

Relationship Between Arterial Stiffness and Stanford Health Assessment Questionnaire Disability in Rheumatoid Arthritis Patients without Overt Arterial Disease

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ABSTRACT. Objective. To quantify the relationship between Stanford Health Assessment Questionnaire (HAQ) disability and arterial stiffness in patients with rheumatoid arthritis (RA).

Methods. A consecutive series of 114 patients with RA but without overt arterial disease, aged 40–65 years, were recruited from rheumatology clinics. A research nurse measured blood pressure (BP), arterial stiffness (heart rate-adjusted augmentation index), fasting lipids, glucose, erythrocyte sedimentation rate (ESR), and rheumatoid factor (RF). A self-completed patient questionnaire included HAQ, damaged joint count, EuroQol measure of health outcome, and Godin physical activity score. Multiple linear regression (MLR) adjusted for age, sex, smoking pack-years, cholesterol, mean arterial BP, physical activity, daily fruit and vegetable consumption, arthritis duration, ESR, and RA criteria.

Results. Mean age was 54 years (81% women) with a median HAQ of 1.13 (interquartile range 0.50; 1.75). Median RA duration was 10 years, 83% were RF-positive, and median ESR was 16 mm/h. Mean arterial stiffness was 31.5 (SD 7.7), BP 125/82 mm Hg, cholesterol 5.3 mmol/l, and 24% were current smokers. Current therapy included RA disease-modifying agents (90%), prednisolone (11%), and antihypertensive therapy (18%). Arterial stiffness was positively correlated with HAQ ($r = 0.42$; 95% CI 0.25 to 0.56). On MLR, a 1-point increase in HAQ disability was associated with a 2.8 increase (95% CI 1.1 to 4.4; $p = 0.001$) in arterial stiffness. Each additional damaged joint was associated with a 0.17 point increase (95% CI 0.04 to 0.29; $p = 0.009$) in arterial stiffness. The relationship between EuroQol and arterial stiffness was not statistically significant.

Conclusion. In patients with RA who are free of overt arterial disease, higher RA disability is associated with increased arterial stiffness independently of traditional cardiovascular risk factors and RA characteristics. (First Release March 15 2010; *J Rheumatol* 2010;37:946–52; doi:10.3899/jrheum.091052)

Key Indexing Terms:

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Rheumatoid arthritis (RA) and atherosclerosis share similar pathophysiological features of chronic inflammation¹. It has been suggested that “accelerated atherosclerosis” is an extraarticular feature of RA attributable to chronic inflammation². Patients with RA appear to be at an increased risk of cardiovascular (CV) death compared with the general population. A recent metaanalysis of 7 high-quality cohort studies reported a pooled increased relative risk of CV death in patients with RA of 21% (95% CI 6% to 39%)³. However, this increased CV risk may be attributable to patients with RA having a greater exposure to traditional CV risk factors (such as smoking, dyslipidemia, hypertension, and physical inactivity) than the general population⁴.

If chronic inflammation is the driving force behind both atherosclerosis and RA-related disability, then measurement of arthritis-related disability may be useful in assessment of the future risk of CV events in patients with RA. We hypoth-

esized that patients with RA who have more severe inflammatory joint disease would have both a higher level of arthritis-related disability and a higher level of arterial dysfunction. The most widely used and validated disease-specific quality of health measure for RA is the Stanford Health Assessment Questionnaire (HAQ) disability index^{5,6}. Three large prospective cohort studies have demonstrated that the HAQ disability score is an independent predictor of overall mortality⁷⁻⁹. It has yet to be demonstrated whether the HAQ is predictive of CV death in patients with RA.

Several studies have assessed arterial stiffness in patients with RA using the SphygmoCor device (AtCor Medical Ltd., West Ryde, NSW, Australia)¹⁰⁻¹⁸. This device permits noninvasive pulse wave analysis (PWA) using applanation tonometry at the radial artery and allows rapid clinical assessment of central aortic pressures without the need for cardiac catheterization¹⁹⁻²². In peripheral arteries the outgoing systolic pulse wave is reflected back toward the heart, where it augments the central aortic pressure in late systole. The augmentation pressure (AP) is the amount by which this reflected arterial pulse increases the central aortic pressure. The augmentation index (AIX) is the AP expressed as a proportion of the central aortic pulse pressure (AP/PP). Augmentation index is determined by left ventricular ejection, pulse wave velocity, and peripheral arterial resistance, and is also related to endothelial dysfunction^{19,20}. It is considered by many researchers to be a useful composite index of arterial stiffness²³. AIX is predictive of adverse cardiac events and may be a useful proxy for subclinical atherosclerosis^{24,25}.

