Arterial wave reflection and subclinical atherosclerosis in rheumatoid arthritis

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Abstract

Objective

Atherosclerotic cardiovascular disease risk is increased in rheumatoid arthritis (RA). Wave reflection occurs at arterial branching points, which are particularly prone to atherosclerosis. We explored the relationship of wave reflection with atherosclerosis in RA.

Methods

One hundred and sixty three RA patients (110 white, 31 Asian, 17 black and 5 of mixed ancestry) without cardiovascular disease participated. Arterial stiffness, wave reflection, pressure pulsatility, plaque in the extracranial carotid artery tree and the mean of the left and right common carotid arteries intima-thickness were determined. Associations were identified in multivariable regression models.

Results

One SD increase in reflected wave pressure (OR (95% CI) = 2.54 (1.41–4.44), p=0.001), reflection magnitude (OR (95% CI) = 1.84 (1.17–2.89), p=0.008), central pulse pressure (OR (95% CI) = 1.89 (1.12–3.22), p=0.02) and peripheral pulse pressure (OR (95% CI) = 2.09 (1.23–3.57), p=0.007) were associated with plaque. The association of wave reflection with plaque was independent of arterial stiffness and pressure pulsatility, and was present in both hypertensive and normotensive RA patients. In receiver operator characteristic curve analysis, the optimal cutoff value for reflected wave pressure in predicting plaque presence was 25 mmHg with a sensitivity, specificity, positive predictive value and negative predictive value of 45.2%, 89.3%, 78.6% and 66.2%, respectively; a reflected wave pressure of >25 mmHg was associated with plaque in univariate and adjusted analysis (p<0.0001 for both). Arterial function was not independently related to carotid intima-media thickness.

Conclusion

Consideration and therapeutic targeting of wave reflection may improve cardiovascular disease prevention in RA.

Key words

wave reflection, arterial stiffness, pressure pulsatility, atherosclerosis, rheumatoid arthritis

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Introduction

Aging and exposure to cardiovascular risk factors is associated with impaired arterial function (1-14). This results in haemodynamic changes that increase left ventricular afterload and reduce coronary blood flow (1-14). Impaired arterial function predicts end organ damage, heart failure and cardiovascular mortality (1-14).

The state-of-the-art estimation of arterial stiffness is by measurement of pulse wave velocity (5). However, besides age and blood pressure, there is little or no association between cardiovascular risk factors and pulse wave velocity (13). Whether arterial stiffness is related to atherosclerosis in non-RA subjects remains uncertain as studies addressing this association have produced conflicting results (13). In this regard, increased arterial wave reflection and pressure pulsatility represent other arterial properties that predict cardiovascular event rates (1-5, 7-14). Wave reflection occurs at arterial branching points and is further influenced by arterial wall content (5, 7-9).

The increased risk of atherosclerotic cardiovascular disease in rheumatoid arthritis (RA) is well documented (15). Patients with RA categorised as having moderate cardiovascular risk when risk charts are used often have carotid plaques (16). This finding unveils the high subclinical atherosclerotic burden observed in these patients. A recent meta-analysis reported enhanced pulse wave velocity and augmentation index in RA (17). Avalos and colleagues (18) found that the augmentation index was related to coronary artery calcification in RA but this association was attenuated (p=0.09) upon adjustment for potential confounders. We recently reported that pulse wave velocity and augmentation index are not independently associated with carotid atherosclerosis in Spanish patients with RA (19). Arterial branching points are the sites that are particularly prone to atherosclerosis due to a departure from the axially aligned unidirectional flow and reduced wall shear stress (20, 21). In this study, we hypothesised that wave reflection as assessed in separation analysis (5, 7-10), is associated with atherosclerosis in RA. Additionally, we aimed to validate our previously reported findings on the lack of association of pulse wave velocity and augmentation index with atherosclerosis in patients with RA (19).

Patients and methods

Patients

We enrolled 163 consecutive patients (110 white, 31 Asian, 17 black and 5 of mixed ancestry) that fulfilled the 2010 ACR/European League Against Rheumatism (EULAR) criteria for RA (22) and were free of established cardiovascular disease at the Milpark Hospital, Johannesburg, South Africa. This cross-sectional study obtained approval from the University of Witwatersrand Human (Medical) Research Ethics Committee (approval number: M06-07-33; protocol number: M120562) in Johannesburg, South Africa. Each participant gave written, informed consent.

Baseline characteristics

Standardised methods were used to record baseline characteristics (23). Briefly, demographic features, lifestyle factors, anthropometric measures, metabolic risk factors, RA characteristics and cardiovascular and anti-rheumatic agent use were evaluated. Disease activity was estimated by the Clinical Disease Activity Index (CDAI) and Disease Activity Score in 28 joints (DAS28), and physical impairment by the Stanford Health Assessment Questionnaire disability index. C-reactive protein was measured by immunoturbidimetry and insulin using a chemiluminescent microparticle immunoassay (Abbott Laboratories, Abbott Park, IL 60064 USA).

