EXTENDED REPORT

Lower limb arterial incompressibility and obstruction in rheumatoid arthritis

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Background: Despite increased cardiovascular morbidity and mortality in rheumatoid arthritis, the peripheral arteries remain understudied.
Objective: To examine the lower limb arteries in age and sex matched, non-smoking subjects with and without rheumatoid arthritis.
Methods: The ankle-brachial index (ABI) was measured at the posterior tibial and dorsal pedal arteries. Arteries were classified as obstructed with ABI $\leqslant$0.9, normal with ABI $>$0.9 but $\leqslant$1.3, and incompressible with ABI $>$1.3. Multinomial logistic regression was used to estimate differences in ABI between patients and controls, adjusting for cardiovascular risk factors, rheumatoid arthritis manifestations, inflammation markers, and glucocorticoid dose.
Results: 234 patients with rheumatoid arthritis and 102 controls were studied. Among the rheumatoid patients, 66 of 931 arteries (7%) were incompressible and 30 (3%) were obstructed. Among the controls, three of 408 arteries (0.7%) were incompressible ($p=0.002$) and four (1%) were obstructed ($p=0.06$). At the person level, one or more abnormal arteries occurred among 45 rheumatoid patients (19%), *v* five controls (5%, $p=0.001$). The greater frequency of arterial incompressibility and obstruction in rheumatoid arthritis was independent of age, sex, and cardiovascular risk factors. Adjustment for inflammation markers, joint damage, rheumatoid factor, and glucocorticoid use reduced rheumatoid arthritis *v* control differences. Most arterial impairments occurred in rheumatoid patients with 20 or more deformed joints. This subgroup had more incompressible (15%, $p\leqslant0.001$) and obstructed arteries (6%, $p=0.005$) than the controls, independent of covariates.
Conclusions: Peripheral arterial incompressibility and obstruction are increased in rheumatoid arthritis. Their propensity for patients with advanced joint damage suggests shared pathogenic mechanisms.

Patients with rheumatoid arthritis are at higher than normal risk of cardiovascular morbidity and mortality.[1–6] Recent studies have documented an excess rate of myocardial infarction in rheumatoid arthritis, and possibly other types of cardiovascular events as well.[7 8] In addition, studies of the central arteries in rheumatoid patients have shown increased thickness of the intimal layer,[9–12] suggesting that this disease predisposes to atherosclerosis, perhaps through an effect of systemic inflammation.[13]

If rheumatoid arthritis is an atherosclerosis prone disease, the peripheral arteries should be affected in addition to the central ones. Indeed, cases of severe peripheral vascular disease affecting rheumatoid patients have been described.[14–16] However, the frequency and extent of impaired peripheral arterial function in rheumatoid arthritis are not well established. This information is important for an understanding of atherosclerosis and cardiovascular disease in general, and of how such disorders affect patients with rheumatoid arthritis. Clinically, characterisation of peripheral arterial function in rheumatoid arthritis could promote early diagnosis and treatment of affected patients to prevent arterial occlusion and its complications.

We examined the peripheral arteries among the non-cigarette-smoking members of a cohort of rheumatoid patients, and compared them with those of an age and sex matched sample of healthy non-smoking controls. We included only non-smokers in both groups to eliminate confounding by this important risk factor for arterial disease. We used statistical adjustment to account for other cardiovascular risk factors.

METHODS

Rheumatoid arthritis patients

From 1996 to 2000, we enrolled patients who met classification criteria for rheumatoid arthritis[17] into ORALE (outcome of rheumatoid arthritis longitudinal evaluation), a study of the disablement process in rheumatoid arthritis.[18] We recruited patients consecutively from six local outpatient rheumatology clinics: a county funded clinic; a Veterans Administration clinic; a private, university based faculty practice; a community based seven rheumatologist private practice; an Army medical centre; and an Air Force medical centre. Each of these clinics provides ongoing primary rheumatological care to outpatients with rheumatic diseases referred from their covered populations, which are distinct. Combined, these clinic populations represent a broad range of socioeconomic and cultural backgrounds. All enrolled patients resided in Bexar County, Texas, or nearby communities.

We have described our sample in previous publications.[19 20] Following their initial recruitment, we have contacted patients on an annual basis for a follow up evaluation. Between February 2000 and January 2002, we invited all ORALE patients back to our institution's general clinical research centre (GCRC) for an additional visit, this time for a cardiovascular evaluation that included assessment of the peripheral arteries and a carotid artery imaging protocol that we have described earlier.[13] In the present analysis, we

Abbreviations: ABI, ankle-brachial index; BMI, body mass index; ORALE, outcome of rheumatoid arthritis longitudinal evaluation

Table 1 Characteristics of rheumatoid patients and controls

Variable	RA (n = 234)	Controls (n = 102)	p Value
Age (median (range))	59 (40 to 84)	59 (40 to 81)	0.9
Women (n (%))	210 (90)	90 (88)	0.7
Cardiovascular risk factors			
Diabetes (n (%))	39 (17)	1 (1)	⩽0.001
Systolic BP (mm Hg) (median (range))	139 (94 to 240)	136 (98 to 202)	0.7
Diastolic BP (mm Hg) (median (range))	74 (46 to 150)	77 (52 to 124)	0.3
Hypercholesterolaemia (n (%))	118 (50)	57 (56)	0.4
BMI (kg/m^2) (median (range))	28.2 (14.2 to 56.4)	25.8 (18.4 to 43.3)	⩽0.001
Current/past cigarette smoking (n (%))	0	0	–
FH of cardiovascular disease (n (%))	95 (45)	55 (54)	0.1
Disease duration (median (range))	12.3 y (6 w to 55 y)	0	
Tender joint (median (range))	10 (0 to 47)	0	–
Swollen joints (median (range))	9 (3 to 19)	0	–
Deformed joints (median (range))	16 (0 to 48)	0	–
Subcutaneous nodules (n (%))	101 (43)	0	–
Drugs for rheumatoid arthritis			
Methotrexate (n (%))	126 (54)	0	–
Prednisone (n (%))	106 (45)	0	–
Average ESR (mm/h) (median (range))	31 (1 to 141)	18 (1 to 62)	⩽0.001
Average CRP (mg/l) (median (range))	7.9 (0.2 to 260)	2.4 (0.1 to 29.9)	⩽0.001
Rheumatoid factor positive (n (%))	149 (65)	1 (1)	⩽0.001

BMI, body mass index; BP, blood pressure; CRP, C reactive protein; ESR, erythrocyte sedimentation rate; FH, family history; RA, rheumatoid arthritis; w, weeks; y, years.

include only the patients who had never smoked cigarettes and were aged 40 years or more at the time of the arterial assessment.

