—	—	**0.74**	**< 0.01**	**0.16**	**0.05**
SBP	**0.27**	**< 0.01**	**0.32**	**< 0.01**	**0.66**	**< 0.01**	**0.26**	**< 0.01**	**0.79**	**< 0.01**	**0.67**	**< 0.01**	—	—	**–0.25**	**< 0.01**	**0.51**	**< 0.01**
DBP	—	—	—	—	**–0.34**	**< 0.01**	—	—	—	—	**–0.37**	**< 0.01**	—	—	—	—	**–0.31**	**< 0.01**
Mean BP	—	—	—	—	—	—	—	—	—	—	**0.46**	**< 0.01**	—	—	—	—	—	—
BMI[3]	—	—	**–0.19**	**0.02**	—	—	—	—	—	—	—	—	**–0.29**	**< 0.01**	**0.20**	**0.01**	—	—
Exercise	—	—	—	—	—	—	—	—	—	—	—	—	—	—	**0.19**	**0.02**	—	—
Alcohol	—	—	—	—	—	—	—	—	—	—	—	—	**–0.27**	**< 0.01**	—	—	—	—
Statin	—	—	—	—	—	—	—	—	**0.28**	**< 0.01**	—	—	—	—	—	—	—	—
Insulin Rx	—	—	—	—	**–0.24**	**< 0.01**	—	—	**–0.30**	**< 0.01**	**–0.29**	**< 0.01**	—	—	**–0.19**	**0.02**	**–0.30**	**< 0.01**
RA duration[4]	—	—	—	—	—	—	**0.17**	**0.04**	—	—	—	—	—	—	—	—	—	—
CRP	**–0.17**	**0.05**	—	—	—	—	—	—	—	—	**–0.24**	**< 0.01**	—	—	—	—	**–0.20**	**0.01**
RF-positive	—	—	—	—	**0.20**	**0.01**	—	—	—	—	**0.18**	**0.03**	—	—	**–0.19**	**0.02**	—	—
WCC	—	—	—	—	**0.16**	**0.05**	**0.19**	**0.02**	—	—	**0.16**	**0.05**	—	—	—	—	—	—
Methotrexate	**0.19**	**0.03**	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Chloroquine	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Tetracycline	—	—	—	—	—	—	—	—	—	—	—	—	**–0.20**	**0.02**	—	—	—	—
TNF-α	**–0.25**	**< 0.01**	—	—	—	—	—	—	—	—	—	—	—	—	**0.23**	**< 0.01**	—	—
Total chol.	—	—	**0.24**	**< 0.01**	—	—	**0.26**	**< 0.01**	—	—	—	—	—	—	**–0.18**	**0.03**	—	—
HDL chol.	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
HOMA-IR	—	—	**–0.20**	**0.01**	—	—	—	—	—	—	—	—	**–0.21**	**< 0.01**	—	—	—	—
Model R²	**0.37**		**0.48**		**0.71**		**0.48**		**0.68**		**0.68**		**0.48**		**0.63**		**0.46**	

Significant associations are shown in bold. Relationships were assessed in stepwise backward regression models; all patient characteristics (other than waist circumference, waist-to-hip ratio, and no. deformed joints) were consistently entered as independent variables with exceptions as stated below, and race was additionally forced into the models. The Chronic Kidney Disease Epidemiology Collaboration was rejected in the analysis because of co-linearity with age. [1]Systolic and diastolic blood pressure were replaced by mean arterial pressure in the model. [2] White = 1; Asian = 2; black = 3; mixed = 4. [3]Height was not entered into the model. [4]Age at time of the study was replaced by age at disease onset in the model. SBP: systolic blood pressure; DBP: diastolic blood pressure; BP: blood pressure; BMI: body mass index; Rx: treatment; RA: rheumatoid arthritis; CRP: C-reactive protein; RF: rheumatoid factor; WCC: white cell (leukocyte) count; TNF: tumor necrosis factor; chol: cholesterol; HDL: high-density lipoprotein; HOMA-IR: homeostatic model assessment for insulin resistance.

amplification (partial r = 0.20, p = 0.01) and HOMA-IR with peripheral pulse pressure (partial r = –0.21, p < 0.01).

