Carotid arterial stiffness in patients with rheumatoid arthritis assessed by speckle tracking strain imaging: its association with carotid atherosclerosis

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Abstract

Objective

Although a series of trials support the intima-media thickness (IMT) of carotid artery as a good predictor for the cardiovascular events in patients with rheumatoid arthritis (RA), the link between IMT, vascular elastic property and the disease activity of RA is not defined. We investigated the association between carotid atherosclerosis, elastic properties of the carotid arterial wall and clinical parameters of RA.

Methods

One hundred and twenty RA patients and fifty healthy controls were included. Peak systolic global circumferential and posterior radial strain of carotid artery were measured to assess the elastic properties. Beta stiffness index was used as conventional method for the distensibility of the carotid artery. RA activity was assessed by high sensitivity C-reactive protein (hsCRP) and disease activity score with 28 joints (DAS 28) and health assessment questionnaire (HAQ).

Results

Carotid plaques were more common in RA patients. RA patients with plaques were older and had an increased mean IMT, hsCRP, DAS 28, and longer disease duration compared with those without plaques. Peak systolic global circumferential and posterior radial strain were congruent with β stiffness index, and significantly lower in the RA group. Age, disease duration, hsCRP, DAS 28 showed significant correlations with mean IMT and parameters of carotid elastic property.

Conclusions

Carotid atherosclerosis was more common in RA patients, and carotid arterial stiffness had significant correlation with disease duration and disease activity of RA. Speckle tracking strain imaging is a comparative method for the assessment of elastic properties of carotid artery of RA patients.

Key words

rheumatoid arthritis, carotid atherosclerosis, strain, ultrasonography

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Introduction

Rheumatoid arthritis (RA) is a well-known chronic inflammatory disease. Life expectancy in RA is reduced in 3 to 10 years compared to that of the normal population, and death rate in severe RA is similar to that found in patients with lymphoma and coronary artery disease (1-3). This higher mortality is mainly due to cardiovascular disease, as a consequence of accelerated atherosclerosis found in RA (4-8). Recent studies have showed a higher prevalence of severe coronary artery disease and higher incidence of silent acute myocardial infarction (AMI) and sudden death in RA population, which may suggest that atherosclerotic disease is diagnosed later in RA patients (9, 10).

Previous studies in patients without RA pointed out the importance of inflammation in the atherosclerotic process (11-13). Indeed, some biological markers of systemic inflammation, such as C-reactive protein (CRP) and fibrinogen, have showed significant correlations with the extension of atherosclerosis, cardiovascular and cerebrovascular clinical events (14, 15). There are, however, no sufficient data about the effects of the inflammatory marker on the progression of atherosclerosis in RA patients who were chronically inflammatory state.

A decrease of arterial distensibility seems to be a common pathologic change that leads to the occurrence and progression of the atherosclerosis associated with cardiovascular disease (CVD) (16). In the daily clinical practice, non-invasive methods, measuring surrogate markers for arterial stiffness, are mainly based upon pulse transit time, analysis of arterial pressure pulse and its wave form or estimation of vascular stiffness from distending pressure and diameter measurements, which can be expressed as distensibility, compliance, elastic modulus, or β stiffness index. Arterial distensibility is, however, only an estimate of the mean strain and modulus at best because the entire soft tissue surrounding the vessel is responding to the change in the volume of the vessel, and the standard boundary identification methods of the vessel wall may not be as reliable as speckle tracking methods (17). Recent developments in ultrasonographic imaging created a technical basis for a new diagnostic approach to atherosclerotic disease by offering the possibility of two-dimensional (2D) strain imaging for estimation of vascular tissue motion and deformation (strain) using speckle tracking. The technique identifies specific acoustic markers, speckles in the grey-scale image and subsequently track these speckles frame by frame throughout the cardiac cycle. This enables angle-independent calculations of motion and deformation variables such as velocity, displacement, strain and strain rate. A number of speckle tracking algorithms have been developed and the technique has been successfully applied primarily in cardiac applications (18).

In this study, we hypothesised that the values of strain of the carotid artery wall based on the speckle tracking imaging would be comparable with conventional measures of vascular stiffness using M-mode sonography and non-invasive blood pressure measurements. We also investigated the association between carotid atherosclerosis, elastic properties of the common carotid artery (CCA) and clinical, laboratory parameters of inflammatory activity in RA patients.