Controls

We have described the control selection process previously.[13] We stratified the never smoking rheumatoid patients in the ORALE sample into 18 categories defined by sex and five year age intervals from 40 to 85. Within these categories, we aimed to recruit one volunteer in good health who had never smoked for every two rheumatoid patients. To recruit volunteers, we advertised on billboards in our institution, in local churches and community centres, and in the local newspaper. We visited independent living facilities for aged people, and recruited by word of mouth. Respondents whose age/sex category was not yet filled, who were in good health by self report, had never smoked cigarettes, and did not have rheumatoid arthritis or systemic lupus erythematosus were invited. A substantial proportion of early respondents had an extremely high body mass index, which can impair vascular imaging protocols. To minimise technical errors, we added a screening requirement that the body mass index computed from self reported height and weight should not exceed 30 kg/m^2. In addition to the cardiovascular assessments, all controls were interviewed about their medical history, including a review of current drug treatment. We paid each control $50.

Data collection procedures

Our study was approved by the institutional review board. All subjects gave written informed consent. A physician and a trained research associate evaluated the subjects.

Peripheral artery assessment

After the subject had been in the supine position in a hospital bed for 15 minutes, a physician used a Parks 8.1 MHz pocket Doppler probe (model 841-A, Parks Medical Electronics, Aloha, Oregon, USA) and four size-appropriate cuffs to measure the systolic pressure in the dorsal pedal, posterior tibial, and brachial arteries in all four limbs. The physician who obtained the systolic pressure measurements was not aware of any hypothesis related to these measurements. We calculated the ankle-brachial index (ABI) for each lower extremity artery by dividing its pressure by the mean of the right and left brachial pressures.[21] Each subject could have up to four values for the ABI. We classified the arteries as obstructed at an ABI of 0.9 or less; normal at >0.9 to 1.3; and incompressible at >1.3.[21] Inter-rater reliability of the ABI, measured on 20 consecutive study patients assessed independently by two study physicians, showed a Spearman–Brown reliability coefficient of 0.96.

Association between ABI and arterial calcification

To further explore reports that an ABI of >1.3 reflects arterial calcification, we examined the hand radiographs of rheumatoid patients from the full ORALE cohort (both smokers and non-smokers) who had an ABI of >1.3 in the four lower limb arteries. We compared these patients with randomly selected ORALE patients matched by age and sex, whose ABI was normal in all four lower limb arteries. One of us (AE), masked to the ABI values, sought evidence of calcification in the radial or ulnar arteries in the hand *x* rays.

Cardiovascular risk factor ascertainment

We measured the systolic blood pressure to capture hypertension as a cardiovascular risk factor, and height and weight to calculate the body mass index (BMI, kg/m^2). Hypercholesterolaemia was defined as a fasting plasma cholesterol of 5.2 mmol/l (200 mg/dl) or higher, or as taking lipid lowering drugs, or by self report of a physician's diagnosis. Cases of hypercholesterolaemia among the rheumatoid patients were confirmed in the medical records. All control cases with hypercholesterolaemia were either taking lipid lowering drugs or had raised plasma cholesterol. Diabetes mellitus was defined as a fasting blood glucose of 7.0 mmol/l (126 mg/dl) or higher, or as taking antidiabetic drugs, or by self report of physician's diagnosis. All self reports that did not meet these criteria were confirmed by medical record review. We excluded current and past smokers from both the rheumatoid group and the control group. We chose this approach over matching or statistical adjustment to control for smoking because accurate matching on this variable posed important logistic problems. We did not collect any information about second hand exposure to tobacco smoke among cases or controls.

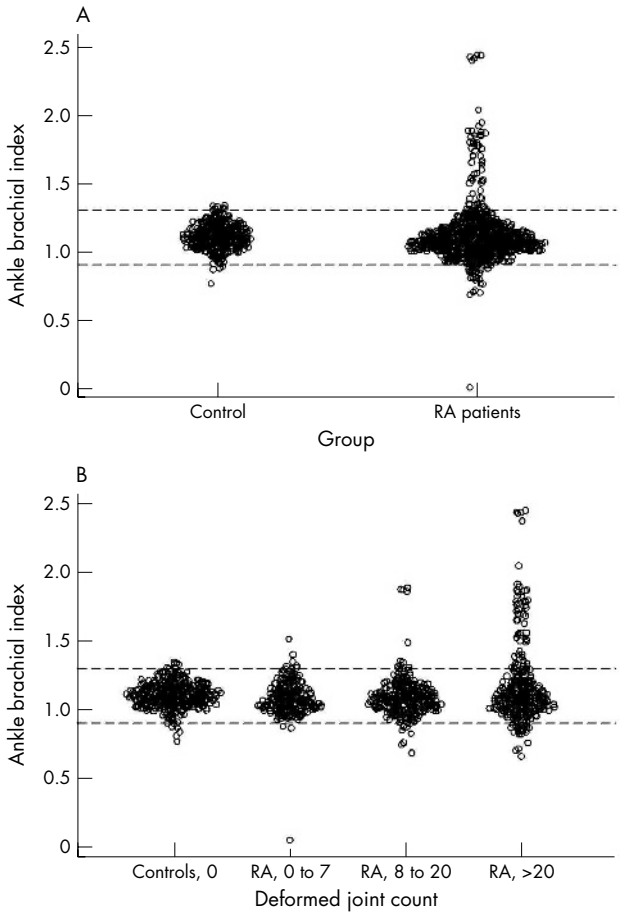

Figure 1 (A) Ankle-brachial index (ABI) in 931 arteries from patients with rheumatoid arthritis and 408 arteries from controls. The two dotted horizontal lines represent the upper and lower boundaries for the normal ABI. Values above the top dotted line indicate arterial incompressibility. Values below the lower dotted line indicate arterial obstruction. The mean ABI is similar in both groups, but the rheumatoid group shows tails extending above and below the normal range. Among controls, three of the arteries (0.7%) were incompressible and four were obstructed (1%), while in the rheumatoid group 66 of the arteries (7%) were incompressible and 30 were obstructed (4%). (B) Stratification according to the number of deformed joints showed that most of the values outside the normal range occur among rheumatoid patients with more than 20 deformed joints. In this group, 53 arteries (15%) were incompressible and 20 (6%) were obstructed. This increase in the proportion of abnormal arteries among rheumatoid patients with >20 deformed joints was independent of age, sex, cardiovascular risk factors, and markers of inflammation. See text for details.

