The Journal of Rheumatology 2021:48;352–60
doi:10.3899/jrheum.200146
First Release January 15 2021

The Journal of Rheumatology

Biomechanical Properties of Common Carotid Arteries Assessed by Circumferential 2D Strain and β Stiffness Index in Patients With Ankylosing Spondylitis

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ABSTRACT. ***Objective.*** Ankylosing spondylitis (AS) is associated with an elevated risk of cardiovascular disease (CVD) related to atherosclerosis, preceded by arterial stiffness. We aimed to examine common carotid artery (CCA) biomechanical properties using ultrasound to calculate β stiffness index (indicating arterial stiffness) and, a more recently developed technique, 2-dimensional (2D) speckle tracking strain (indicating arterial motion and deformation, strain) to (1) compare with age- and sex-matched controls, and (2) analyze relationships between strain and stiffness with disease characteristics and traditional risk factors for CVD in patients with AS.

Methods. In this cross-sectional study, a cohort of 149 patients with AS, mean age 55.3 ± 11.2 years, 102 (68.5%) men, and 146 (98%) HLA-B27–positive, were examined. Bilateral CCA were examined for circumferential 2D strain and β stiffness index. A subgroup of 46 patients was compared with 46 age- and sex-matched controls, both groups without hypertensive disease, diabetes, myocardial infarction, or stroke.

Results. Mean bilateral circumferential 2D strain was lower in AS patients compared with controls (7.9 ± 2.6% vs 10.3 ± 1.9%, $P < 0.001$), whereas mean bilateral β stiffness index was higher (13.1 ± 1.7 mmHg/mm vs 12.3 ± 1.3 mmHg/mm, $P = 0.02$). In multivariable linear regression analyses, strain was associated with age, erythrocyte sedimentation rate, history of anterior uveitis, and treatment with conventional synthetic disease-modifying antirheumatic drugs (DMARD) and/or biological DMARD (R^2 0.33), while stiffness was associated with age (R^2 0.19).

Conclusion. Both CCA circumferential 2D strain and β stiffness index differed between patients with AS and controls. Strain was associated with AS-related factors and age, whereas only age was associated with stiffness, suggesting that the obtained results reflect different pathogenic vascular processes.

Key Indexing Terms: ankylosing spondylitis, cardiovascular disease, common carotid artery, ultrasound

This study was supported by grants from The Swedish Research Council, Västerbotten's Association Against Rheumatism, The Swedish Association Against Rheumatism, the County of Västerbotten (agreement concerning research and education of doctors), King Gustaf Vth 80-year Foundation, The Norrland's Heart Foundation, and Mats Kleberg's Foundation.

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Accepted for publication June 22, 2020.

Ankylosing spondylitis (AS), a subgroup of the spondyloarthritis (SpA) diseases, is a chronic rheumatic inflammatory disease primarily affecting the sacroiliac joints and spine but also, to a lesser extent, peripheral joints[1]. It has been demonstrated that patients with AS have an increased risk of cardiovascular disease (CVD) compared to the general population[2–8]. The European League Against Rheumatism has recognized CVD as an important comorbidity in patients with inflammatory joint disorders including SpA and emphasizes the need for risk assessment and risk management[9]. Several clinically important manifestations of CVD are related to atherosclerosis such as coronary artery disease (CAD), stroke, and peripheral arterial disease. It is suggested that chronic systemic inflammation, in addition to traditional cardiovascular (CV) risk factors, contributes to the atherosclerotic process[10]. The atherosclerotic process is characterized by the degeneration of smooth muscle cells and elastin fibers in parallel with the proliferation of more rigid collagen fibers in the vessel walls and intra- and extracellular deposition of lipids. These changes might lead to the development of increased arterial stiffness and also to the increase of the intima-media thickness (IMT) and plaque formation, which can be evaluated by ultrasound (US) of the common carotid arteries (CCA)[11].

However, the limitations of measuring carotid IMT (cIMT) have been recognized because the association between cIMT progression and CV risk in the general population has remained unproven[12]. Therefore, the development of better methods to evaluate atherosclerotic changes is warranted. Biomechanical properties of the arteries, such as stiffness, can also be evaluated by US where the β stiffness index can be calculated from the relation between systemic blood pressure and arterial diameter. The β stiffness index has been found to be significantly associated with coronary atherosclerosis[13]. Further, the β stiffness index correlated with the carotid atherosclerotic grade, vessel wall area, and wall thickness, suggesting that the β stiffness index of the CCA reflects not only biomechanical properties of the artery but also its atherosclerotic damage[14]. However, the US method used for β stiffness index calculation is angle-dependent and only measures mechanics in 1 dimension. Technological advancements in US have resulted in a method assessing 2-dimensional (2D) strain, using a speckle tracking technique, which measures vascular motion and deformation biomechanics in 2D. Speckle tracking was originally developed for examining the myocardium, providing additional information to conventional cardiac US methods[15]. Previously, the speckle tracking-based 2D strain technique has been applied in vascular studies with the aim of improving the understanding of the atherosclerotic process and to detect early subclinical disease[16,17]. Previous studies demonstrated that 2D speckle tracking strain correlated with cIMT[18,19,20] and that strain, in contrast to cIMT, was associated with the severity and extent of CAD[20].

The primary aim of this cross-sectional study was to investigate, for the first time in patients with AS, to our knowledge, the biomechanical properties of the CCA with both circumferential 2D strain and β stiffness index and to compare the results with age- and sex-matched controls. A secondary aim was to explore relationships between circumferential 2D strain and β stiffness index with AS disease characteristics and traditional risk factors for CVD in order to estimate the explanatory value of these factors for the biomechanical properties of the CCA.