Patients and methods

Study population

One hundred and twenty RA patients (57.6±9.9 years, 88 women) according to the ACR criteria (19) from the outpatient clinic of the Rheumatology Division were consecutively included. Fifty healthy volunteers (54.8±8.8 years, 37 women) from the health screening center were selected as control group. Exclusion criteria for both groups were smoking (in the last 5 years), diabetes mellitus (DM), hypertension, pregnancy, renal failure, chronic hepatopathy, nephrotic syndrome, hypothyroidism and history of cardiovascular disease (hypertension, coronary artery disease, history of coronary angiography, congestive heart failure). All subjects using any lipid-lowering drugs such as statins or fibrates (in the last 3 months) were also excluded. Health Assess-

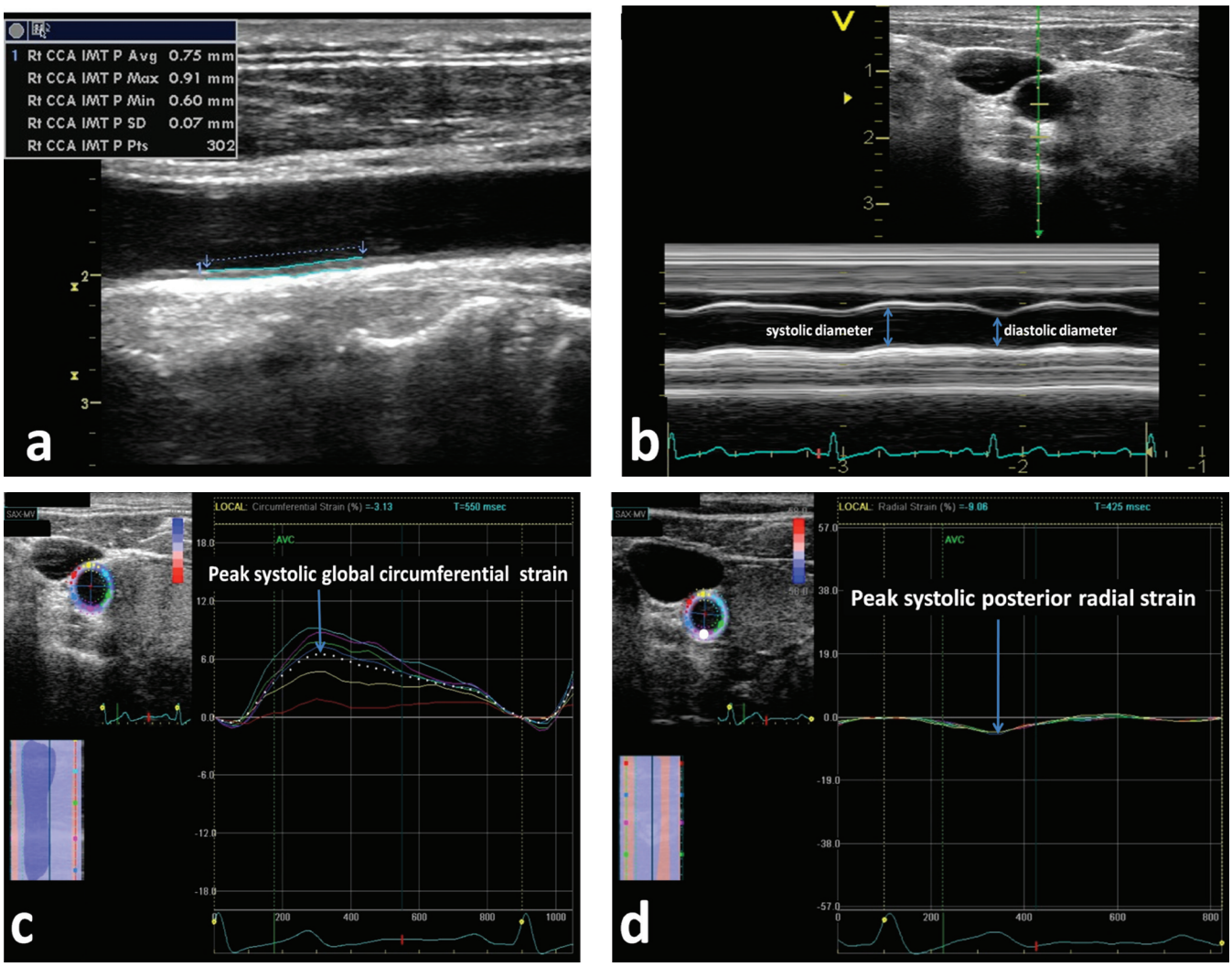

Fig. 1. An automated tracking algorithm outlined the intima–media complex of common carotid artery (**a**). Systolic and diastolic diameters of common carotid artery were obtained from short axis view (**b**). Regions of interest with computation area of 1x1 mm were placed in the intima-media complex from the short axis view of the common carotid artery (**c** and **d**). Peak systolic global circumferential strain (**c**) and posterior radial strain (**d**) and during systole were used for the analysis.

ment Questionnaire (HAQ) (20) and Disease Activity Score with 28 joints (DAS 28) (21) were assessed in RA patients. The study was approved by the Institutional Review Board and informed consent was obtained from all participants.