Patients with RA are at increased risk of CV death, and chronic inflammation may contribute directly to both arthritis-related disability and atherosclerosis. The HAQ disability score may be useful in the assessment of subclinical atherosclerosis in patients with RA, but no previous study has adequately assessed this. Consequently our primary aim was to quantify the relationship between arterial stiffness and HAQ disability in patients with RA who are free of overt arterial disease.

MATERIALS AND METHODS

We recruited adults aged 40–65 years with a rheumatologist's diagnosis of RA from a consecutive series of patients attending rheumatology outpatient clinics in Aberdeen, Scotland. We identified and excluded patients with overt arterial disease (angina, myocardial infarction, stroke, transient ischemic attack, arterial revascularization, and peripheral arterial disease) using an initial patient questionnaire, detailed medical record review, and resting 12-lead electrocardiogram (ECG). We also excluded patients with atrial fibrillation, heart failure, and valvular heart disease. No participants had had any infection or been immunized within the previous 2 weeks.

Patients attended for a standardized clinical assessment in the morning, having fasted overnight and avoided tobacco, alcohol, and caffeine. Participants rested supine in a quiet room for at least 10 minutes, before undergoing PWA according to current guidelines²⁶. Blood pressure (BP) was measured 3 times at the right brachial artery using a validated oscillometric device (IntelliSense BP monitor HEM-757, Omron, Kyoto, Japan)²⁷. PWA was also done 3 times using the SphygmoCor device (SCOR v. 7.01) with a handheld tonometer probe at the right radial artery.

Analysis is based on the mean of the 3 BP and PWA measurements. The SphygmoCor device employs a validated generalized transfer function to convert the peripheral arterial pulse wave, recorded noninvasively at the radial artery, into the equivalent central aortic arterial pulse wave^{19,20,23}. It produces both an unadjusted and adjusted AIX ("standardized" to a heart rate of 75 bpm: AIX@75). Since AIX is known to vary with heart rate, AIX@75 was used for the main analysis²⁸.

All PWA measurements were made by a single skilled operator with a high level of repeatability [Bland-Altman limits of agreement: AIX@75 within-observer 0.1 (SD 8.0); between-observer 1.0 (SD 3.9)]²⁹. All PWA recordings were required to have a quality index (QI%, based on average pulse height, pulse height variation, and diastolic variation) of at least 95%. Following PWA, a fasting venous blood sample was obtained for lipid profile, glucose, erythrocyte sedimentation rate (ESR; Westergren method), and rheumatoid factor (RF). Standing body weight and height were measured (with shoes, socks, and bulky clothing removed) using a single set of electronic digital scales with combined stadiometer (Seca, model Delta 707, Hamburg, Germany).

Health status was measured using a self-reported patient questionnaire, completed on the same day as PWA. This included both a standardized disease-specific instrument (HAQ) and a generic health instrument (EuroQol). The HAQ asks about health over the previous week in relation to dressing/grooming, arising, eating, walking, hygiene, reach, grip, and activities; additional questions concern the use of aids and the need for help from others⁵. EuroQol asks about health on the day of assessment in 5 areas: mobility, self-care, usual activities, pain-discomfort, and anxiety-depression³⁰. The EuroQol, a brief generic quality of health instrument, has also been widely used and validated in patients with RA^{30,31}. Patients completed a damaged joint count (joints replaced or permanently damaged with limited movement or deformity as a result of arthritis on 45-joint mannequin); and rated their overall general health and overall arthritis-related health on a 100-point linear scale (visual analog scale, VAS) from best health (0) to worst (100). Participants self-completed lifestyle questions concerning smoking, diet, alcohol, and exercise (Godin physical activity score)³².

Our principal interest was in the relationship between disease-related disability and arterial stiffness. The English (UK) versions of the HAQ and EuroQol were scored using standard methods without any imputation required for missing data^{5,6,30}. Since AIX varies by heart rate, it was standardized to a rate of 75 bpm²⁸. The EuroQol utility score was multiplied by 100 to make it more easily comparable to the other two 100-point scales (overall health and overall arthritis).