Hypertension was diagnosed when the average systolic blood pressure of ≥140 and/or diastolic blood pressure of ≥90mmHg and/or anti-hypertensive medication was employed. Dyslipidaemia was identified when the atherogenic index, *i.e.* the cholesterol/high density lipoprotein (HDL) ratio was > 4 (15) and/or lipid lowering agents were used. Diabetes was diagnosed in patients that employed glucose lowering agents or had a fasting plasma glucose of ≥ 7mmol/l. The glomerular filtration rate was estimated by the Chronic Kidney Disease Epidemiology Collaboration

(CKD-EPI) equation (24) and the homeostatic model assessment of insulin resistance (25) was calculated.

Arterial function measurements

Central haemodynamic parameters were evaluated using radial applanation tonometry and SphygmoCor software (26). Pulse wave velocity (27), aortic blood pressure and reflected and forward wave pressures were determined using a high-fidelity SPC-301 micromanometer (Millar instument, Inc., Houston, Texas), interfaced with a computer utilising SphygmoCor software, version 9.0 (AtCor Medical Pty. Ltd., West Ryde, New South Wales, Australia). After resting for 15 minutes in the supine position, arterial waveforms at the radial (dominant arm), carotid and femoral artery pulses were recorded for a time period of 10 consecutive waveforms (heart beats). The pulse wave was calibrated by manual measurement (auscultation) of brachial BP taken immediately before the recordings. Using a validated generalised transfer function incorporated in the SphygmoCor software, the peripheral pressure waveform 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 less that 80 mV, the recorded results were discarded. Aortic pulse wave velocity was determined from sequential waveform measurements at carotid and femoral sites as previously described. The time delay in pulse waves between the carotid and femoral sites was determined using an ECG-derived R wave as a fudicial point. Pulse transit time was taken as the average of 10 consecutive beats. The distance which the pulse wave travels was determined as the difference between the distance from the femoral sampling site to the suprasternal notch and the distance from the carotid sampling site to the suprasternal notch.

The carotid-femoral pulse wave velocity was calculated as the distance between the carotid and femoral pulses in meters divided by transit time in seconds. Central systolic blood pressure was derived from the aortic wave form and central aortic pulse pressure was calculated from the difference between central systolic blood pressure and central diastolic blood pressure. 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 employing a modified triangular waveform. Augmentation index was defined as the augmented pressure (difference between second and first systolic shoulder) expressed as a percentage of central pulse pressure. Reflection magnitude was calculated as (reflected wave amplitude/forward wave amplitude) x 100 and pulse pressure amplification as the radial pulse pressure divided by the 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 pressures were obtained in all patients and technically sound wave reflection, and pulse wave velocity measurements in 157 and 150 participants, respectively. The intra-observer variability of tonometry measurements is low in our setting (26).

Carotid artery ultrasound

Carotid artery ultrasound was performed using high resolution B-mode ultrasound (LOGIC E9, GE Healthcare, USA) with software that provides semi-automated border detection and markedly reproducible data. Images of at least 1cm length of the distal common carotid arteries were obtained using a linear array 5–13 MHz probe. The optimal angle of incidence was used, defined as the longitudinal angle of approach where both branches of the internal and external carotid artery are visualised simultaneously. The carotid intima-media thickness (c-IMT) was defined as the mean of the left and right common carotid arteries thickness. Plaque in the extracranial carotid tree was defined according to the Mannheim consensus criteria (28). A single qualified technician who was blinded to the cardiovascular risk profiles of the patients, performed all carotid ultrasound measurements. The intra-observer variability of ultrasound measurements is low in our setting (23).

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.

The relationships of arterial function parameters with c-IMT and plaque were assessed in multivariable linear and logistic regression models, respectively. These results were expressed as partial correlation coefficient (r) and odds ratio (OR) (95% confidence interval (CI)), respectively; corresponding *p*-values were provided. As age, sex, race, heart rate, body height, body weight and brachial mean blood pressure are established potential confounders in the present context (5, 9, 10), these characteristics were entered into each of the initial models. Subsequently, other baseline characteristics (see Table I) that had bivariate associations with the arterial function variables were additionally entered as potential confounders in fully adjusted models on atherosclerosis.

Receiver operator characteristic (ROC) curve analysis was implemented when arterial function measures were consistently related to atherosclerotic plaque. We calculated the Youden index and applied Bayes' theorem.

Statistical analysis was performed using IBM SPSS statistics program (v. 23.0, IBM, USA). A *p*-value of ≤0.05 was considered significant. This included the construction of a ROC curve.

Results

Patient characteristics

Recorded patient characteristics are given in Table I. Mean (SD) age and RA duration were 58.4 (11.7) and 16.0 (10.1) years, respectively. Hypertension, dyslipidaemia and diabetes were observed in 41.7%, 49.1% and 6.1% of the patients, respectively. Disease activity was overall mild with a mean (SD) DAS28 of 2.9 (1.7) and median (IQR) CDAI of 5 (1–13). All except 12 (7.4%) patients were using synthetic or biologic disease-modifying agents. The median (IQR) pulse wave velocity was 8.1 (6.2–9.4) m/sec and 46.6% of the patients had plaque.

Table I. Recorded characteristics in 163 RA patients.