CCA ultrasound (US)

CCA US with intima-media thickness (IMT) measurement and analysis for the presence of plaques was blindly performed by the same examiner in all subjects using a Vivid 7 (GE Medical System, Milwaukee, WI) equipped with a 14 MHz linear-array scanner, which was capable of providing conventional two-dimensional (2D) ultrasound image and strain image. All subjects were examined in a supine position, neck extended, and the chin facing the opposite side. Carotid arteries were examined bilaterally in the longitudinal and transversal planes. After placing the region of interests in the far wall of the common carotid artery, mean IMT was estimated in a region free of atherosclerotic plaques with the use of an automatic tracking system (22, Fig. 1a). IMT was considered normal if below 0.9 mm and plaque was defined if greater than 1.5 mm (23, 24).

Carotid distensibility metrics

Carotid distensibility of an artery segment is a reflection of the mechanical stress affecting the arterial wall during the cardiac cycle. The stress was defined as the difference in systolic blood pressure (SBP) and diastolic blood pressure (DBP) and strain as the artery system's response. The carotid distensibility metrics were calculated using the following algorithms (25-27):

1) Strain as the amount of deformation relative to the unstressed state and expressed as percent change in the arterial diameter: strain = (SD-DD)/DD, where SD was the systolic and DD the diastolic CCA diameter (Fig 1b);
2) Stiffness (β) as stress (SBP-DBP)-to-strain ratio: ln (SBP/DBP)/strain;
3) Distensibility as 1/β and adjusted to IMT: 1/β=1/ [ln (SBP/DBP)/strain × IMT].

Speckle tracking strain imaging in carotid artery

An optimal short axis image of the CCA during a breath-hold at end expiration was obtained and digitally stored for offline analysis. Three heartbeats were collected from each view and selected 1-cycle was analysed offline with an EchoPAC Dimension system (General Electric, Horten, Norway). Regions of interest (ROI) with computation area of 1x1 mm were placed in the intima–media complex from the short axis view of the CCA, as shown in Figure 1. Circumferential peak systolic strain (%) was measured as an average of the whole, circular ROI giving respective 'global' strain (Fig 1c). 'Global' values for radial strain could not be calculated due to limitations of the Echopac software and consequently, radial peak systolic strain was only obtained 'regionally' from a discrete point (20×20 pixels) located in the far wall of the vessel (Fig. 1d, large white dot). During systole, circumferential strain assumes positive values due to stretching, or expansion of the vessel wall whereas radial strain becomes negative as a result of the compression of the vessel wall. The frame rate for the 2-dimensional strain was 60±15 frames/sec, and the ROI were placed to the adjacent arterial wall if plaque existed. Interobserver and intraobserver variabilities were 16% and 18% for strain, respectively.

Laboratorial evaluation

All RA patients and controls were fasting for at least 12 hours at the beginning of the study before blood tests. Rheumatoid factor was quantified using turbid immunometry (Advia 1800, Siemens) with cut-off >15 IU/ml for positive values. The plasma concentrations of high sensitivity C-reactive protein (hsCRP) was measured by performing fully automated turbid immunometry (Advia 1800, Siemens).

Statistical analysis

Statistical analysis was performed with the statistical program SPSS for Windows version 12.0 (Chicago, Il). Results are presented as the mean ± standard deviation (SD) or percentage. Comparisons were performed between RA and control groups using Student *t*-test for quantitative variables and chi-square or the exact Fisher test for qualitative variables. Correlations between variables were made by calculating the correlation coefficient through Pearson correlation tests. Statistical significance was set as below 0.05.

Table I. Clinical characteristics and parameters of the carotid artery of the study population.