The number of patients recruited permitted 11 independent variables ($\sqrt{114}$) to be included in multivariable analysis. Multiple linear regression (MLR) was used to simultaneously adjust for 10 independent variables: patient characteristics (age, sex); major CV risk factors (smoking pack-years, fasting cholesterol, mean arterial BP); features of arthritis [study ESR, duration of arthritis, American College of Rheumatology (ACR) RA criteria³³]; and dietary and lifestyle factors (daily fruit and vegetables, Godin physical activity score)³². We confirmed that MLR assumptions were met (by plotting histograms of residuals and plotting residuals against predicted values). The relationship between arterial stiffness (AIX@75) and the 4 other health status measures (EuroQol, overall health, overall arthritis, damaged joint count) was also assessed by adjusting for the same 10 independent variables. Analysis was done using SPSS v. 17. Categorical variables were summarized using frequencies (percentages); normally distributed continuous variables are summarized as means (standard deviation, SD); skewed variables are summarized as medians (interquartile range, IQR). All participants provided informed written consent. The study was approved by Grampian Research Ethics Committee (study reference 04/S0801/67) and adhered to the Declaration of Helsinki.

RESULTS

We recruited 114 patients [mean age 54 yrs; 93 women (81%)] with a rheumatologist's diagnosis of RA (83% with

RF > 29 IU/ml) and median arthritis duration of 10 years (IQR 4–17 yrs). The majority were currently prescribed disease-modifying antirheumatic drugs (DMARD; 91%) for rheumatic disease and nonsteroidal antiinflammatory drug (NSAID) therapy (70%). Median ESR at assessment was 16 mm/h (IQR 8–28), with a median HAQ disability score of 1.13 (IQR 0.50–1.75; Table 1). Only 56% of patients met 4/7 ACR criteria for RA. Women had a longer duration of arthritis than men, a higher ESR at assessment, a higher HAQ score, and were somewhat younger (Table 1). Mean fasting cholesterol was 5.3 mmol/l, BP was 125/82 mm Hg (18% on antihypertensive drugs), and 24% were current smokers (41% never smoked; 35% ex-smokers). Two patients had diabetes (identified by fasting glucose; no one else with diabetes) and 2 patients were prescribed a statin. Other CV drugs (British National Formulary) included bendroflumethazide (n = 16), atenolol (n = 11), angiotensin-converting enzyme inhibitors (n = 5), and calcium channel blockers (n = 4). Mean augmentation index (AIX@75) was 31.5 (SD 7.7) and was higher in women than men. Women had a lower BP than men (124/81 vs 129/83 mm Hg); were less likely to be a current smoker (20% vs 38%); and were more likely to eat fruit and vegetables daily. Although they were more physically active overall than men (Table 1), women were less likely to engage in vigorous physical activity sufficient to work up a sweat (38% vs 43%, respectively).

A higher HAQ score and damaged joint count indicate a higher level of disease severity, while a higher EuroQol score and overall health/arthritis score (based on a 100-point scale) indicate a higher quality of life. As would be anticipated, the HAQ was positively correlated with the damaged joint count and negatively correlated with the EuroQol, health-overall, and arthritis-overall scores (Table 2). The highest correlation (Spearman's ρ -0.73) was between the disease-specific (HAQ) and the generic (EuroQol)

health-related quality of life (HRQOL) instruments. Women and men had similar EuroQol, health-overall, and arthritis-overall scores (a higher score indicating better health on a scale up to 100). The severity of arthritis was somewhat higher among women than men when assessed by damaged joint count and HAQ (Table 2).

The HAQ was positively correlated with arterial stiffness (AIX@75), with a Pearson correlation coefficient r of 0.42 (95% CI 0.25–0.56; Figure 1). On unadjusted analysis, a 1-point increase in the HAQ was associated with a 4.2-point (95% CI 2.5–6.0) increase in AIX@75. The HAQ alone explained 17% (adjusted R^2) of the variability in arterial stiffness. On multivariable analysis, a 1-point increase in HAQ was associated with a 2.8 increase (95% CI 1.1–4.4; $p = 0.001$) in AIX@75. The regression model was highly statistically significant and explained almost half of the variability (adjusted R^2) in arterial stiffness (Table 3). Based on a comparison of standardized regression coefficients, female sex, mean arterial BP, and HAQ demonstrated the strongest relationship with arterial stiffness (with coefficients of 0.38, 0.33, and 0.27, respectively; $p \leq 0.001$). The limited influence of age in the regression model (standardized regression coefficient 0.04, $p = 0.6$) probably relates to the restriction of our study to adults aged 40–65 years.

Mean AIX (unadjusted for heart rate) was 34.8 (SD 8.3). AIX for men was 29.0 (SD 9.4), and for women 36.1 (SD 7.4). HAQ was correlated with AIX ($r = +0.29$; 95% CI 0.11–0.45), and on unadjusted analysis a 1-point increase in HAQ was associated with a 3.2 increase (95% CI 1.2–5.1) in AIX (although the HAQ alone explained only 8% of the variability in AIX). On multivariable analysis (with the same 10 variables as in Table 3), a 1-point increase in HAQ was associated with a 2.5 increase (95% CI 0.3–4.7, $p = 0.03$) in AIX. While the multivariable model was highly statistically significant ($p = 0.0003$), it explained only 20% (adjusted R^2) of the variability in AIX.