Demographic characteristics		ACPA positive	71.4
Age at study time, years	58.4 (11.7)	CDAI	5 (1-13)
Female gender	79.1	DAS 28	2.9 (1.7)
White	67.5	ESR, mm/h	13 (4-26)
Asian	19.0	CRP, mg/l	3.3 (1.2-8.0)
Black	10.4	Leukocyte count, n/nl	6.0 (2.1)
Mixed	3.1	Deformed joints, n	7 (1)
Lifestyle factors		Extra-articular manifestations	22.7
Exercise	31.3	HAQ-DI	0.375 (0.000-0.875)
Alcohol use	30.1	Synthetic DMARD	
Current smoking	9.8	Methotrexate	76.1
Anthropometry		Chloroquine	50.3
BMI, kg/m^2	26.7 (5.5)	Leflunomide	40.5
Waist circumference, cm	92 (14)	Sulphasalazine	16.6
Waist-hip ratio	0.88 (0.08)	Tetracycline	16.0
Metabolic risk factors		Azathioprine	6.7
Hypertension	41.7	Current synthetic DMARD, n	2.1 (1.1)
Systolic BP, mm Hg	129 (15)	Biological DMARD	
Diastolic BP, mm Hg	81 (8)	Abatacept	3.1
Total cholesterol, mmol/l	4.5 (1.0)	TNF-α inhibitors	9.2
HDL cholesterol, mmol/l	1.68 (0.46)	NSAID	34.4
LDL cholesterol, mmol/l	2.5 (0.9)	Prednisone use	2.5
Triglycerides, mmol/l	1.0 (0.7-1.3)	CKD-EPI, ml/min/1.73 m^2	99 (87-108)
Total C – HDL C ratio	2.8 (0.8)	Heart rate, beats/min	73 (12)
Total C – HDL C ratio >4	8.6	Arterial function	
Dyslipidaemia	49.1	Pulse wave velocity, m/sec	8.1 (6.2-9.4)
Diabetes	6.1	Augmentation index, %	31 (11)
Glucose, mmol/l	4.9 (0.7)	Reflected wave pressure, mm Hg	21 (8)
Insulin,	6.4 (4.6-9.0)	Reflection magnitude	76 (23)
HOMA-IR, μU.mmol/ml.l	1.40 (0.96-1.98)	Central SBP, mm Hg	126 (15)
Cardiovascular agent use		Central DBP, mm Hg	84 (9)
Antihypertensives	41.1	Central pulse pressure, mm Hg	42 (13)
Statins	41.7	Peripheral pulse pressure, mm Hg	48 (13)
Ezetimibe	11.7	Pulse pressure amplification	1.20 (1.15-1.31)
Oral glucose-lowering agents	2.5	Forward wave pressure, mm Hg	29 (9)
Insulin, μU/ml	1.8	Carotid atherosclerosis	
RA characteristics		Mean IMT, mm	0.655 (0.137)
Disease duration, years	16.0 (10.1)	Plaque	46.6
RF positive	74.2		

Continuous variables are expressed as mean (SD), median (interquartile range) or proportions as appropriate. RA: rheumatoid arthritis; BMI: body mass index; BP: blood pressure; HDL: high-density lipoprotein; LDL: low-density lipoprotein; C: cholesterol; HOMA-IR: Homeostatic Model Assessment of insulin resistance; RF: rheumatoid factor; ACPA: anti-citrullinated protein antibody; CDAI: Clinical disease activity score; DAS28: Disease Activity Score in 28 joints; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; HAQ-DI: Stanford Health Assessment Questionnaire disability index; DMARD: disease modifying anti-rheumatic drugs; TNF-α: tumour necrosis factor-alpha; NSAID: non-steroidal anti-inflammatory drugs; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration; SBP: systolic blood pressure; DBP: diastolic blood pressure; IMT: mean intima-media thickness.

Associations of arterial function with atherosclerosis in 163 RA patients

Table II shows that in univariate analysis, pulse wave velocity (partial r=0.277, p=0.001), reflected wave pressure (partial r=0.276, p<0.001), central systolic blood pressure (partial r=0.334, p<0.001), central pulse pressure (partial r=0.313, p<0.001), peripheral pulse pressure (partial r=0.165, p=0.04) and forward wave pressure (partial r=0.298, p<0.001) were associated with C-IMT. After adjustment for established potential confounders, pulse wave velocity, peripheral pulse pressure and forward wave pressure were no longer related to c-IMT whereas augmentation index (partial r=0.125, p=0.04) became associated with c-IMT. In fully adjusted models, except for central pulse pressure (partial r=0.161, p=0.05), arterial function measures were unrelated to c-IMT.

In univariate analysis, 1 SD increase in pulse wave velocity (OR (95% CI) = 1.67 (1.13–2.48), p=0.01), reflected wave pressure (OR (95% CI) = 1.82 (1.28–2.59), p=0.001), central systolic blood pressure (OR (95% CI) = 1.75 (1.22–2.50), p=0.002), central pulse pressure (OR (95% CI) = 2.13 (1.46–3.12), p<0.001), peripheral pulse pressure (OR (95% CI) = 2.13 (1.46–3.12), p<0.001) and forward wave pressure (OR = 1.78 (1.25–2.54), p<0.001) were each associated with carotid plaque. Upon adjustment for established potential confounders, pulse wave velocity, central systolic blood pressure and forward wave pressure were no longer associated with carotid plaque whereas reflection magnitude (OR (95% CI) = 1.76 (1.14–2.71), p=0.01) became related to plaque. In fully adjusted models, reflected wave pressure (OR (95% CI) = 2.54 (1.41–4.44), p=0.001), reflection magnitude (OR (95% CI) = 1.84 (1.17–2.89), p=0.008), central

Table II. Relationships of arterial function measures with C-IMT and plaque in 163 RA patients.