	RA patients (n=120)	Control (n=50)	*p*-value
Age, yrs	57.6 ± 9.9	54.8 ± 8.8	0.15
Female, n (%)	88 (73%)	37 (74%)	0.99
BMI, kg/m	22.6 ± 6.4	22.7 ± 5.8	0.87
Systolic blood pressure, mmHg	126.3 ± 12.8	123.5 ± 9.6	0.18
Diastolic blood pressure, mmHg	78.6 ± 10.2	82.4 ± 4.7	0.25
Total cholesterol, mg/dl	195.3 ± 28.6	187.9 ± 30.2	0.23
Mean IMT, mm	0.72 ± 0.08	0.66 ± 0.14	0.043
Plaque, n (%)	34 (28.3%)	3 (6%)	<0.001
stiffness (β)	7.47 ± 6.77	3.78 ± 1.81	<0.001
Distensibility	0.34 ± 0.24	0.48 ± 0.17	0.015
Conventional strain, %	9.61 ± 5.86	13.13 ± 4.20	0.002
Peak systolic global circumferential strain, %	3.7 ± 1.52	7.13 ± 2.09	<0.001
Peak systolic posterior radial strain, %	-3.15 ± 1.5	-4.16 ± 1.04	<0.001

All values are presented as the mean ± SD.
BMI: body mass index; RA: rheumatoid arthritis; IMT: intima-media thickness; RA: rheumatoid arthritis.

Table II. Characteristics of RA patients with and without carotid arterial plaque.

	RA patients with plaques (n=34)	RA patients without plaques (n=86)	*p*-value
Age, yrs	64.5 ± 8.7	54.8 ± 9.2	<0.001
Disease duration, yrs	6.54 ± 6.12	4.25 ± 3.40	0.029
Total cholesterol, mg/dl	199.8 ± 24.3	193.7 ± 30.05	0.38
Systolic blood pressure, mmHg	129.4 ± 14.55	127.8 ± 12.19	0.65
Diastolic blood pressure, mmHg	76.7 ± 12.5	79.3 ± 9.25	0.28
C-reactive protein, mmol/L	15.74 ± 11.70	8.13 ± 8.77	0.007
Rheumatoid factor, IU/ml	133.79 ± 157.14	88.46 ± 154.14	0.24
DAS 28	3.92 ± 2.81	2.95 ± 1.36	0.032
HAQ	0.36 ± 0.71	0.18 ± 0.51	0.21
Mean IMT, mm	1.11 ± 0.18	0.92 ± 0.13	<0.001
Maximal IMT, mm	1.70 ± 0.55	1.32 ± 0.37	0.031
stiffness (β)	12.11 ± 8.52	4.26 ± 1.70	<0.001
distensibility	0.15 ± 0.12	0.46 ± 0.21	<0.001
Conventional Strain, %	5.10 ± 3.43	12.85 ± 4.90	<0.001
Peak systolic global circumferential strain, %	2.61 ± 1.34	4.21 ± 1.5	<0.001
Peak systolic posterior radial strain, %	-2.0 ± 1.21	-3.87 ± 1.20	<0.001

All values are presented as the mean ± SD.
RA: rheumatoid arthritis; DAS 28: disease activity score (28 joints analysed); HAQ: health assessment questionnaire; IMT: intima-media thickness.

Results

Clinical characteristics of subjects

There were no significant differences between RA and control groups in terms of age and the other clinical parameters that are known to affect the arterial elasticity (Table I). Mean disease duration of RA was 5.42±2.57 years and rheumatoid factor was positive in 80% of RA patient. At the time of the study, one hundred thirteen RA patients (94.3%) were taking prednisone (≤7.5mg/day), 14.8% bucillamine, 39.8% leflunomide, 5.7% tacrolimus, 4.5% infliximab, 3.4% etanercept, 1.1% adalimumab, 1.1% sulfasalazine, 7.9% methotrexate, 10.2% hydroxychloroquine diphosphate, and 45.5% non-steroidal anti-inflammatory drugs (NSAIDs).

The parameters of stiffness and atherosclerosis of the carotid artery

The parameters of carotid arterial stiffness and atherosclerosis of RA patients and controls are shown in Table I. The mean IMT was significantly increased in

Table III. Correlation coefficients between the parameters of carotid artery and clinical parameters of RA group (n=120).