Table 1. Characteristics of 114 patients with rheumatoid arthritis without overt arterial disease. Values are numbers (percentages) unless otherwise indicated.

Characteristic	Women, n = 93	Men, n = 21	All, n = 114
Mean age, yrs (SD)	53.4 (6.8)	55.0 (6.1)	53.7 (6.6)
Median duration of arthritis, yrs (IQR)	10.3 (4.6; 16.9)	7.2 (3.1; 15.2)	9.6 (4.4; 16.9)
Median study ESR, mm/h (IQR)	18 (8; 28)	10 (4; 30)	16 (8; 28)
Rheumatoid factor-positive (> 29 IU/ml)	79, 85%	15, 71%	94, 83%
ACR RA criteria 4/7	52, 56%	12, 57%	64, 56%
Mean arterial blood pressure, mm Hg (SD)	98 (11.6)	101 (11.0)	98 (11.5)
Mean fasting total cholesterol, mmol/l (SD)	5.3 (1.2)	5.2 (1.1)	5.3 (1.1)
Median pack-years of smoking (IQR)	5 (0; 22)	23 (0; 33)	6 (0; 25)
Median physical activity (Godin) score (IQR)	41 (31; 65)	21 (15; 40)	37 (25; 59)
Daily fruit and vegetables in diet	69, 74%	14, 67%	83, 73%
Median HAQ score (IQR)	1.13 (0.63; 1.75)	0.75 (0.25; 1.75)	1.13 (0.50; 1.75)
Mean augmentation index, AIX@75 (SD)	32.6 (7.1)	26.8 (8.9)	31.5 (7.7)

IQR: interquartile range; ESR: erythrocyte sedimentation rate; ACR: American College of Rheumatology; RA: rheumatoid arthritis; HAQ: Health Assessment Questionnaire.

Table 2. HAQ and other self-reported health status measures in 114 patients with rheumatoid arthritis without overt arterial disease.

	Correlation with HAQ, Spearman ρ	Observed Range (Potential Range)	Women, n = 93 Median (IQR)	Men, n = 21 Median (IQR)	All, n = 114 Median (IQR)
HAQ	—	0 to 2.9 (0 to 3.0)	1.13 (0.63; 1.75)	0.75 (0.25; 1.75)	1.13 (0.50; 1.75)
Damaged joint count	0.53	0 to 43 (0 to 45)	7 (2; 15)	3 (1; 12)	6.5 (2; 15)
Arthritis overall	-0.61	15 to 98 (0 to 100)	75 (53; 84)	74 (51; 89)	74 (52; 86)
Health overall	-0.43	34 to 100 (0 to 100)	79 (70; 86)	80 (70; 85)	79 (70; 86)
EuroQol (EQ-5D)*	-0.73	-7 to 100 (-59 to 100)	69 (59; 80)	66 (52; 76)	69 (59; 76)

* EuroQol (EQ-5D) utility score has been multiplied by 100 to make it more easily comparable with the overall arthritis/health scales. A higher HAQ score and damaged joint count indicate a higher level of disability/disease severity. A higher EQ-5D overall-arthritis and overall-health score indicates better health on a scale up to 100. HAQ: Health Assessment Questionnaire; IQR: interquartile range.

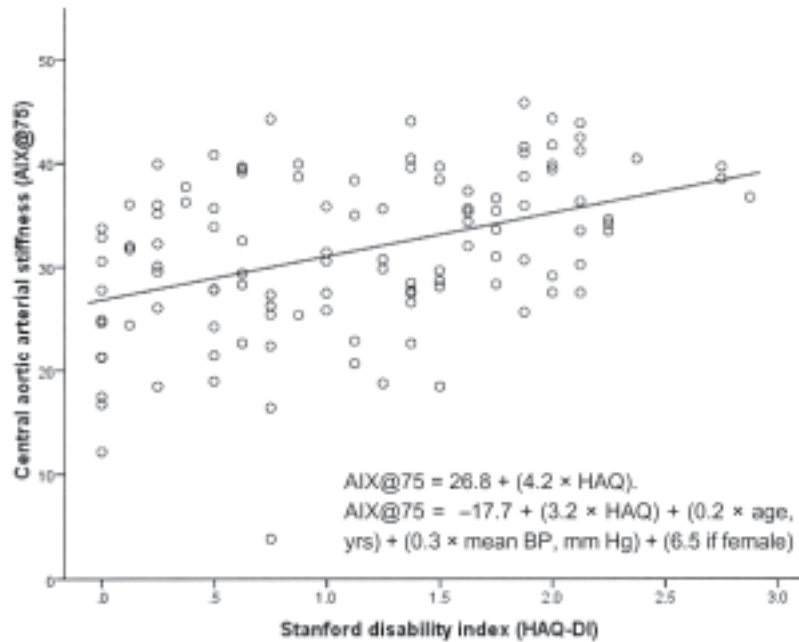


Figure 1. The relationship between disability (Stanford HAQ) and arterial stiffness (AIX@75) in 114 patients with RA without overt arterial disease.