	C-IMT						Plaque					
	Univariate model		Known confounder[1] adjusted model		Fully adjusted[2] multivariate model		Univariate model (for 1 SD increase)		Known confounder[1] adjusted model (for 1 SD increase)		Fully adjusted[2] Model (for 1 SD increase)	
	r	*p*	Partial r	*p*	Partial r	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*
PWV[3]	**0.277**	**0.001**	-0.051	0.6	-0.045	0.6	**1.67 (1.13-2.48)**	**0.01**	1.11 (0.74-1.65)	0.6	1.03 (0.66-1.62)	0.9
AI[4]	0.017	0.8	**0.125**	**0.04**	0.128	0.1	1.05 (0.76-1.44)	0.8	1.56 (0.98-2.48)	0.06	1.56 (0.94-2.70)	0.08
RWP[5]	**0.276**	**<0.001**	**0.128**	**0.04**	0.128	0.1	**1.82 (1.28-2.59)**	**0.001**	**2.50 (1.44-4.35)**	**0.001**	**2.54 (1.41-4.44)**	**0.001**
RM[6]	0.043	0.6	0.079	0.2	0.105	0.2	1.17 (0.89-1.53)	0.2	**1.76 (1.14-2.71)**	**0.01**	**1.84 (1.17-2.89)**	**0.008**
CSBP[7]	**0.334**	**<0.001**	**0.169**	**0.006**	**0.161**	**0.05**	**1.75 (1.22-2.50)**	**0.002**	1.72 (0.98-3.01)	0.06	1.54 (0.85-2.79)	0.1
CPP[8]	**0.313**	**<0.001**	**0.129**	**0.04**	0.131	0.1	**2.13 (1.46-3.12)**	**<0.001**	**1.96 (1.18-3.26)**	**0.009**	**1.89 (1.12-3.22)**	**0.02**
PPP[9]	**0.165**	**0.04**	-0.026	0.7	-0.066	0.4	**2.13 (1.46-3.12)**	**<0.001**	**1.95 (1.21-3.13)**	**0.006**	**2.09 (1.23-3.57)**	**0.007**
PPA[10]	-0.074	0.4	-0.094	0.1	-0.114	0.2	1.05 (0.76-1.43)	0.8	0.81 (0.45-1.46)	0.5	0.65 (0.34-1.27)	0.2
FWP[11]	**0.298**	**<0.001**	0.072	0.3	0.078	0.3	**1.78 (1.25-2.54)**	**<0.001**	1.31 (0.87-1.98)	0.2	1.27 (0.82-2.00)	0.3

Associations were determined in multivariable linear and logistic regression models for C-IMT and plaque, respectively. Known confounders[1] comprised age, sex, race, body height, body weight, heart rate and mean blood pressure. Significant relationships are shown in bold. C-IMT: carotid intima-media thickness; SD: standard deviation; OR: odds ratio; CI: confidence interval; PWV: pulse wave velocity; AI: augmentation index; RWP: reflected wave pressure; RM: reflection magnitude; CSBP: central systolic blood pressure; CPP: central pulse pressure; PPP: peripheral pulse pressure; PPA: pulse pressure amplification; FWP: forward wave pressure.
Variables additionally included in the different fully adjusted models[2] were: [3]Waist-hip ratio, total cholesterol-HDL ratio, extra-articular manifestations and statin, tumour necrosis factor-α inhibitor and abatacept therapy. [4]Total cholesterol and HDL cholesterol concentrations, homeostatic model assessment for insulin resistance and tumour necrosis factor-α inhibitor therapy. [5]Number of synthetic disease modifying agents currently used. [6]HDL cholesterol concentrations, and tumour necrosis factor-α inhibitor and leflunomide therapy. [7]Total cholesterol-HDL cholesterol ratio and statin and chloroquine therapy.[8]Total cholesterol-HDL cholesterol ratio and statin and chloroquine therapy. [9]Total cholesterol-HDL cholesterol, C-reactive protein concentrations and statin, tetracycline and chloroquine therapy. [10]Waist-hip ratio, total cholesterol and glucose concentrations, and leflunomide and tumour necrosis factor-α inhibitor therapy. [11]Total cholesterol-HDL cholesterol ratio and statin therapy.