	Mean IMT (P)	Beta stiffness index (P)	Distensibility (P)	Peak systolic global circumferential strain (P)	Peak systolic posterior radial strain (P)
Age	0.39 (<0.001)	0.37 (<0.001)	-0.50 (<0.001)	-0.31 (<0.001)	0.39 (<0.001)
Disease duration	0.32 (0.003)	0.24 (0.023)	-0.23 (0.032)	-0.33 (0.002)	0.44 (<0.001)
Systolic blood pressure	0.10 (0.26)	0.09 (0.42)	-0.21 (0.01)	-0.30 (0.001)	0.26 (0.004)
Diastolic blood pressure	-0.03 (0.76)	-0.23 (0.03)	0.07 (0.58)	0.056 (0.54)	0.01 (0.93)
Total cholesterol	0.05 (0.56)	0.01 (0.98)	-0.10 (0.37)	-0.26 (0.003)	0.22 (0.017)
hs CRP	0.48 (<0.001)	0.35 (0.0003)	-0.26 (0.008)	-0.18 (0.043)	0.37 (0.0002)
Rheumatoid factor	0.14 (0.19)	0.11 (0.31)	-0.17 (0.11)	-0.09 (0.39)	0.13 (0.23)
DAS 28	0.27 (0.007)	0.43 (<0.001)	-0.31 (0.002)	-0.23 (0.021)	0.38 (<0.001)
HAQ	-0.02 (0.87)	-0.11 (0.30)	-0.01 (0.97)	-0.003 (0.98)	-0.13 (0.24)

hs CRP: high sensitivity C-reactive protein; DAS 28: disease activity score (28 joints analysed); HAQ: health assessment questionnaire; IMT: intima-media thickness.

RA patients, and plaques were also more frequently observed in RA patients. Significantly increased carotid stiffness (β) index, reduced distensibility and strain parameters were also observed in RA patients. However, there were no significant differences in parameters of arterial distensibility among the medications such as steroid, disease modifying antirheumatic drugs (DMARDs) and antitumour necrosis factor (TNF) agents.

We divided RA patients into 2 groups, patients with and without carotid arterial plaques, for further analysis (Table II). RA patients with plaques were older and had significantly longer disease duration, higher hsCRP and DAS28, increased mean IMT and higher stiffness (β) index than those without plaques. The values of peak systolic global circumferential strain and posterior radial strain were significantly lower in the RA patients with plaques, and the values of conventional strain in the same group were lower, as well.

Correlation between the parameters of carotid artery and the disease activity of the RA group

Carotid mean IMT and parameters of arterial distensibility had a significant correlation with age in RA patients (mean IMT; r=0.39, stiffness; r=0.37, distensibility; r=-0.50, peak systolic posterior radial strain; r=0.39, peak systolic global circumferential strain; r=-0.31, all $p<0.001$). Also, mean IMT and parameters of arterial distensibility correlated with disease duration, hsCRP and DAS 28 (Table III). On univariate analysis, peak systolic global circumferential and posterior radial strain were significantly correlated with mean IMT (r=-0.18, $p=0.048$ and r=0.21, $p=0.022$, respectively) and carotid distensibility (r=0.60, $p<0.001$ and r=-0.62, $p<0.001$, respectively). With multiple regression analysis, age, disease duration, hsCRP, DAS28 were identified as contributing factor to the increased carotid IMT or stiffness (Table IV). Systolic and diastolic blood pressure showed no significant effect on peak systolic global circumferential and posterior radial strain with multiple regression analysis (Table IV).

Conventional and speckle tracking strain imaging echocardiography for the assessment of carotid arterial elasticity

Correlation analysis showed that the values of global circumferential strain and radial systolic strain were congruent with those of the conventional methods. The value of distensibility and stiffness index showed a significant correlation with peak systolic global circumferential strain and posterior radial strain (Fig. 2).

Discussion

In this study, we estimated the elastic properties of the carotid arterial wall by speckle tracking imaging-based strain parameters in the detection of differences in the elastic properties of the CCA in RA patients, and these parameters are shown to be useful to quantify the radial (or axial) and circumferential thickening of the carotid arterial wall. The addressed issue is of clinical importance, since several studies conducted in recent years have identified arterial stiffness as an early manifestation of atherosclerotic cardiovascular disease, and showed that decreased elasticity of the arterial wall may be present even before the occurrence of any clinical symptoms or atherosclerotic plaques (28, 29). There is, therefore, a growing need for new, sensitive, and accurate non-invasive methods for the evaluation of elastic properties of the arterial wall that would provide an efficient identification of individuals at the early stage of atherosclerotic disease.

Several parameters have been commonly used for the determination of arterial stiffness. Carotid femoral pulse wave velocity (PWV) is calculated from measurements of pulse transit time and the distance travelled by the pulse between the femoral and right common carotid arteries and has been shown to be a validated marker of arterial stiffening over the central arteries (30, 31). Elastic modulus and β stiffness index in the carotid artery or aorta (25-27) also have been used for the measurement of arterial stiffness. However, the value of these variables is somewhat limited. Elastic modulus expresses the relationship between stress (change in transluminal pressure) and strain (fractional change in lumen diameter) as a ratio and describes the overall stiffness of the arterial wall, but is blood pressure dependent. Beta stiffness index is constructed to attenuate the effect of blood pressure on vascular stiffness measurements, but its blood pressure independency has been questioned since an effect of blood pressure has been observed in a cohort of patients with stroke (32). The fact that blood

Table IV. Multiple linear regression analysis of mean IMT and parameters of arterial stiffness of common carotid artery in RA groups.