The size of our study restricted the number of independent variables that could be included in the multivariable analysis. Several factors measured in the study are not included in the multivariable model reported in Table 3. The addition of individual cardiovascular variables (body mass index, fasting glucose, family history of coronary artery disease, CV drug therapy, treated hypertension) and rheumatological variables (RF-seropositive, current therapy with DMARD, NSAID, or prednisolone) made no appreciable difference in the HAQ regression coefficient, which ranged from 3.09 (with the inclusion of NSAID therapy) to 2.58 (with the inclusion of Carstairs deprivation score). The inclusion of additional variables did not improve the overall goodness to fit of the regression model.

The HAQ score was significantly correlated ($p < 0.001$, nonparametric Spearman's ρ) with the other 4 health status measures. The strongest was a negative correlation with the EuroQol ($\rho -0.73$; Table 2). On multivariable analysis (adjusting for the same 10 independent variables), a 10-point increase in the EuroQol score was associated with a nonsignificant -0.36 reduction (95% CI -0.85 to $+0.14$; $p = 0.16$) in arterial stiffness (Table 3). The number of damaged joints was positively correlated with the HAQ ($\rho +0.53$), and on multivariable analysis each additional damaged joint was associated with a statistically significant 0.17-point increase (95% CI 0.04–0.29; $p = 0.009$) in arterial stiffness.

Overall arthritis and overall health scores (on a 100-point

Table 3. Relationship between arterial stiffness (augmentation index, AIX@75) and 5 health status measures in 114 patients with rheumatoid arthritis without overt arterial disease. EQ-5D score has been multiplied by 100 to make it more easily comparable with overall-arthritis and overall-health scores. Arterial stiffness (augmentation index standardized to a heart rate of 75 bpm, AIX@75) is the dependent variable. Relationship reported between AIX@75 and health status measures has been adjusted for 10 variables (age, sex, pack-years of smoking, fasting total cholesterol, mean arterial blood pressure, Godin physical activity score, daily fruit and vegetables, study ESR, arthritis duration, ACR RA criteria) using multiple linear regression.

Measure	Regression Coefficients			Summary of Regression Models		
	Regression Coefficient (B)	95% CI	p	Multiple Correlation Coefficient (R)	Adjusted R ²	p (ANOVA)
Stanford HAQ	2.76	1.11 to 4.40	0.001	0.73	0.48	< 0.0001
Damaged joint count	0.17	0.04 to 0.29	0.009	0.72	0.46	< 0.0001
Arthritis overall	-0.08	-0.14 to -0.02	0.008	0.72	0.46	< 0.0001
Health overall	-0.08	-0.17 to 0.00	0.05	0.71	0.45	< 0.0001
EQ-5D	-0.04	-0.09 to 0.01	0.16	0.70	0.44	< 0.0001

EQ-5D: health questionnaire with 5 dimensions; ESR: erythrocyte sedimentation rate; ACR: American College of Rheumatology; RA: rheumatoid arthritis; HAQ: Health Assessment Questionnaire.

VAS) were negatively correlated with HAQ scores ($p = -0.61$ and -0.43 , respectively). On fully adjusted analysis, a 10-point increase in overall-arthritis score was associated with a statistically significant -0.78 reduction (95% CI -1.35 to -0.20 ; $p = 0.008$) in arterial stiffness. A 10-point increase in overall health score was associated with a -0.82 reduction (95% CI -1.65 to $+0.01$; $p = 0.05$) in arterial stiffness, but this was not statistically significant.

The regression models for these 4 health status measures explained a similar amount of the variation in arterial stiffness (adjusted R^2) as the regression model including the HAQ, but only the arthritis-based health status measures (HAQ, damaged joint count, and overall arthritis) demonstrated a statistically significant relationship with arterial stiffness (Table 3).