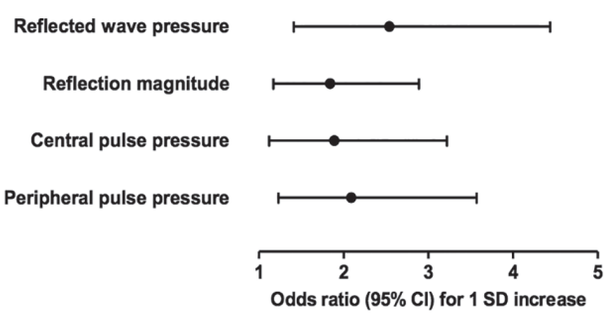

Fig. 1. Relationships of arterial function measures with carotid plaque.

pulse pressure (OR (95% CI) = 1.89 (1.12–3.22), *p*=0.02) and peripheral pulse pressure (OR (95% CI) = 2.09 (1.23–3.57), *p*=0.007) were associated with plaque. These results are further illustrated in Figure 1. Upon additional adjustment for pulse wave velocity in the latter 4 models, reflected wave pressure (OR (95% CI) = 2.56 (1.45–4.52), *p*=0.001), reflection magnitude (OR (95% CI) = 1.94 (1.22–3.09), *p*=0.005), central pulse pressure (OR (95% CI) = 1.91 (1.11–3.29), *p*=0.02) and peripheral pulse pressure (OR (95% CI) = 2.11 (1.22–3.65), *p*=0.008) remained related to plaque. Also, upon additional adjustment for dyslipidaemia, diabetes and smoking in the latter 4 models, reflected wave pressure (OR (95% CI) = 2.38 (1.35–4.20), *p*=0.003), reflection magnitude (OR (95% CI) = 1.91 (1.19–3.06), *p*=0.007), central pulse pressure (OR (95% CI) = 1.82 (1.08–3.09), *p*=0.03) and peripheral pulse pressure (OR (95% CI) = 1.81 (1.12–3.00), *p*=0.01) remained related to plaque.

Cardiovascular and biologic agents can influence arterial function (5, 29). Therefore, we reassessed the reflected wave pressure-, reflection magnitude-, central pulse pressure- and peripheral pulse pressure–plaque relationships in the last 2 columns in Table II with consistent additional adjustment for the use of angiotensin converting enzyme inhibitors (n=23), angiotensin receptor blockers (n=27), calcium channel blockers (n=32), beta receptor blocking agents (n=14), statins, tumour necrosis factor-α inhibitors and abatacept. Reflected wave pressure (OR (95% CI) = 2.15 (1.20–3.84), *p*=0.01), reflection magnitude (OR (95% CI) = 1.56 (0.99–2.47), *p*=0.05), central pulse pressure (OR (95% CI) = 1.71 (0.99–2.94), *p*=0.05) and peripheral pulse pressure (OR (95% CI) = 2.21 (1.26–3.89), *p*=0.006) remained associated with carotid plaque. By contrast, when we reassessed the central systolic blood pressure-c-IMT relationship (column 6 and 7 in Table II) with additional adjustment of cardiovascular and biologic agent use, the respective association was no longer significant (partial r=0.112, *p*=0.2).

Wave reflection, pressure pulsatility and carotid plaque in RA

In Table III, wave reflection and pressure pulsatility measures were entered together in 4 different established confounder and cardiovascular and biologic agent use adjusted regression models for carotid plaque. Reflected wave pressure and reflection magnitude remained consistently associated with plaque. Central and peripheral pulse pressure were no longer significantly associated with plaque when entered together with wave reflection measures.

Wave reflection is related to carotid plaque in hypertensive and normotensive patients with RA

In Table IV, the established confounder adjusted associations of arterial func-

Table III. Independent relationships of 1 SD increase in arterial function measures in combination with plaque in 163 RA patients

Model	OR (95% CI)	*p*
Model 1[1]		
RWP	**8.34 (1.55-44.77)**	**0.01**
CPP	0.27 (0.06-1.24)	0.09
Model 2[1]		
RWP	**1.89 (0.99-3.65)**	**0.05**
PPP	1.22 (0.71-2.09)	0.5
Model 3[1]		
RM	**1.61 (1.04-2.50)**	**0.03**
CPP	1.55 (0.93-2.56)	0.09
Model 4[1]		
RM	**1.61 (1.04-2.49)**	**0.03**
PPP	1.52 (0.96-2.39)	0.07

[1]Adjusted for known confounders of age, sex, race, body height, body weight, heart rate and mean blood pressure as well as cardiovascular drug and biologic agent use. Significant associations are shown in bold.
SD: standard deviation; RWP: reflected wave pressure; CPP: central pulse pressure; PPP: peripheral pulse pressure; RM: reflection magnitude.

Table IV. Independent relationships of arterial function measures with C-IMT and plaque in hypertensive and normotensive patients with RA.