	Univariate analysis			Multivariate analysis		
	Coefficient(β)	B(95% CI)	*p*-value	R^2	Coefficient (β)	*p*-value
Age	0.374	0.005 (0.003 to 0.008)	<0.001	0.140	0.491	<0.001
Disease duration	0.316	0.008 (0.003to 0.013)	0.003	0.100	0.110	0.275
Systolic blood pressure	0.118	0.001 (-0.001 to 0.003)	0.242	0.014	0.213	0.074
Diastolic blood pressure	0.001	0.000 (-0.003 to 0.003)	0.995	0.000	-0.171	0.146
Total cholesterol	0.048	0.000 (-0.001 to 0.001)	0.632	0.002	0.050	0.597
hsCRP	0.458	0.005 (0.003 to 0.007)	<0.001	0.209	0.294	0.023
DAS 28	0.271	0.013 (0.004 to 0.023)	0.007	0.073	0.350	0.008
HAQ	-0.037	-0.007 (-0.045 to 0.032)	0.734	0.001	-0.012	0.896
Mean IMT (R^2=0.390, adjusted R^2=0.328 in multivariate analysis)						
Age	0.402	0.007 (0.004 to 0.011)	<0.001	0.162	0.233	0.037
Disease duration	0.235	0.009 (0.001to 0.017)	0.028	0.055	0.034	0.744
Systolic blood pressure	0.137	0.002 (-0.001 to 0.005)	0.421	0.008	0.214	0.080
Diastolic blood pressure	-0.189	-0.003 (-0.007to 0.000)	0.033	0.052	-0.243	0.045
Total cholesterol	0.103	0.001 (-0.001to 0.002)	0.311	0.011	0.038	0.690
hsCRP	0.345	0.005 (0.002to 0.008)	<0.001	0.119	0.144	0.048
DAS 28	0.429	0.029 (0.016 to 0.041)	<0.001	0.184	0.224	0.094
HAQ	-0.147	-0.041 (-0.100to 0.018)	0.173	0.021	-0.167	0.072
Beta stiffness index (R^2=0.361, adjusted R^2=0.296 in multivariate analysis)						
Age	-0.330	-0.062 (-0.098 to -0.026)	0.001	0.109	-0.436	<0.001
Disease duration	-0.327	-0.102 (-0.165 to -0.038)	0.002	0.107	-0.066	0.522
Systolic blood pressure	-0.329	-0.048 (-0.076 to -0.020)	0.001	0.108	-0.119	0.338
Diastolic blood pressure	-0.092	-0.018 (-0.056 to 0.021)	0.365	0.008	-0.107	0.385
Total cholesterol	-0.120	-0.007 (-0.020 to 0.005)	0.238	0.014	-0.061	0.523
hsCRP	-0.181	-0.030 (-0.062 to 0.003)	0.073	0.033	-0.277	0.030
DAS 28	-0.232	-0.167 (-0.309 to -0.025)	0.021	0.054	0.181	0.158
HAQ	-0.003	-0.007 (-0.502 to 0.488)	0.977	0.000	0.013	0.890
Peak systolic global circumferential strain(R^2=0.366, adjusted R^2=0.301 in multivariate analysis)						
Age	0.433	0.059 (0.034 to 0.084)	<0.001	0.188	0.177	0.104
Disease duration	0.439	0.126 (0.071to 0.182)	<0.001	0.193	0.227	0.028
Systolic blood pressure	0.134	0.014 (-0.007to 0.035)	0.185	0.018	0.046	0.707
Diastolic blood pressure	0.046	0.006 (-0.021to0.034)	0.653	0.002	-0.008	0.949
Total cholesterol	0.145	0.007 (-0.002 to 0.016)	0.152	0.021	0.019	0.844
hsCRP	0.392	0.046 (0.024 to 0.068)	<0.001	0.153	0.261	0.038
DAS 28	0.381	0.199 (0.101 to 0.297	<0.001	0.145	0.118	0.350
HAQ	-0.121	-0.257 (-0.713to 0.199)	0.265	0.015	-0.152	0.098

Peak systolic posterior radial strain (R^2=0.383, adjusted R^2=0.320 in multivariate analysis).

pressure and lumen diameter for calculation of β stiffness index are measured at different locations imposes further limitations on the accuracy of these variables. Also, β stiffness index is based on a 1 dimensional (D) approach that does not take into account any local variations in arterial compliance.