DISCUSSION

We have demonstrated that in patients with RA, the level of arterial stiffness is significantly correlated with several health status measures. A 1-point increase in HAQ disability is associated with a statistically significant 3-point increase in arterial stiffness, independent of RA characteristics, major cardiovascular risk factors, and physical inactivity. Such an increase in arterial stiffness is equivalent to 6 years of normal arterial aging in healthy women between 45 and 55 years³⁴. It is also comparable with the reduction in arterial stiffness observed in patients with RA after 6 weeks of treatment with atorvastatin¹⁷. A 1-point difference in HAQ between patients with RA equates with a 74% increased relative risk of death over 10 years⁹.

In our study, a research nurse obtained high-quality PWA measurements in optimal circumstances. We had few missing data and were able to include all participants in the multivariable analysis. We included patients with CV risk factors (such as smoking, hypercholesterolemia, and hypertension, adjusting for these in the analysis), but carefully

excluded those with overt arterial disease (and limited age to 40–65 yrs) to avoid ceiling/flooring effects in arterial stiffness. Since AIX varies with heart rate, the main analysis used AIX standardized to a heart rate of 75 bpm (AIX@75)²⁸. Resting heart rate is an independent risk factor for cardiovascular events (a faster heart rate is associated with increased risk)³⁵. Consequently, heart rate may be a marker for subclinical atherosclerosis. We recruited participants from a consecutive series of patients attending routine rheumatology clinics and the characteristics of patients were comparable to those attending outpatient clinics elsewhere in the UK³⁶.

Our cross-sectional study has some important limitations. Cardiovascular risk factors measured on a single occasion (such as BP and cholesterol) may not always accurately reflect previous levels. The prevalence of hypertension in our study (18%) is lower than described elsewhere³⁷ and probably relates to the exclusion of patients with overt arterial disease (who would be anticipated to have higher levels of cardiovascular risk factors such as hypertension). We included ACR criteria as a variable in the regression analysis because of concerns that our study population might be clinically heterogeneous. While all participants had a rheumatologist's diagnosis of RA, only 56% met ACR criteria for RA³³. This may relate to a typographical error in our patient questionnaire, which asked about morning stiffness for 6 months (rather than 6 weeks). ACR criteria also "accumulate" over time³⁸. In our study, 66% (36/55) of patients with a duration of arthritis greater than 10 years met ACR criteria. Pulse wave velocity was not measured and the relatively small size of our study restricted the number of independent variables that could be included in our multivariable analysis. Finally, recruitment of patients attending hospital clinics may have excluded patients with quiescent, mild, or burned-out disease managed solely in primary care.

Despite a careful search of the literature, we have been

unable to identify studies that reported in detail on the relationship between arterial stiffness and HAQ disability (or other health status measures) in patients with RA. Several studies measured AIX in patients with RA using the SphygmoCor device, but none adequately explored the relationship between arterial stiffness and health status¹⁰⁻¹⁸. Only 1 study included the HAQ and reported a weak correlation (Spearman's $\rho = 0.19$) with arterial stiffness¹⁰, which is lower than the correlation (Spearman's $\rho = 0.42$) observed in our study. Two studies reported including a 100-point patient-derived current disease activity score (DAS)¹² and a global assessment score¹⁵, but neither study reported any results relating to these scores. Three studies included the 28-joint count DAS28 composite and reported on the correlation of DAS28 with the AIX (coefficients of 0.13, 0.21, and 0.24)^{10,12,15}.

Three prospective cohort studies, each of more than 1000 patients with RA, have shown the HAQ to be predictive of overall mortality, although none reported on cardiovascular mortality⁷⁻⁹. A study of 1384 patients with RA followed over 10 years in the United States reported an adjusted hazard ratio of 1.74 (95% CI 1.43–2.11) for all-cause mortality for each 1-point increase in HAQ score⁷. The Norfolk Arthritis Register, a community-based UK inception cohort study of 1098 patients with inflammatory polyarthritis, reported an adjusted OR for death of 1.29 (95% CI 1.03–1.62) for patients with a HAQ ≥ 1.5 at baseline after 10 years of followup⁸. A study of 1387 patients with RA over 20 years in the state of Kansas in the US (7339 person-yrs followup) also found the HAQ to be a strong predictor of all-cause mortality (adjusted OR 2.0, 95% CI 1.5–2.5, for a 1 SD change in HAQ)³⁹. In the same study, patient self-report of global disease severity on a 10-point VAS was also a strong predictor (unadjusted OR 1.8 for a 1 SD change in VAS; $p < 0.001$, 95% CI not reported). Both the HAQ and global disease severity were stronger predictors of death than either laboratory or radiographic measurements³⁹.

Ours is the first study to confirm that RA-related disability assessed using the HAQ is significantly and independently correlated with arterial stiffness in patients with RA who do not have preexisting arterial disease. Research has shown that the HAQ is a strong independent predictor of all-cause mortality. Further research is required to establish whether the HAQ is a strong independent predictor of CV mortality and whether the HAQ should be incorporated into the clinical prediction of CV outcomes in patients with RA.