	C-IMT		Plaque	
	Partial r	*p*	OR (95% CI)	*p*
Hypertensive RA patients (n=68)				
PWV	-0.039	0.8	0.68 (0.29-1.63)	0.4
AI	0.250	0.06	1.41 (0.75-2.65)	0.3
RWP	0.157	0.2	**2.91 (1.28-6.62)**	**0.01**
RM	0.132	0.3	**2.43 (1.02-5.81)**	**0.04**
CSBP	0.242	0.07	2.38 (0.97-5.84)	0.06
CPP	0.160	0.2	**2.31 (1.10-4.82)**	**0.02**
PPP	-0.059	0.7	**2.53 (1.14-5.58)**	**0.02**
PPA	**-0.261**	**0.05**	1.78 (0.64-4.92)	0.3
FWP	0.058	0.7	1.54 (0.84-2.81)	0.2
Normotensive RA patients (n=95)				
PWV	-0.046	0.7	1.35 (0.83-2.20)	0.2
AI	0.096	0.5	2.16 (0.99-4.69)	0.05
RWP	0.167	0.1	**2.93 (1.18-7.28)**	**0.02**
RM	0.093	0.4	**1.82 (1.04-3.20)**	**0.03**
CSBP	0.196	0.07	1.32 (0.59-2.96)	0.5
CPP	0.162	0.1	1.96 (0.87-4.44)	0.1
PPP	-0.034	0.8	1.67 (0.84-3.33)	0.1
PPA	-0.025	0.8	0.44 (0.17-1.13)	0.09
FWP	0.130	0.2	1.12 (0.59-2.15)	0.7

Associations were determined in age, sex, race, body height, body weight, heart rate and mean blood pressure adjusted multivariable linear and logistic regression models for C-IMT and plaque, respectively. Significant relationships are shown in bold. C-IMT: carotid intima-media thickness; SD: standard deviation; OR: odds ratio; CI: confidence interval; PWV: pulse wave velocity; AI: augmentation index; RWP: reflected wave pressure; RM: reflection magnitude; CSBP: central systolic blood pressure; CPP: central pulse pressure; PPP: peripheral pulse pressure; PPA: pulse pressure amplification; FWP: forward wave pressure.

tion measures with C-IMT and plaque were determined in hypertensive and normotensive RA patients. Apart from pulse pressure amplification (partial r=-0.261, p=0.05) in hypertensive patients, arterial function was not independently related to c-IMT. Central pulse pressure and peripheral pulse pressure were associated with plaque in hypertensive (OR (95% CI) = 2.31 (1.10–4.82), p=0.02 and OR (95% CI) = 2.53 (1.14–5.58), p=0.02, respectively) but not in normotensive RA patients. By contrast, reflective wave pressure and reflection magnitude were related to plaque in both hypertensive (OR (95% CI) = 2.91 (1.28–6.62), p=0.01 and OR (95% CI) = 2.43 (1.02–5.81), p=0.04, respectively) and normotensive RA patients (OR (95% CI) = 2.93 (1.18–7.28), p=0.02 and OR (95% CI) = 1.82 (1.04-3.20), p=0.03, respectively). Additional adjustment for cardiovascular and biologic agent use was deemed inappropriate as it would have translated into the application of overfitted models.

Accuracy of reflected wave pressure in predicting plaque presence

In the foregoing analysis, reflected wave pressure comprised the arterial stiffness measure that was most consistently related to carotid plaque prevalence. As shown in Figure 2, the area under the curve (0.658) in receiver operator characteristic curve analysis for reflected wave pressure was significantly (p=0.001) associated with plaque presence. Based on calculation of the Youden index (30) and application of Bayes' theorem (31), the optimal cut-off value for reflected wave pressure in predicting plaque presence was 25 mm Hg with a corresponding sensitivity, specificity, positive predictive value and negative predictive value of 45.2%, 89.3%, 78.6% and 66.2%, respectively. In a univariate logistic regression model, a reflected wave pressure of >25 mm Hg (OR = 6.30 (2.82–14.07), p<0.0001) was associated with plaque. This relationship was strengthened after adjusting for established potential confounders (OR = 13.71 (4.24–44.34), p<0.0001).

Relationships of arterial function with atherosclerosis in women with RA

Women comprised 79.1% of RA patients in the present study. The impact of arterial function on cardiovascular disease can differ by gender (5, 7). Table 5 gives the results of a sensitivity analysis on the potential established confounder and fully adjusted arterial function-carotid plaque relations amongst 135 participating women with RA. Reflected wave pressure, reflection magnitude and central pulse pressure remained strongly associated with plaque whereas the peripheral pulse pressure-plaque relationship was attenuated (p=0.06 in the fully adjusted model). Upon additional adjustment for cardiovascular and biologic agent use, reflected wave pressure (OR (95% CI) = 2.32 (1.22–4.42), p=0.01) and reflection magnitude (OR (95% CI) = 1.78 (1.10–2.87), p=0.01) remained associated with carotid plaque; the central pulse pressure-carotid plaque relationship was no longer significant (OR (95% CI) = 1.81 (0.89–3.35), p=0.06). None of the arterial function measures was independently associated with c-IMT (data not shown). A sensitivity analysis was not performed in men due