Musculoskeletal examination

As described elsewhere,[22] we assessed 48 joints in each patient for the presence or absence of tenderness or pain on motion, for swelling or deformity, and for the presence of subcutaneous nodules.

Laboratory studies

Laboratory tests were carried out with the subject fasting, on the same day as the arterial measurements. For the erythrocyte sedimentation rate (ESR), we used the Westergren technique, and nephelometry for the C reactive protein (Quest Diagnostics, San Juan Capistrano, California, USA). Aiming to capture the effect of systemic inflammation over time, we averaged all available ESR and C reactive protein measurements done during the course of the disablement study. Serum rheumatoid factor was measured by the latex agglutination technique. Total plasma cholesterol was measured using a Synchron LX automated system (Beckman Coulter, Fullerton, California, USA).

Analysis

We used both the individual lower limb artery, and the person, as units of analysis. For artery based analyses, we adjusted the standard errors for non-independence within-person.[23] A subject could have data from up to four arteries: right and left dorsal pedal and right and left posterior tibial. Subjects could have fewer than four lower limb arteries if a lower limb had been amputated, or if a systolic pressure measurement could not be obtained on one or more of the arteries. We examined the probability of arterial obstruction or incompressibility according to rheumatoid arthritis *v* control status, using χ^2 analysis to test for differences. We employed multinomial logistic regression to adjust the rheumatoid arthritis *v* control comparisons for age, sex, cardiovascular risk factors, ESR, C reactive protein concentration, and clinical features of rheumatoid arthritis.[24] In these multinomial logistic models, the referent category was a normal ABI (that is, >0.9 but ⩽1.3), with the outcomes being obstruction (ABI ⩽0.9) or incompressibility (ABI >1.3). Because arterial measurements were clustered within person, we computed robust standard errors, adjusting for intraperson correlation.[23] This procedure provides corrected, more conservative standard errors, to account for non-independence of the arterial findings within person. All analyses were conducted using Stata, version 8 (College Station, Texas, USA).

RESULTS

Rheumatoid arthritis sample

The sample included 779 patients with rheumatoid arthritis recruited between 1996 and 2000 for the ORALE study of the disablement process in rheumatoid arthritis. We began the arterial assessments in February 2000. The disablement process in rheumatoid arthritis study visit at which we obtained the ABI measurements was the fifth for three patients, the fourth for 44, the third for 215, the second for 378, and the first for four. Sixty six patients had died and 32 had moved away from the San Antonio area before we could schedule an appointment for the arterial assessment. This left 681 patients still eligible to participate. Of these, we could not establish contact with 17, and 20 declined participation. We obtained the ABI measurements on 644 subjects (95% of

Table 2 Ankle-brachial index in rheumatoid arthritis and control arteries

Ankle-brachial index	RA (931 arteries)	Controls (408 arteries)	OR (95% CI)	p Value*
Mean (SD)	1.11 (0.20)	1.11 (0.08)	n/a	NS
>1.3 (incompressibility) (n(%))	66 (7)	3 (0.7)	10.57 (2.31 to 48.3)	0.002
>0.9 to 1.3 (normal) (n (%))	835 (90)	401 (98)	1.00 (referent)	–
⩽0.9 (obstruction) (n (%))	30 (3)	4 (1)	3.60 (0.94 to 13.8)	0.06

*p Values were calculated using robust standard errors, adjusted for within-person correlation of arterial measurements.[23]
CI, confidence interval; n/a, not applicable; OR, odds ratio.

Table 3 Rheumatoid arthritis *v* control odds ratio for arterial obstruction or incompressibility, adjusting for the effect of potential confounding variables

	Incompressibility		Obstruction	
Model covariates*	RA *v* controls OR (95% CI)	p Value	RA *v* controls OR (95% CI)	p Value
None	10.57 (2.31 to 48.30)	0.002	3.60 (0.94 to 13.8)	0.06
Age, sex	10.73 (2.32 to 49.61)	0.002	3.58 (0.95 to 13.47)	0.06
Age, sex, diabetes, hypercholesterolaemia, SBP, BMI	9.50 (2.03 to 44.50)	0.004	4.12 (0.99 to 17.05)	0.05
Age, sex, diabetes, hypercholesterolaemia, SBP, BMI, average ESR	6.54 (1.38 to 31.0)	0.02	1.12 (0.26 to 4.90)	0.9
Age, sex, diabetes, hypercholesterolaemia, SBP, BMI, average CRP	6.72 (1.4 to 32.34)	0.02	4.02 (0.95 to 17.01)	0.06
Age, sex, diabetes, hypercholesterolaemia, SBP, BMI, cumulative glucocorticoids	6.91 (1.49 to 32.05)	0.01	3.33 (0.79 to 13.96)	0.1
Age, sex, diabetes, hypercholesterolaemia, SBP, BMI, time on methotrexate	9.37 (1.84 to 47.63)	0.007	5.91 (1.35 to 25.71)	0.02
Age, sex, diabetes, hypercholesterolaemia, SBP, BMI, deformed joint count, subcutaneous nodules, rheumatoid factor	1.45 (0.20 to 10.39)	0.7	0.52 (0.05 to 5.71)	0.6

*A series of multinomial logistic regression models was tested, all of which included rheumatoid arthritis vs. controls status as an independent variable, in addition to the listed covariates.
BMI, body mass index (kg/m^2); CI, confidence interval; CRP, C reactive protein; ESR, erythrocyte sedimentation rate; OR, odds ratio; RA, rheumatoid arthritis; SBP, systolic blood pressure.

those eligible). We show the results here of the 234 non-smoking rheumatoid patients who were 40 to 85 years old at the time of the arterial assessment. Of the 69 living patients on whom we could not assess the ABI because they had moved, declined, or we could not establish contact, 18 were between the ages of 40 and 85 and did not smoke. To assess the extent of selection bias in the sample we studied, we compared baseline characteristics between the 234 non-smoking respondents and the 18 non-smoking non-respondents. All these non-respondents were women. At baseline, they had a higher swollen joint count but fewer joint deformities and lower serum cholesterol than the respondents. There was no difference between respondent and non-respondents in age, disease duration, BMI, blood pressure, tender joint count, ESR, or C reactive protein levels.