Among RA characteristics, disease duration was associated with reflection magnitude (partial r = 0.17, p = 0.04) and RF status was related to central pulse pressure (partial r = 0.18, p = 0.03), reflected wave pressure (partial p = 0.20, p = 0.01), and pulse pressure amplification (partial r = –0.19, p = 0.02). Leukocyte count was also directly related to central pulse pressure (partial r = 0.16, p = 0.05), reflected wave pressure (partial r = 0.16, p = 0.05), and reflection magnitude (partial r = 0.19, p = 0.02). In this regard, the leukocyte count was associated with the logarithmically transformed CDAI (Pearson r = 0.21, p < 0.01), DAS28 (Pearson r = 0.19, p = 0.01), and logarithmically transformed CRP concentrations (Pearson r = 0.34, p < 0.01). Neither RA duration nor RF status and leukocyte count were related to pulse wave velocity and augmentation index.

CRP concentrations were paradoxically related to low central pulse pressure (partial r = –0.24, p < 0.01), pulse wave velocity (partial r = –0.17, p = 0.05), and forward wave pressure (partial r = –0.20, p = 0.01) values.

Regarding RA treatment, TNF-α inhibition was associated with reduced pulse wave velocity (partial r = –0.25, p < 0.01) and increased pulse pressure amplification (partial r = 0.23, p < 0.01) whereas tetracycline use (partial r = –0.20, p = 0.02) was related to low peripheral pulse pressure. MTX use was paradoxically associated with large pulse wave velocity (partial r = 0.19, p = 0.03). The joint deformity count tended to be larger in patients using MTX [median (IQR) = 1 (0–11)] compared to those who did not [median (IQR) = 0 (0–3); p = 0.08]. Therefore, MTX use may have represented a disease severity marker in the present context.

Overall, the recorded patient characteristics explained 37% (pulse wave velocity) to 71% (reflected wave pressure) of the variability in arterial stiffness.

DISCUSSION

Our present study explored the potential effect of a wide range of traditional cardiovascular risk factors and disease characteristics on different aspects of arterial function in patients with RA. The data analysis produced several novel findings. In previous RA studies, pulse wave velocity and augmentation index were the most frequently investigated central hemodynamic measures[21]. In our investigation, disease duration that represents cumulative inflammation and RF positivity that characterizes severe RA[25] were associated with central pulse pressure and wave reflection markers independent of brachial BP and other potential confounders, but unrelated to pulse wave velocity or augmentation index. RF status was further associated with reduced pulse pressure amplification, which also predicts incident cardiovascular events in non-RA populations[3,4,16]. Additionally, the leukocyte count that represented disease activity in this RA population was similarly associated with central pulse pressure and wave reflection, not with pulse wave velocity or augmentation index. Leukocyte count as an inflammatory marker was previously reported to represent an indicator of arterial stiffness in non-RA persons[26] and atherosclerosis in patients with RA[27].

Associations of cumulative inflammation, and disease activity and severity as assessed by area under the curve erythrocyte sedimentation rate (ESR), CDAI, or DAS28 and Health Assessment Questionnaire–Disability Index (HAQ-DI), respectively, with arterial stiffness were reported in some[28,29,30] but not all[31] previous RA studies. In our present study, in contrast to leukocyte counts, no relationships were identified between CDAI or DAS28 and HAQ-DI and any of the 9 evaluated arterial function measures. However, the majority of patients in the present investigation experienced either low disease activity or remission, which could have accounted for our findings.

We found that RA treatment related to arterial stiffness. TNF-α inhibition was associated with reduced pulse wave velocity, in keeping with findings in most previous RA studies[32]. TNF-α inhibition was also associated with increased BP amplification in our present study. Interestingly, Vassilopoulos and colleagues[33] reported a reduction in pulse wave velocity with adalimumab that occurred irrespective of treatment response and was unrelated to decreases in DAS28 among patients with RA. We further report for the first time, to our knowledge, that tetracycline use is associated with a reduced peripheral pulse pressure in RA. In this regard, matrix metalloproteinases (MMP) play a pivotal role in vascular changes induced by HTN and arterial stiffness[34]. Doxycycline, the tetracycline used in our patients, comprises a potent MMP inhibitor and reduces functional and structural alterations in HTN as well as arterial stiffness[34]. The potential role of doxycycline in cardiovascular risk prevention in RA merits further longitudinal investigation.