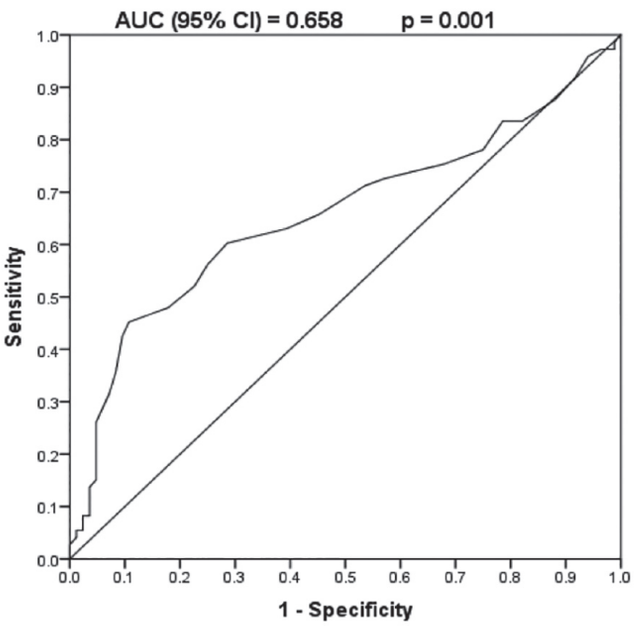

Fig. 2. Receiver operator characteristic curve showing the accuracy of reflected wave pressure in predicting plaque presence among 163 patients with RA.

Table V. Independent relationships of arterial function with carotid plaque in 135 women with RA.

	Known confounder[1] adjusted multivariable model (for 1 SD increase)		Fully adjusted Multivariable model[2] (for 1 SD increase)	
	OR (95% CI)	*p*	OR (95% CI)	*p*
PWV[3]	1.33 (0.77-2.28)	0.3	1.19 (0.62-2.26)	0.6
AI[4]	1.62 (0.98-2.66)	0.06	1.73 (0.97-3.10)	0.06
RWP[5]	**2.87 (1.51-5.47)**	**0.001**	**3.00 (1.54-5.69)**	**0.001**
RM[6]	**1.80 (1.14-2.85)**	**0.01**	**1.91 (1.18-3.09)**	**0.009**
CSBP[7]	1.85 (0.97-3.53)	0.06	1.51 (0.75-3.10)	0.2
CPP[8]	**2.23 (1.23-4.04)**	**0.008**	**2.06 (1.11-3.82)**	**0.02**
PPP[9]	**1.68 (1.03-2.73)**	**0.04**	1.71 (0.99-2.97)	0.06
PPA[10]	0.71 (0.35-1.44)	0.4	0.58 (0.26-1.29)	0.2
RWP[11]	1.34 (0.83-2.19)	0.3	1.26 (0.76-2.09)	0.4

Associations were determined in multivariable logistic regression models. Known confounders[1] comprised age, sex, race, body height, body weight, heart rate and mean blood pressure. Significant relationships are shown in bold. SD: standard deviation; OR: odds ratio; CI: confidence interval; PWV: pulse wave velocity; AI: augmentation index; RWP: reflected wave pressure; RM: reflection magnitude; CSBP: central systolic blood pressure; CPP: central pulse pressure; PPP: peripheral pulse pressure; PPA: pulse pressure amplification; FWP: forward wave pressure. Variables additionally included in a different fully adjusted models[2] were: [3]Waist-hip ratio, total cholesterol-HDL cholesterol ratio, extra-articular manifestations and statin, tumour necrosis factor-α inhibitor and abatacept therapy. [4]Total cholesterol and HDL cholesterol concentrations, homeostatic model assessment for insulin resistance and tumour necrosis factor-α inhibitor therapy. [5]Number of synthetic disease modifying agents currently used. [6]HDL cholesterol concentrations, and tumour necrosis factor-α inhibitor and leflunomide therapy. [7]Total cholesterol-HDL cholesterol and statin and chloroquine therapy. [8]Total cholesterol-HDL cholesterol and statin and chloroquine therapy. [9]Total cholesterol-HDL cholesterol and C-reactive protein concentrations and statin, tetracycline and chloroquine therapy. [10]Waist-hip ratio, total cholesterol and glucose concentrations, and leflunomide and tumour necrosis factor-α inhibitor therapy. [11]Total cholesterol-HDL cholesterol ratio and statin therapy.

to the small number (n=28) involved. Upon replacement of mean blood pressure by brachial systolic and diastolic blood pressure in the models (except for those on peripheral pulse pressure) in tables II, III, IV and V, the results were materially unaltered (data not shown).

Discussion

The present study shows that wave reflection as measured by reflected wave pressure and reflection magnitude is strongly associated with carotid artery plaque in patients with RA. These relationships were independent of potential confounders as well as arterial stiffness and central and peripheral pulse pressure, and were found in both hypertensive and normotensive patients with RA and in a sensitivity analysis amongst women. These findings support our hypothesis that wave reflection represents atherosclerosis in RA.

Overall, reflected wave pressure and reflection magnitude were consistently associated with plaque presence in both univariate and multivariable regression models in the present study. Wave reflection explained the associations of central and peripheral pulse pressure with plaque (Table III). In receiver operator characteristic curve analysis, reflected wave pressure was also related to plaque presence. At a cutoff value of 25 mmHg with a sensitivity, specificity, positive predictive value and negative predictive value of 45.2%, 89.3%, 78.6% and 66.2%, respectively; a reflected wave pressure of >25 mmHg was associated with plaque in univariate and adjusted analysis, respectively. Arterial plaque mostly contains a lipid core (32) and is indeed a marker of high atherosclerotic cardiovascular disease risk for which the use of cardiovascular drugs including lipid lowering agents is indicated (15, 33).The role of wave reflection in cardiovascular disease is increasingly documented in non-RA persons (5, 7-10). This together with our current results suggests that wave reflection can contribute to cardiovascular disease risk and its stratification beyond brachial pressures and other risk factors in RA.