Control sample

For the control sample, we screened 585 subjects who responded to our recruitment notices. Of these, 247 were not eligible because they were current or past cigarette smokers, 19 because they were not in good health, 30 because their estimated BMI by self report exceeded 30 kg/m^2, six were diagnosed with rheumatoid arthritis, nine had an unspecified inflammatory arthritis, and one had a history of lupus erythematosus. Among eligible respondents, 159 were not studied because their age/sex category was full when they responded. An additional six eligible healthy controls were scheduled, but did not keep their appointment, and six more were screened but we could not relocate them to schedule an appointment. Our final sample included 102 non-smoking persons in good health by self report, who were matched by age and sex to the rheumatoid patients. Despite the self reported BMI screening requirement which we added after control recruitment got underway, the measured BMI still exceeded 30 kg/m^2 in 18 control subjects.

The characteristics of rheumatoid patients and controls are shown in table 1. There were no differences in age or sex, or in the frequencies of hypercholesterolaemia, family history of cardiovascular disease, or systolic and diastolic blood pressures. The frequency of diabetes mellitus was greater in the rheumatoid group. The ESR and the C reactive protein concentration were also higher in the rheumatoid patients. The value shown for the ESR among rheumatoid patients was obtained by averaging a median of four ESR determinations (range one to six) over 3.2 years (range one day to 6.9 years). In the case of the C reactive protein, the values represent the average of a median of three determinations over 1.5 years (range one day to 2.9 years). For the controls, these two inflammatory markers were measured once, at the time of the ABI.

Ankle-brachial index

We measured the ABI on 931 arteries from the 234 rheumatoid patients and 408 arteries from 102 controls. On two rheumatoid patients who had undergone below knee amputations, we could only make the systolic pressure

Table 4 Frequency of arterial abnormalities among controls and rheumatoid arthritis patients, the latter stratified according to the number of deformed joints

	Deformed joint count						
	Control		RA		Adjusted p value†		
Variable	0	0 to 7	8 to 20	21 to 48	Model 1	Model 2	Model 3
Incompressible arteries (ABI >1.3)	3 (1%)	3 (1%)	10 (3%)	53 (15%)***	0.001	⩽0.003	0.007
Normal arteries (ABI >0.9 to 1.3)	401 (98%)	245 (98%)	310 (95%)*	280 (79%)***	⩽0.001	⩽0.001	⩽0.001
Obstructed arteries (ABI ⩽0.9)	4 (1%)	2 (1%)	8 (2%)	20 (6%)**	0.04	0.01	0.4
Number of arteries	408	250	328	353			
Number of persons	102	63	82	89			

Values are n or n (%).
Adjustment models: *model 1*: age, sex, disease duration; *model 2*: age, sex, disease duration, cardiovascular risk factors (diabetes mellitus, hypercholesterolaemia, systolic blood pressure, BMI); *model 3*: age, sex, disease duration, cardiovascular risk factors, and average ESR.
*p⩽0.05; **p⩽0.01; ***p⩽0.001 *v* healthy controls.
†Comparison between rheumatoid arthritis patients with joint count ⩾21 and healthy persons.
ABI, ankle-brachial index; BMI, body mass index; ESR, erythrocyte sedimentation rate; RA, rheumatoid arthritis.

Table 5 Number of arteries affected per person, according the ankle-brachial index

	Incompressible (ABI >1.3)		Normal (ABI >0.9 to 1.3)		Obstructed (ABI ⩽0.9)	
No of affected arteries	RA (n = 234)	Control (n = 102)	RA (n = 234)	Control (n = 102)	RA (n = 234)	Control (n = 102)
4	8 (3)	0	188 (80)	97 (95)	4 (2)	0
3	3 (1)	0	21(9)	3 (3)	1 (<1)	0
2	5 (2)	1 (1)	7 (3)	2 (2)	1 (<1)	1 (1)
1	15 (6)	1 (1)	4 (2)	0	9 (4)	2 (2)
0	203 (87)	100 (98)	13 (6)	0	219 (94)	99 (97)
Total arteries (n)	66	3	835	401	30	4
χ^2 Value	10.7 with 4 degrees of freedom		13.5 with 4 degrees of freedom		2.8 with 4 degrees of freedom	
p Value	0.03		0.009		0.6	

Values are n (%) unless stated otherwise.
ABI, ankle-brachial index; RA, rheumatoid arthritis.

measurement in two arteries each. In a third rheumatoid patient, only three arteries could be assessed because of a skin ulcer overlying the posterior tibial artery.

A comparison between rheumatoid arthritis and controls using the ABI as an interval scale revealed nearly identical means for each group (table 2). However, a closer inspection of the ABI distribution in the two groups showed a striking tail in the upward or incompressible direction in the rheumatoid group (fig 1). Among the 931 rheumatoid patient arteries, 66 had an ABI of 1.3 or higher and were considered incompressible (7%), compared with three among the 408 control arteries (0.7%, $p \leqslant 0.001$). Among rheumatoid patients, 30 arteries had an ABI of $\leqslant 0.9$ and were considered obstructed (3%), *v* four arteries among the controls (1%, $p = 0.009$). With adjustment for intraperson clustering using robust standard errors,[23] the higher proportion of incompressible arteries in the rheumatoid group remained significant ($p = 0.002$, table 2), but for obstructed vessels the difference was of borderline significance ($p = 0.06$, table 2).