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REFERENCES

- Ross R. Atherosclerosis — an inflammatory disease. *N Engl J Med* 1999;340:115-26.

- Van Doornum S, McColl G, Wicks IP. Accelerated atherosclerosis: an extraarticular feature of rheumatoid arthritis? *Arthritis Rheum* 2002;46:862-73.
- Avina-Zubieta JA, Choi HK, Sadatsafavi M, Etminan M, Esdaile JM, Lacaille D. Risk of cardiovascular mortality in patients with rheumatoid arthritis: a meta-analysis of observational studies. *Arthritis Rheum* 2008;59:1690-7.
- Quyyumi AA. Inflamed joints and stiff arteries: is rheumatoid arthritis a cardiovascular risk factor? *Circulation* 2006;114:1137-9.
- Bruce B, Fries JF. The Stanford Health Assessment Questionnaire: dimensions and practical applications. *Health Qual Life Outcomes* 2003;1:20.
- Kirwan JR, Reeback JS. Stanford Health Assessment Questionnaire modified to assess disability in British patients with rheumatoid arthritis. *Br J Rheumatol* 1986;25:206-9.
- Callahan LF, Cordray DS, Wells G, Pincus T. Formal education and five-year mortality in rheumatoid arthritis: mediation by helplessness scale score. *Arthritis Care Res* 1996;9:463-72.
- Naz SM, Farragher TM, Bunn DK, Symmons DP, Bruce IN. The influence of age at symptom onset and length of followup on mortality in patients with recent-onset inflammatory polyarthritis. *Arthritis Rheum* 2008;58:985-9.
- Pincus T, Keysor J, Sokka T, Krishnan E, Callahan LF. Patient questionnaires and formal education level as prospective predictors of mortality over 10 years in 97% of 1416 patients with rheumatoid arthritis from 15 United States private practices. *J Rheumatol* 2004;31:229-34.
- Avalos I, Chung CP, Oeser A, Gebretsadik T, Shintani A, Kurnik D, et al. Increased augmentation index in rheumatoid arthritis and its relationship to coronary artery atherosclerosis. *J Rheumatol* 2007;34:2388-94.
- Cypienc A, Laucevicius A, Venalis A, Ryliskyte L, Dadoniene J, Petrulioniene Z, et al. Non-invasive assessment of arterial stiffness indices by applanation tonometry and pulse wave analysis in patients with rheumatoid arthritis treated with TNF-alpha blocker remicade (infliximab). *Proc West Pharmacol Soc* 2007;50:119-22.
- Klocke R, Cockcroft JR, Taylor GJ, Hall IR, Blake DR. Arterial stiffness and central blood pressure, as determined by pulse wave analysis, in rheumatoid arthritis. *Ann Rheum Dis* 2003;62:414-8.
- Maki-Petaja KM, Hall FC, Booth AD, Wallace SM, Yasmin, Bearcroft PW, et al. Rheumatoid arthritis is associated with increased aortic pulse-wave velocity, which is reduced by anti-tumor necrosis factor-alpha therapy. *Circulation* 2006;114:1185-92.
- Maki-Petaja KM, Booth AD, Hall FC, Wallace SM, Brown J, McEniery CM, et al. Ezetimibe and simvastatin reduce inflammation, disease activity, and aortic stiffness and improve endothelial function in rheumatoid arthritis. *J Am Coll Cardiol* 2007;50:852-8.
- Pieringer H, Schumacher S, Stuby U, Biesenbach G. Augmentation index and large-artery remodeling in patients with longstanding rheumatoid arthritis compared with healthy controls. *Semin Arthritis Rheum* 2009;39:163-9.
- Roman MJ, Devereux RB, Schwartz JE, Lockshin MD, Paget SA, Davis A, et al. Arterial stiffness in chronic inflammatory diseases. *Hypertension* 2005;46:194-9.
- Van Doornum S, McColl G, Wicks IP. Atorvastatin reduces arterial stiffness in patients with rheumatoid arthritis. *Ann Rheum Dis* 2004;63:1571-5.
- Wallberg-Jonsson S, Caidahl K, Klintland N, Nyberg G, Rantapaa-Dahlqvist S. Increased arterial stiffness and indication of endothelial dysfunction in long-standing rheumatoid arthritis. *Scand J Rheumatol* 2008;37:1-5.
- Smulyan H, Siddiqui DS, Carlson RJ, London GM, Safar ME.