In contrast, speckle tracking method provides 2D data that are obtained directly in the arterial wall itself. The commonly used plaque classification is based on evaluation of their echo-lucency in grey-scale images, but the 2D-strain approach offers a direct measurement of vascular elastic properties in different parts of the plaque area and in the adjacent vascular sectors. This creates the possibility for the detection of heterogeneous motion pattern and local variations in different sectors of vascular wall. This is in keeping with the observation made in the recent study which reported that the circumferential strain variables from the 2D-images of the abdominal aorta appeared to discriminate better than β stiffness index between different age groups (33). Furthermore, the advantage of speckle tracking imaging is reported to be in left ventricular images (34, 35). Considering the tubular shape of the common carotid artery, the benefit of a measuring global circumferential strain would be potentially superior to Doppler imaging.

This study confirmed that decreased elastic properties of the carotid artery wall and atherosclerosis were more prevalent in RA. We found that lower speckle-based strain values were associated with advancing age, longer disease duration, deteriorating values of other parameters of atherosclerosis, and the disease activity of RA even after adjustment for blood pressure. The correlations of speckle-based strain values with age and other parameters of atherosclerosis were similar to conventional parameters of carotid distensibility. However, as noted in our analysis, systolic and diastolic blood pressure showed no significant effect on speckle-based strain values. Although blood pressure