We used multinomial logistic regression to explore potential mechanisms for the increased frequency of arterial incompressibility or obstruction in the rheumatoid group (table 3). In these sequential models, the outcome was a three category variable identifying arteries that were normal, obstructed, or incompressible, with normal as the referent category. We used a hierarchical approach, beginning with a model that contained only the rheumatoid arthritis *v* control indicator as the independent variable. Subsequent models added age and sex, cardiovascular risk factors, blood markers of inflammation, glucocorticoid treatment, and clinical manifestations of rheumatoid arthritis. The results of these multivariate models are summarised in table 3. Because the controls were recruited to have the same age and sex distribution as the rheumatoid cases, these two variables had a negligible influence on the rheumatoid arthritis *v* control risk differentials (table 3). Adding the cardiovascular risk factors diabetes, systolic blood pressure, hypercholesterolaemia, and body mass index to the adjustment model caused the rheumatoid arthritis *v* control odds ratio for incompressibility to decrease slightly. ESR and the C reactive protein each had additional negative effects on the rheumatoid arthritis *v* control incompressibility odds ratio, but without effacing the rheumatoid arthritis–control difference. However, upon adding clinical manifestations of rheumatoid arthritis to the model, the rheumatoid arthritis *v* control odds ratio approached unity for both arterial incompressibility and obstruction (table 3). The behaviour of the rheumatoid arthritis *v* control odds ratios through this series of models suggested to us that the mechanism for the increased frequency of arterial abnormalities in rheumatoid arthritis involved cardiovascular risk factors only to a modest extent, with stronger influences from the blood markers of inflammation, and a major influence of clinical manifestations of rheumatoid arthritis.

We conducted two sensitivity analyses. First, because we excluded some potential controls whose BMI exceeded 30 kg/m^2, we repeated the analysis after excluding the 81 rheumatoid patients and 18 controls with BMI above this cut off point. The results remained essentially unchanged, with the age, sex, cardiovascular risk factor, and ESR adjusted rheumatoid arthritis–control risk ratio for arterial incompressibility remaining at 6.13 (95% confidence interval (CI), 1.80 to 20.9) ($p = 0.002$).

We conducted a second sensitivity analysis because of the higher frequency of diabetes in the rheumatoid arthritis sample. We wished to exclude the possibility that the observed differences were related to this comorbid condition. We accomplished this by retesting the above models after excluding all diabetic subjects. This did not modify the risk ratios: the rheumatoid arthritis *v* control risk ratio for arterial incompressibility after excluding diabetic subjects was 10.2 (2.21 to 47.4) ($p = 0.003$). For arterial obstruction, the rheumatoid arthritis *v* control risk ratio after excluding diabetic subjects was 3.70 (0.93 to 14.7) ($p = 0.06$).

To explore further the role of the clinical manifestations of rheumatoid arthritis in the rheumatoid arthritis *v* control differences in arterial function, we stratified the arthritis according to deformed joint count tertiles. We then examined the proportion of incompressible and obstructed arteries in each stratum, comparing them with the corresponding proportions among the controls. These findings are shown graphically in the bottom panel of fig 1, and in table 4. Both obstructed and incompressible arteries were significantly more frequent among patients in the highest joint deformity tertile (⩾20 deformed joints) than among the controls (rheumatoid arthritis *v* control odds ratio for arterial obstruction = 7.16 (95% CI, 1.69 to 30.3), $p = 0.008$; rheumatoid arthritis *v* control odds ratio for arterial incompressibility = 25.3 (5.39 to 118.6), $p<0.001$). These differences were independent of age, sex, and cardiovascular risk factors (table 4).

The distribution of arterial abnormalities on a per person basis paralleled the vessel level data. All four lower limb arteries were normal in 97 of the controls (95%), but this was the case in only 188 of the rheumatoid patients (80%). Likewise, none of the controls had all four arteries affected by incompressibility or obstruction, compared with 3% and 2%, respectively, for the rheumatoid patients (table 5).

Factors associated with impaired arterial function

In the multinomial logistic regression models that we used to adjust the rheumatoid arthritis–control comparisons, ESR

was significantly associated with arterial obstruction (risk ratio 1.03 (95% CI, 1.02 to 1.06) per mm/hour difference in ESR, $p \leqslant 0.001$). Factors associated with incompressibility included age (risk ratio = 1.07 (1.04 to 1.11) per year difference in age, $p = 0.02$) and ESR (risk ratio = 1.02 (1.00 to 1.03) per mm/hour difference in ESR, $p = 0.02$). It should be noted that this study sample does exclude cigarette smokers, smoking being a major risk factor for peripheral arterial disease.

Association between ABI and arterial calcification

In the full ORALE cohort, including smokers and non-smokers, there were 20 patients with four incompressible lower limb arteries, 19 of whom had hand *x* rays available. For comparison, we randomly selected 19 patients of the same age and sex with normal lower limb arteries who also had hand *x* rays available. Among the patients with incompressible arteries, radiographic radial or ulnar calcification was apparent in 15 (79%). Among the patients with normal arteries, calcification was present in two (11%). The odds ratio for vascular calcification associated with an incompressible ABI was 31.9 (95% CI, 5.1 to 199.5), and its sensitivity and specificity in classifying patients with vascular calcification were 0.88 and 0.80, respectively.

DISCUSSION

We have documented an increased prevalence of impaired peripheral artery function in the sample of patients with rheumatoid arthritis, compared with healthy people of the same age and sex. We used the ABI, a simple, reliable, and non-invasive technique, to assess the function of the lower limb arteries at the bedside.[21] Its validity as a marker of peripheral atherosclerosis is supported by its association with claudication, and with cardiovascular morbidity and mortality.[25–28] We used statistical methods to account for potential confounding by age, sex, cardiovascular risk factors, and inflammation markers, and to disentangle the role of disease severity in any observed difference between rheumatoid arthritis and controls. We also carried out a sensitivity analysis excluding persons with diabetes mellitus, to rule out the possibility of confounding by this comorbid condition.