- Clinical utility of aortic pulses and pressures calculated from applanated radial-artery pulses. *Hypertension* 2003;42:150-5.
20. Wilkinson IB, Hall IR, MacCallum H, Mackenzie IS, McEniery CM, van der Arend BJ, et al. Pulse-wave analysis: clinical evaluation of a noninvasive, widely applicable method for assessing endothelial function. *Arterioscler Thromb Vasc Biol* 2002;22:147-52.
 21. Williams B, Lacy PS, Thom SM, Cruickshank K, Stanton A, Collier D, et al. Differential impact of blood pressure-lowering drugs on central aortic pressure and clinical outcomes: principal results of the Conduit Artery Function Evaluation (CAFÉ) study. *Circulation* 2006;113:1213-25.
 22. Pauca AL, O'Rourke MF, Kon ND. Prospective evaluation of a method for estimating ascending aortic pressure from the radial artery pressure waveform. *Hypertension* 2001;38:932-7.
 23. Mackenzie IS, Wilkinson IB, Cockcroft JR. Assessment of arterial stiffness in clinical practice. *QJM* 2002;95:67-74.
 24. London GM, Blacher J, Pannier B, Guerin AP, Marchais SJ, Safar ME. Arterial wave reflections and survival in end-stage renal failure. *Hypertension* 2001;38:434-8.
 25. Weber T, Auer J, O'Rourke MF, Kvas E, Lassnig E, Lamm G, et al. Increased arterial wave reflections predict severe cardiovascular events in patients undergoing percutaneous coronary interventions. *Eur Heart J* 2005;26:2657-63.
 26. Van Bortel LM, Duprez D, Starmans-Kool MJ, Safar ME, Giannattasio C, Cockcroft J, et al. Clinical applications of arterial stiffness, Task Force III: recommendations for user procedures. *Am J Hypertens* 2002;15:445-52.
 27. El Assaad MA, Topouchian JA, Asmar RG. Evaluation of two devices for self-measurement of blood pressure according to the international protocol: the Omron M5-I and the Omron 705IT. *Blood Press Monit* 2003;8:127-33.
 28. Wilkinson IB, MacCallum H, Flint L, Cockcroft JR, Newby DE, Webb DJ. The influence of heart rate on augmentation index and central arterial pressure in humans. *J Physiol* 2000;525 Pt 1:263-70.
 29. Crilly M, Coch C, Bruce M, Clark H, Williams D. Indices of cardiovascular function derived from peripheral pulse wave analysis using radial applanation tonometry: a measurement repeatability study. *Vasc Med* 2007;12:189-97.
 30. Rabin R, de Charro F. EQ-5D: a measure of health status from the EuroQol Group. *Ann Med* 2001;33:337-43.
 31. Marra CA, Woolcott JC, Kopec JA, Shojania K, Offer R, Brazier JE, et al. A comparison of generic, indirect utility measures (the HUI2, HUI3, SF-6D, and the EQ-5D) and disease-specific instruments (the RAQoL and the HAQ) in rheumatoid arthritis. *Soc Sci Med* 2005;60:1571-82.
 32. Godin G, Shephard RJ. A simple method to assess exercise behavior in the community. *Can J Appl Sport Sci* 1985;10:141-6.
 33. 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.
 34. McEniery CM, Yasmin, Hall IR, Qasem A, Wilkinson IB, Cockcroft JR. Normal vascular aging: differential effects on wave reflection and aortic pulse wave velocity: the Anglo-Cardiff Collaborative Trial (ACCT). *J Am Coll Cardiol* 2005;46:1753-60.
 35. Kannel WB, Kannel C, Paffenbarger RS Jr, Cupples LA. Heart rate and cardiovascular mortality: the Framingham Study. *Am Heart J* 1987;113:1489-94.
 36. Panoulas VF, Douglas KM, Milionis HJ, Stavropoulos-Kalinglou A, Nightingale P, Kita MD, et al. Prevalence and associations of hypertension and its control in patients with rheumatoid arthritis. *Rheumatology* 2007;46:1477-82.
 37. Panoulas VF, Metsios GS, Pace AV, John H, Treharne GJ, Banks MJ, et al. Hypertension in rheumatoid arthritis. *Rheumatology* 2008;47:1286-98.
 38. Wiles N, Symmons DP, Harrison B, Barrett E, Barrett JH, Scott DG, et al. Estimating the incidence of rheumatoid arthritis: trying to hit a moving target? *Arthritis Rheum* 1999;42:1339-46.
 39. Wolfe F, Michaud K, Gefeller O, Choi HK. Predicting mortality in patients with rheumatoid arthritis. *Arthritis Rheum* 2003;48:1530-42.