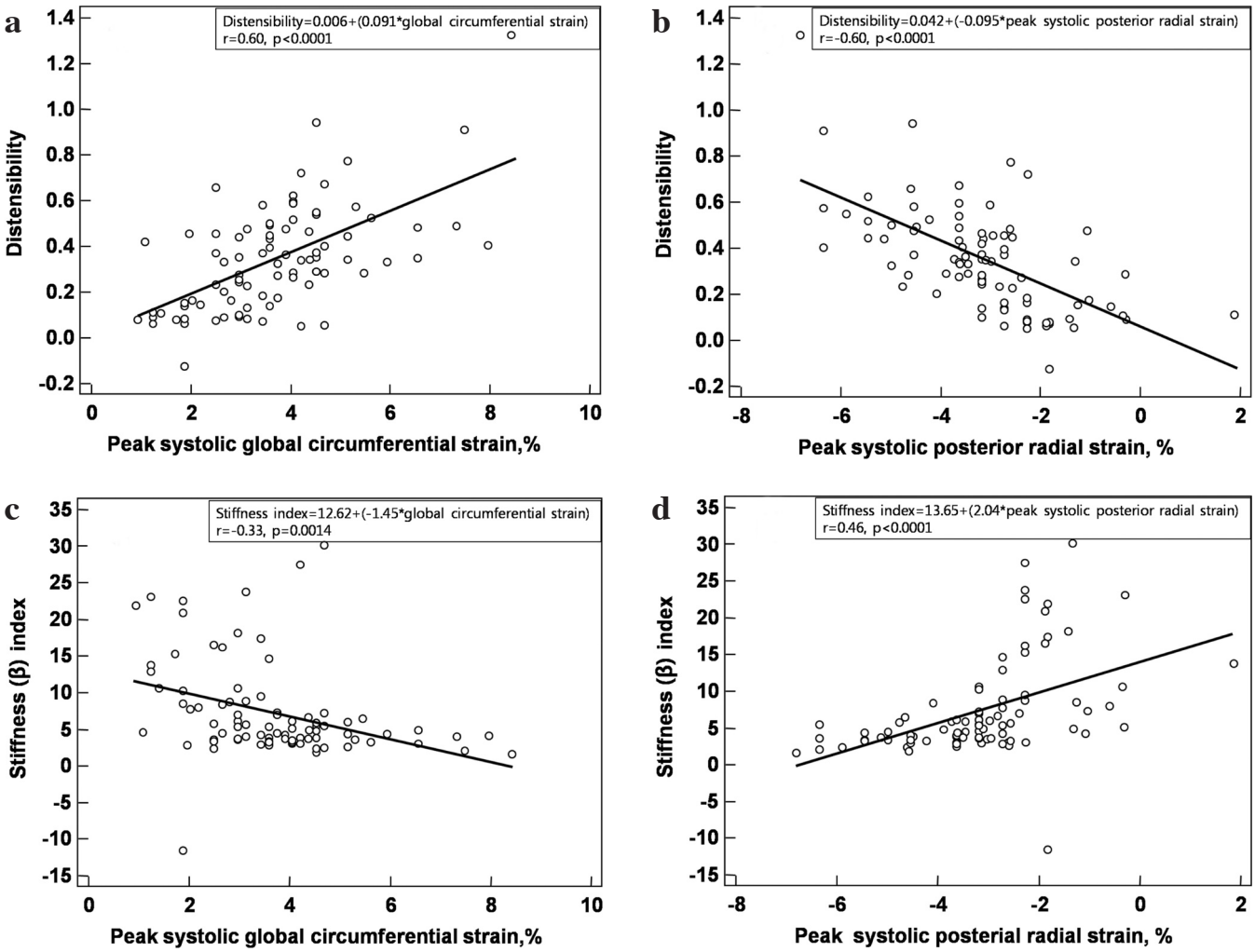

Fig. 2. Correlation between the conventional and speckle tracking echocardiography based strain values for the assessment of carotid arterial elasticity. The values of distensibility (**a** and **b**) and stiffness index (**c** and **d**) showed a significant positive or negative correlation with the peak systolic global circumferential strain and posterior radial strain values.

has been recognised to contribute arterial stiffening through medial hypertrophy, it reflects the stiffness of the entire vascular tree, but speckle-based strain values measures only local carotid stiffness which reflects the sequelae of pathologic processes or remodelling due to various medical conditions. So we could hypothesise that a simple blood pressure measurement may not be an adequate surrogate for speckle-based strain values, and perhaps both provide complementary information on vascular health. Therefore, the extension of arterial wall motion deformation behaviour, as measured by speckle tracking imaging, has the potential to provide useful information on atherosclerosis and arterial stiffness.

Although two recent studies did not find any difference in IMT measurement between RA patients and controls (36, 37), our study showed the increased IMT in RA patients, which was also shown in the other studies (38, 39). In addition, variation was reported in the relationship between strain values and IMT. This suggested that arterial wall stiffness, as estimated by speckle tracking imaging, may present a different aspect of atherosclerosis from these conventional parameters of atherosclerosis. The different mechanism between functional and structural alternations of vessel walls secondary to atherosclerosis has been described in some studies. Bots *et al*. (40) and van Popele *et al*. (26) demonstrated the absence of a clear association between arterial stiffness and IMT, suggesting that structural abnormalities reflected atherosclerosis beyond a certain level. Paini *et al*. (41) also reported that the aorta stiffened more than the carotid artery with age and CV risk factors. These observations may indicate the importance of the integrated approach to assess the severity of atherosclerosis.

In our RA population, plaques were observed in older patients, with a trend to be detected in those with longer disease duration and higher disease activity, suggesting a possible role of chronic RA inflammation and supporting the notion that time of exposition of the endothelium to systemic inflammation can be important to the development of atherosclerosis. However, no association was observed between IMT and plaques with HAQ scores, which evaluates functional capacity. The HAQ only assesses physical discomfort by a

visual analogue scale for pain intensity, and disability is assessed by a self-report questionnaire of 20 questions in eight categories. The HAQ can show the subjective disease activity and an impact of disease on the quality of life, but did not seem to reflect the degree of inflammation.

Also, we could not find significant differences in parameters of arterial distensibility among the medications. RA-associated increased aortic stiffness has been reported to be reduced by anti-TNF therapy which concomitantly improves endothelial function (42). Aortic stiffness correlated with current but not historical measures of inflammation, which suggests that arterial stiffness may be modifiable. However, the design differences should be considered when interpreting our findings because we have no data on the effects of steroid, DMARDs, and anti-TNF therapy on the parameters of arterial distensibility before and after treatment when the patient is his or her own control. This point should be included in the limitations of this study. This study has some more limitations that should be considered, which is related to the small number of patients and selection of study population. Further study with a larger population comparing carotid femoral PWV and speckle-based strain parameters should be undertaken to overcome this limitation. Also, we evaluated hs CRP levels only once at baseline and did not evaluate the effects of changes in the levels of these markers over time. Variation over time in the levels of inflammatory markers would lead a false estimation, so follow-up studies which evaluate the effects of changes in inflammation has to be undertaken.

In summary, speckle tracking strain imaging is a sensitive method for the assessment of elastic properties in the CCA, being in this respect superior to the conventional measures of vascular stiffness. Carotid atherosclerosis is more frequently detected in RA, and its prevalence was correlated with inflammatory markers. These findings reinforce the need to evaluate subclinical atherosclerosis in RA patients, and to find predictors of atherosclerotic lesions.

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