The increased frequency of arterial impairment that we encountered in the rheumatoid group was not explained by cardiovascular risk factors. However, on adjustment for blood markers of inflammation there was a reduction in the rheumatoid arthritis *v* control difference. A similar effect was observed when glucocorticoids were included in the model. These findings indicate that both inflammation and glucocorticoids may play a role in the observed differences. Adjustment for clinical manifestations of rheumatoid arthritis, notably joint deformities, led to near effacement in the rheumatoid arthritis *v* control differences. This means that the patients with the most severe rheumatoid arthritis are the ones most likely to have arterial impairment.

Figure 2 Calcification of the ulnar and radial arteries in two patients with advanced joint damage caused by rheumatoid arthritis. In both of these patients, neither the dorsal pedal nor the posterior tibial arteries bilaterally could be compressed at a cuff pressure of more than 250 mm Hg.

Despite recent interest in cardiovascular disease in rheumatoid arthritis, the peripheral arteries have been understudied. Peripheral vascular disease is not commonly recognised clinically in rheumatoid arthritis, perhaps because the sedentary life caused by musculoskeletal impairment may not favour exercise induced ischaemic symptoms. Moreover, if these symptoms occur they may be mistaken for osteoarticular pain. In fact, several cases of peripheral vascular disease causing chronic leg ulcers in rheumatoid patients have been reported, in some cases even leading to limb amputation.[14–16] Our findings suggest that impairment of peripheral arterial function in rheumatoid arthritis may be more common than previously suspected.

Co-occurrence of impaired arterial function and advanced joint damage has potential clinical implications. As noted above, the recognition of cardiovascular disease in rheumatoid arthritis is a challenge to the clinician. Arterial impairments may go unrecognised until irreversible ischaemia occurs.[29] Our findings may provide some help in this area, by suggesting that patients with the most advanced joint damage may be the most atherosclerosis prone, and thus the most deserving of attention for symptoms and signs of atherosclerotic cardiovascular disease.

These findings are in line with evidence that patients with rheumatoid arthritis are prone to central[9–13] and peripheral atherosclerosis. Previous studies using pulse wave analysis have shown arterial stiffness and increased vascular resistance in rheumatoid arthritis.[30–32] Flow mediated vasodilatation is also abnormal in this disease, suggesting that sufferers have impaired endothelial function.[33 34]

It has been suggested that endothelial dysfunction induced by subclinical vasculitis may be responsible for accelerated atherosclerosis in rheumatoid arthritis,[35] and one previous study described peripheral arterial obstruction, defined by a low ABI.[36]

Our data extend earlier work on three fronts. First, we have studied larger and more diverse patient and control samples. Second, we conducted a stepwise multivariate analysis to disentangle the contribution of cardiovascular risk factors, rheumatoid arthritis manifestations, and inflammatory markers to the abnormal arterial function. Third and most important, we included arterial incompressibility as one of our primary outcomes of interest. Altogether, the picture that emerges from this and earlier studies is one of widespread arterial vasculopathy in rheumatoid arthritis, with loss of elasticity of the central and peripheral arterial beds as a characteristic feature.

The finding of peripheral arterial incompressibility is novel, and has not been described before in rheumatoid arthritis. The published evidence from other diseases indicates that arterial incompressibility results from medial arterial calcification,[37–39] also known as Mönckeberg's sclerosis.[40] Figure 2 shows examples of ulnar and radial artery calcification in two of our patients with lower limb arterial incompressibility. Both also had advanced joint damage. Medial arterial calcification causes stiffening of the vascular wall. It can occur in chronic renal failure, diabetes mellitus, and aging.[41 42] Although medial arterial calcification is a predictor of cardiovascular complications and mortality,[43] its risk factors differ from those of coronary heart disease and obstructive peripheral artery disease.[43] Thus arterial medial calcification may represent a process distinct from

atherosclerosis. Arterial calcification in rheumatoid arthritis associated with glucocorticoid use was described by Kalbak more that 30 years ago.[44] The present findings advance that early study by showing that arterial wall stiffness occurs predominantly in patients with advanced joint damage, independent of glucocorticoid dose.

From the perspective of research into the mechanism of atherogenesis, our findings may also provide some direction. Inflammation, integrated over time, has a powerful influence of the amount of accrued joint damage.[45 46] Thus our findings could be interpreted as evidence that arterial impairments show a preference for patients with the greatest amount of accumulated systemic inflammation. This supports a pathogenic role of systemic inflammation in atherosclerosis. In this respect, it is of interest that adjustment for the ESR led to loss of significance in the increased frequency of arterial obstruction among patients with more than 20 deformed joints (table 4).

Our findings also raise the intriguing possibility that joint damage and arterial calcification could share pathogenic mechanisms independent of, or in addition to, systemic inflammation. Osteoclasts, which play a central role in the bone erosion that occurs in rheumatoid arthritis joints,[47] are strongly influenced by osteoprotegerin.[48] This molecule, which acts as a regulator of bone metabolism, is also expressed in the arterial wall, where it is believed to prevent the pathological deposition of hydroxyapatite calcium.[48] Supporting this possibility, osteoprotegerin knock out mice experience both accelerated osteoporosis and vascular calcification.[49] The association between joint damage and arterial incompressibility that we have encountered could thus be linked to a common deficiency of osteoprotegerin, or a related mediator of osteoclasts and calcium metabolism.

Some caution in interpretation is warranted. The control group comprised healthy people, which raises the possibility that the frequency of arterial impairment in patients with rheumatoid arthritis may not be increased compared with people with other chronic diseases. Further research is needed to explore this possibility. We recruited the rheumatoid arthritis sample from rheumatology practices. Thus these findings are better generalisable to the rheumatoid arthritis population seeking care from rheumatologists than to people with rheumatoid arthritis who receive care from non-specialists and who may have a milder disease spectrum. We excluded anyone who had ever smoked cigarettes from both the patient and control groups, to eliminate the potential confounding influence of this strong risk factor for peripheral atherosclerosis.[50] This means that the prevalence of arterial dysfunction in rheumatoid arthritis is likely to be considerably greater when patients who smoke are included. Conversely, we also excluded people younger than 40, among whom arterial abnormalities occur less often. The rheumatoid patients we studied had a high frequency of diabetes mellitus. This may in part be related to the greater proportion of Mexican Americans—who have a high rate of diabetes—in the patient group. However, this does not explain the increased prevalence of arterial impairment in the rheumatoid group, as it was observed even among subjects free of diabetes in the sensitivity analysis.