BMI and insulin resistance were associated with reduced augmentation index and peripheral pulse pressure. BMI additionally related to increased pulse pressure amplification. An inverse relationship of adiposity and insulin resistance with arterial function markers has been increasingly documented in non-RA subjects[35,36,37,38]. Indeed, excess adiposity is associated with reduced wave reflection in indigenous Australians[35] as well as Korean subjects[36] with metabolic syndrome. In indigenous Australians, fasting insulin concentrations were also related to decreased wave reflection[35]. Circulating concentrations of free fatty acids that are major initiators of insulin resistance are associated with a reduced augmentation index and central systolic BP and increased pulse pressure amplification[37]. The Toon Health study reported an inverse relationship between insulin resistance and central BP[38]. Upon applying separation analysis in diabetic patients, Chirinos and colleagues[39] recently reported reduced wave reflection that may account for increased penetration of pulsatile energy to distal vascular beds, and thereby enhance microvascular disease. Compensatory hyperinsulinemia in response to insulin resistance may induce vasodilation, leading to reduced central pressures and wave reflection[38]. In this regard, insulin treatment was also associated with reduced central pressures and wave reflection in our present study. Although insulin administration lowers arterial stiffness in healthy as well as diabetic persons[40], the latter finding should be interpreted with caution because only 3 patients with RA used insulin in this investigation.

A third of our patients exercised regularly and/or consumed low or moderate alcohol quantities (data not shown). A metaanalysis documented that aerobic exercise reduces pulse wave velocity and the augmentation index in non-RA persons[41]. Individualized exercise was documented to reduce cardiovascular risk in RA[42]. Light and moderate alcohol consumption is associated with pulse wave velocity in non-RA subjects[43]. In this study, exercise was related to pulse pressure amplification and alcohol consumption to reduced peripheral pulse pressure.

Hypercholesterolemia increases arterial stiffness and central but not peripheral BP[44]. Total and low-density lipoprotein cholesterol as well as triglyceride concentrations were both related to central BP and wave reflection markers in previous non-RA studies[45]. In the present investigation, total cholesterol concentrations were independently associated with increased augmentation index and reflection magnitude, and reduced pulse pressure amplification.

Arterial stiffness and wave reflections are the most important determinants of systolic and pulse pressure[10,46]. In concert, these hemodynamic changes increase cardiac workload and affect coronary, cerebral, and renal blood flow, and are associated with atherosclerosis[10,46]. Our results suggest that lifestyle intervention, adequate treatment of traditional cardiovascular risk factors, and disease control may reduce cardiovascular risk by improving arterial function in RA. Notably in this regard, we found more

consistent relationships of cardiovascular risk factors and RA characteristics with wave reflection and pressure pulsatility than with arterial stiffness.

We evaluated a comprehensive panel of arterial function measures and consistently adjusted for recognized and newly identified potential confounders. However, we assessed a large number of associations and used backward regression models on data obtained in a study with a cross-sectional design, which precludes drawing conclusions on the direction of causality. These limitations may have contributed to our finding of an inverse relationship of CRP concentrations with pulse wave velocity and central pulse pressure, and a direct association of statin therapy with central systolic BP. Indeed, CRP concentrations are reportedly associated with increased pulse wave velocity in RA[21] and several studies have shown a beneficial effect of statin therapy on arterial stiffness in non-RA persons[47], as well as in those with RA[48]. We did not include a healthy control group, and future interventional studies are clearly indicated. Cumulative ESR values and CRP concentrations[28] represent better markers of inflammation accrued over time than disease duration, but were not recorded in the present study.

Traditional cardiovascular risk factors and disease characteristics are consistently related to vascular hemodynamic alterations in RA. The relative effect of arterial stiffness, wave reflection, and pressure pulsatility in the enhanced CVD risk among patients with RA needs further investigation.

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