We recently reported that pulse wave velocity was associated with c-IMT and plaque in univariate but not confounder adjusted analysis among 194 Spanish RA patients (19). Additionally, the augmentation index was consistently unrelated to c-IMT and plaque in the latter investigation (19). Although our current results validate these findings, the potential impact of arterial stiffness and wave reflection as assessed by the augmentation index requires further elucidation in future larger and longitudinal studies.

In contrast to arterial plaque, intima-media thickening mostly represents vascular remodelling in response to

blood pressure rather than atherosclerosis (34). C-IMT is particularly related to stroke (35) and its risk factors (36). In the present study, we found univariate associations of arterial stiffness and measures of wave reflection and pressure pulsatility with c-IMT but these relationships became insignificant after adjustment for potential confounders.

Arterial stiffening increases wave reflection and both of these arterial properties enlarge pulse pressure with a higher systolic and lower diastolic blood pressure (5). Despite these interlinking mechanisms, arterial stiffness, wave reflection and pressure pulsatility are also each determined by different factors, represent disparate aspects of arterial function and can contribute independently to cardiovascular risk (5). Our current findings are congruent with these previously reported observations. Additionally, we recently reported differential effects of traditional cardiovascular risk factors and disease characteristics on arterial stiffness, wave reflection and pressure pulsatility in patients with RA (12). Further mechanistic studies on arterial function in RA are clearly indicated.

The European Society of Hypertension/European Society of Cardiology guidelines for the management of arterial hypertension currently recommend determining arterial stiffness by pulse wave velocity in the identification of patients with target organ damage (37). It is therefore noteworthy that in contrast to other arterial function parameters, both reflected wave pressure and reflection magnitude were associated with carotid plaque in not only hypertensive but also normotensive patients with RA in the current status. This suggests that wave reflection may enhance cardiovascular risk and its stratification irrespective of hypertension status in RA.

Strikingly, peripheral pulse pressure was as strongly related to plaque presence as central pulse pressure in this RA investigation. In this regard, Dart and colleagues (38) previously reported that peripheral pulse pressure but not the carotid augmentation index and systemic arterial compliance predict incident cardiovascular events in elderly women with hypertension. In elderly compared to younger persons, brachial blood pressure more accurately estimates central pressure as pulse pressure amplification is reduced. This likely explains the equally strong association of brachial and central pulse pressure with plaque prevalence in the present context (38). Seventy-nine percent of our RA patients were women with a mean age of 58 years.

Our findings have treatment implications. Among antihypertensive agents, angiotensin converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB) and calcium channel blockers reduce wave reflection (39). By contrast, beta blockers can increase wave reflection and the respective effect of diuretics is neutral (39). Hypertension is frequent and its management reportedly inadequate in RA (15). The 2015/2016 update of the European League Against Rheumatism recommendations for cardiovascular disease risk management in patients with inflammatory joint diseases no longer advocate the preferred use of ACEI or ARB in the treatment of hypertension (15). Our current results together with previously reported evidence support ACEI, ARB or calcium channel blocker based first line treatment for hypertension in RA. In this regard, ACEI or ARB use is also associated with enhanced beta cell function in RA (40). Notably, Sveaas and colleagues (41) recently reported that high intensity endurance and strength exercise during 3 months results in significant decreases in pulse wave velocity as well as augmentation index in patients with axial spondyloarthritis. A recent meta-analysis revealed that aerobic but not resistance exercise reduces arterial stiffness and wave reflection in non-RA subjects (42). The effect of different exercise modalities on arterial function in patients with inflammatory joint disease requires further investigation. Resistance exercise is particularly indicated for the management of lean body mass loss associated with RA (43). Finally, tumour necrosis factor-α inhibition decreases pulse wave velocity whereas its effects on the augmentation index are inconsistent in RA (44). The influence of disease modifying agents on wave reflection as assessed in separation analysis has not been reported in RA.

Recently, Ikdahl and colleagues (45) reported an association between pulse wave velocity and incident cardiovascular events (n=10) in RA. In contrast to wave reflection and pressure pulsatility, arterial stiffness was not independently related to carotid atherosclerosis in our current and previous investigation (19). This suggests that the effects of arterial stiffness on cardiovascular disease risk in RA may be mediated by mechanisms other than enhanced atherosclerosis such as decreased coronary blood flow and increased left ventricular afterload, which predisposes to arrhythmias (5, 46).

We assessed the associations of 9 different arterial function indices with carotid artery plaque and IMT in comprehensively adjusted regression models among a relatively large multi-ethnic group of RA patients. Relationships between arterial function and atherosclerosis may be bidirectional (1). The main limitation of this investigation is the lack of a control population. Accordingly, whether our findings are RA specific should be the subject of future studies. Also, our study design was cross-sectional and therefore precluded identifying cause-effect relationships.

In conclusion, wave reflection is associated with severe atherosclerosis in RA. The role of wave reflection as an assessment tool and potential therapeutic target in cardiovascular risk management among patients with RA merits further study.

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