Conclusions

Our results suggest that rheumatoid arthritis may be associated with impaired peripheral arterial function, with most of the impairment occurring in patients who are in advanced stages of joint damage. These findings may have clinical implications and suggest future avenues for research into the mechanisms of atherogenesis in rheumatoid arthritis and other inflammatory disorders.

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REFERENCES

1 **Pincus T**, Callahan LF, Sale WG. Severe functional declines, work disability and increased mortality in 75 rheumatoid arthritis patients studied over nine years. *Arthritis Rheum* 1984;**27**:864–72.
2 **Mitchell DM**, Spitz PW, Young DY, Bloch DA, McShane DJ, Fries JF. Survival, prognosis, and causes of death in rheumatoid arthritis. *Arthritis Rheum* 1986;**29**:706–14.
3 **Jacobsson LTH**, Knowler WC, Pillemer S, Hanson RL, Pettitt DJ, Nelson RG, *et al*. Rheumatoid arthritis and mortality. A longitudinal study in Pima Indians. *Arthritis Rheum* 1993;**36**:1045–53.
4 **Wolfe F**, Mitchell DM, Sibley JT, Fries JF, Bloch DA, Williams CA, *et al*. The mortality of rheumatoid arthritis. *Arthritis Rheum* 1994;**37**:481–94.
5 **Myllykangas-Luosujarvi R**, Aho K, Kautiainen H, Isomaki H. Cardiovascular mortality in women with rheumatoid arthritis. *J Rheumatol* 1995;**22**:1065–7.
6 **Goodson NJ**, Wiles NJ, Lunt M, Barrett EM, Silman AJ, Symmons DP. Mortality in early inflammatory polyarthritis: cardiovascular mortality is increased in seropositive patients. *Arthritis Rheum* 2002;**46**:2010–19.
7 **del Rincon I**, Williams K, Stern MP, Freeman GL, Escalante A. High incidence of cardiovascular events in a rheumatoid arthritis cohort not explained by traditional cardiac risk factors. *Arthritis Rheum* 2001;**44**:2737–45.
8 **Solomon DH**, Karlson EW, Rimm EB, Cannuscio CC, Mandl LA, Manson JE, *et al*. Cardiovascular morbidity and mortality in women diagnosed with rheumatoid arthritis. *Circulation* 2003;**107**:1303–7.
9 **Park Y-B**, Ahn CW, Choi HK, Lee SH, In BH, Lee HC, *et al*. Atherosclerosis in rheumatoid arthritis: morphologic evidence obtained by carotid ultrasound. *Arthritis Rheum* 2002;**46**:1714–19.
10 **Wallberg-Jonsson S**, Backman C, Johnson O, Karp K, Lunstrom E, Sundqvist K-G, *et al*. Increased prevalence of atherosclerosis in patients with medium term rheumatoid arthritis. *J Rheumatol* 2001;**28**:2597–602.
11 **Kumeda Y**, Inaba M, Goto H, Nagata M, Henmi Y, Furumitsu Y, *et al*. Increased thickness of the arterial intima-media detected by ultrasonography in patients with rheumatoid arthritis. *Arthritis Rheum* 2002;**46**:1489–97.
12 **Wallberg-Jonsson S**, Ohman ML, Rantappaa-Dalqvist S. Cardiovascular morbidity and mortality in patients with seropositive rheumatoid arthritis in Northern Sweden. *J Rheumatol* 1997;**24**:445–51.
13 **del Rincon I**, Williams K, Stern MO, Freeman GL, Escalante A. Association between carotid atherosclerosis and systemic inflammation in rheumatoid arthritis and healthy people. *Arthritis Rheum* 2003;**48**:1833–40.
14 **Henke PK**, Siheepod P, Proctor MC, Upchurch GR, Stanley JC. Clinical relevance of peripheral vascular disease in patients with rheumatoid arthritis and systemic lupus erythematosus. *J Vasc Surg* 2003;**38**:111–15.
15 **Hafner J**, Schneider E, Burg G, Cassina PC. Management of leg ulcers in patients with rheumatoid arthritis or systemic sclerosis: the importance of concomitant arterial and venous disease. *J Vasc Surg* 2000;**32**:322–9.
16 **Lachmann SM**. The mobility outcome for amputees with rheumatoid arthritis. *Br J Rheumatol* 1993;**32**:1083–8.
17 **Arnett FC**, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, *et al*. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum* 1988;**31**:315–24.
18 **Escalante A**, del Rincon I. How much disability in rheumatoid arthritis is explained by rheumatoid arthritis? *Arthritis Rheum* 1999;**42**:1712–21.
19 **del Rincon I**, Battafarano DF, Arroyo RA, Murphy FT, Fischbach M, Escalante A. Ethnic variation in the clinical manifestations of rheumatoid arthritis: role of HLA-DRB1 alleles. *Arthritis Rheum* 2003;**49**:200–8.
20 **del Rincon I**, Battafarano DF, Arroyo RA, Murphy FT, Escalante A. Heterogeneity between men and women in the influence of the HLA-DRB1 shared epitope on the clinical expression of rheumatoid arthritis. *Arthritis Rheum* 2002;**46**:1480–8.
21 **Hiatt WR**. Drug therapy: medical treatment of peripheral arterial disease and claudication. *N Engl J Med* 2001;**344**:1608–21.
22 **Orces CH**, del Rincon I, Abel MP, Escalante A. The number of deformed joints as a surrogate measure of damage in rheumatoid arthritis. *Arthritis Rheum* 2002;**47**:67–72.
23 **Rogers WH**. Sg17: regression standard errors in clustered samples. *Stata Tech Bull* 1993:19–23.
24 **Kleinbaum DG**, Klein M. *Logistic regression, A self-learning text*, 2nd ed. New York: Springer-Verlag, 2002.
25 **Belch JJ**, Topol EJ, Agnelli G, Bertrand M, Califf RM, Clement DL, *et al*. Critical issues in peripheral arterial disease detection and management: a call to action. *Arch Intern Med* 2003;**163**:884–92.

26 **Hirsch AT**, Criqui MH, Treat-Jacobson D, Regensteiner JG, Creager MA, Olin JW, *et al*. Peripheral arterial disease detection, awareness, and treatment in primary care. *JAMA* 2001;**286**:1317–24.
27 **Murabito JM**, Evans JC, Larson MG, Nieto K, Levy D, Wilson PW. The ankle-brachial index in the elderly and risk of stroke, coronary disease, and death: the Framingham Study. *Arch Intern Med* 2003;**163**:1939–42.
28 **Collins TC**, Petersen NJ, Suarez-Almazor M, Ashton CM. The prevalence of peripheral arterial disease in a racially diverse population. *Arch Intern Med* 2003;**163**:1469–74.
29 **del Rincon I**, Escalante A. Atherosclerotic cardiovascular disease in rheumatoid arthritis. *Curr Rheumatol Rep* 2003;**5**:278–86.
30 **Wong M**, Toh L, Wilson A, Rowley K, Karschimkus C, Prior D, *et al*. Reduced arterial elasticity in rheumatoid arthritis and the relationship to vascular disease risk factors and inflammation. *Arthritis Rheum* 2003;**48**:81–9.
31 **Klocke R**, Cockroft JR, Taylor GJ, Hall IR, Blake DR. Arterial stiffness and central blood pressure, as determined by pulse wave pressure, in rheumatoid arthritis. *Ann Rheum Dis* 2003;**62**:414–18.
32 **Van Doornum S**, McColl G, Jenkins A, Green DJ, Wicks IP. Screening for atherosclerosis in patients with rheumatoid arthritis: comparison of two in vivo tests of vascular function. *Arthritis Rheum* 2003;**48**:72–80.
33 **Hansel S**, Lassig G, Pistrosch F, Passauer J. Endothelial dysfunction in young patients with long-term rheumatoid arthritis and low disease activity. *Atherosclerosis* 2003;**170**:177–80.
34 **Gonzalez-Juanatey C**, Testa A, Garcia-Castelo A, Garcia-Porrua C, Llorca J, Vidan J, *et al*. HLA-DRB1 status affects endothelial function in treated patients with rheumatoid arthritis. *Am J Med* 2003;**114**:647–52.
35 **Bacon PA**, Stevens RJ, Carruthers DM, Toung SP, Kitas GD. Accelerated atherogenesis in autoimmune rheumatic diseases. *Autoimmun Rev* 2002;**1**:338–47.
36 **Alkaabi JK**, Ho M, Levison R, Pullar T, Belch JJF. Rheumatoid arthritis and macrovascular disease. *Rheumatology* 2003;**42**:292–7.
37 **Emanuele MA**, Buchanan BJ, Abraira C. Elevated leg systolic pressures and arterial calcification in diabetic occlusive vascular disease. *Diabetes Care* 1981;**4**:289–92.
38 **Orchard TJ**, Strandness DE. AHA Medical/Scientific Statement. Workshop Proceedings. Assessment of peripheral artery disease in diabetics. Report and recommendation of an international workshop sponsored by the American Diabetes Association and the American Heart Association. September 18–20, 1992, New Orleans, Louisiana. *Circulation* 1993;**88**:819–28.
39 **Zierler RE**, Sumner DS. Physiologic assessment of peripheral arterial occlusive disease. In: Rutherford RB, eds. *Vascular surgery*. Philadelphia: WB Saunders, 2000:140–65.
40 **Mönckeberg JG**. Uber die reine Mediaverkalkung der Extremitatenarterien und ihr Verhalten zur Arteriosklerose. *Virchows Arch Pathol Anat Physiol Klin Med* 1903;**171**:141–67.
41 **Leskinen Y**, Salenius JP, Lehtimäki T, Huhtala H, Saha H. The prevalence of peripheral arterial disease and medial arterial calcification in patients with chronic renal failure: requirement for diagnostics. *Am J Kidney Dis* 2002;**40**:472–9.
42 **Maser RE**, Wolfson SK, Ellis D, Stein EA, Drash AL, Becker DJ, *et al*. Cardiovascular disease and arterial calcification in insulin-dependent diabetes mellitus: interrelations and risk factor profiles. Pittsburgh Epidemiology of Diabetes Complications Study-V. *Arterioscler Thromb* 1991;**11**:958–65.
43 **Lehto S**, Niskanen L, Suhonen M, Ronnemaa T, Laasko M. Medial artery calcification. A neglected harbinger of cardiovascular complication in non-insulin-dependent diabetes mellitus. *Arterioscler Thromb Vascular Biol* 1996;**16**:978–83.
44 **Kalbak K**. Incidence of arteriosclerosis in patients with rheumatoid arthritis receiving long-term corticosteroid therapy. *Ann Rheum Dis* 1972;**31**:196–200.
45 **Wolfe F**, Sharp JT: Radiographic outcome of recent-onset rheumatoid arthritis. A 19-year study of radiographic progression. *Arthritis Rheum* 1998;**41**:1571–82.
46 **Plant MJ**, Williams AL, O'Sullivan MM, Lewis PA, Coles EC, Jessop JD. Relationship between time-integrated C-reactive protein levels and radiologic progression in patients with rheumatoid arthritis. *Arthritis Rheum* 2000;**43**:1473–7.
47 **Redlich K**, Hayer S, Ricci R, David JP, Tohidast-Akrad M, Kollias G, *et al*. Osteoclasts are essential for TNF-alpha-mediated joint destruction. *J Clin Invest* 2002;**110**:1419–27.
48 **Simonet WS**, Lacey DL, Dunstan CR, Kelley M, Chang MS, Luthy R, *et al*. Osteoprotegerin: a novel secreted protein involved in the regulation of bone density. *Cell* 1997;**89**:309–19.
49 **Bucay N**, Sarosi I, Dunstan CR, Morony S, Tarpley J, Capparelli C, *et al*. Osteoprotegerin-deficient mice develop early onset osteoporosis and arterial calcification. *Genes Dev* 1998;**12**:1260–8.
50 **Burns DM**. Epidemiology of smoking-induced cardiovascular disease. *Prog Cardiovasc Dis* 2003;**46**:11–29.