MATERIALS AND METHODS

Patients and controls. All patients attending the rheumatology clinic in Region Västerbotten in northern Sweden with a diagnosis of AS (International Classification of Diseases, 10th revision code M45.9) between May 2002 and November 2015 were identified through the digital administrative system (n = 523). The diagnosis of AS was validated through a review of the medical records and patients not fulfilling the modified New York criteria[21] were excluded, leaving 346 patients. Two-hundred forty-six patients between 18 and 75 years of age, still living in Region Västerbotten, with at least 1 visit at the rheumatology clinic within the last 5 years were invited between 2016 and 2017 to take part in a study called the Backbone Study. A flowchart of the inclusion process is shown in Figure 1. Exclusion criteria were dementia, other inflammatory rheumatic diseases, pregnancy, or difficulties in understanding the Swedish language. One-hundred and fifty-five (63%) patients fulfilling the criteria were willing to participate in the Backbone study, which investigated severity and comorbidities in AS. For the current study, 6 patients were further excluded due to a lack of or inadequate imaging data required for speckle tracking 2D circumferential strain analysis, leaving 149 patients. Out of the 246 patients, the 149 patients included in this report had a similar median age 55.0 (IQR 45.5–62.5) years compared with the 97 patients not taking part (52.0 yrs, IQR 38.5–63.0 yrs, $P = 0.07$; date of all AS diagnosis validation in the medical records: December 31, 2015). There was a sex difference between the included patients (102/149, 68.5% men) compared to those not taking part (81/97, 83.5% men; $P = 0.008$).

The patients with AS underwent clinical examinations and answered questionnaires regarding lifestyle habits, medication, AS-related data such as a history of anterior uveitis, peripheral arthritis, and CV-related factors such as previous myocardial infarction, surgical myocardial revascularization, or stroke. Patients having been told by a physician to have hypertension and being on an antihypertensive drug were defined as having hypertensive disease. Patients having been told by a physician to have diabetes and being on an antidiabetic drug were defined as having diabetes mellitus. The Bath Ankylosing Spondylitis Activity Index, Ankylosing Spondylitis Disease Activity Score using C-reactive protein (ASDAS-CRP), Bath Ankylosing Spondylitis Functional Index, and Bath Ankylosing Spondylitis Metrology Index (BASMI) were assessed[22]. The patients answered a questionnaire regarding health-related quality of life 36-item Short Form health survey (SF-36)[23,24], and we report herein the overall physical component and mental component summary scores. Blood samples were drawn in the morning after an overnight fast and erythrocyte sedimentation rate (ESR), high-sensitivity C-reactive protein (hsCRP), and lipids were analyzed by standard laboratory techniques, consecutively.

From the 149 patients in this report, a subset of 46 patients (31 men, 15 women) without diabetes and hypertensive disease, and without a history of myocardial infarction, surgical myocardial revascularization, or stroke were selected consecutively from the list of inclusions and compared with 46 age- and sex-matched controls recruited from the hospital staff. The same inclusion criteria were applied for the controls, besides not having any inflammatory rheumatic disease.

Radiography. Spinal radiographic changes were assessed from the lateral projection of the spinal radiographs and were graded using the modified Stoke Ankylosing Spondylitis Spinal Score (mSASSS). The anterior corners of vertebrae C2–T1 and T12–S1 were graded with a score between 0 and 3 (0 = normal; 1 = erosion, sclerosis, or squaring; 2 = syndesmophyte; and 3 = bridging syndesmophyte). The overall scoring scale ranges from 0 to 72, with 72 representing complete ankylosis[25]. To have an mSASSS score ≥ 2 at a vertebral corner was classified as having a syndesmophyte. Severe spinal radiographic changes were defined as ≥ 3 consecutive intervertebral bridges in the cervical spine and/or the lumbar spine, similar to the definition of grade 4 (severe) in the Bath Ankylosing Spondylitis Radiology Index[26]. The radiographs were performed at a mean time of 32.9 ± 15.1 days after inclusion in the study. One experienced radiologist performed all scoring (MG).

US examination. The same operator (LL) carried out bilateral CCA US examinations on all patients and controls. A GE Vivid E9 US system with a GE 9L 2.5–8 MHz linear transducer (GE) was used. All participants were examined in a supine position, resting quietly with their head tilted at a 45° angle away from the side being assessed. Blood pressure (BP) was taken using the right upper arm and a manual sphygmomanometer after a 5-minute rest in a supine position. A superimposed ECG was used to identify end-systole (end of T wave) and end-diastole (Q-wave). Standard B-mode short-axis (SAX) and long-axis (LAX) views of the right and left CCA were obtained. Image optimization was performed as appropriate for each examination. CCA images included the carotid bulb as a reference. CCA measurements were taken 1–2 cm into the proximal CCA from the bulb. A 5-beat loop of CCA from the short-axis view was stored for further analysis. All examinations were stored in the Digital Imaging and Communications in Medicine (DICOM) format. As previously described, the US examinations were post-processed and analyzed using TomTec[27,28]. We used TomTec Arena™ version 4.0 (TomTec Imaging Systems GMBH, Germany) and the postprocessing was performed by the same operator (LL).

Speckle tracking strain. The mid-left ventricular SAX circumferential strain option (based on the speckle tracking US method for left ventricular

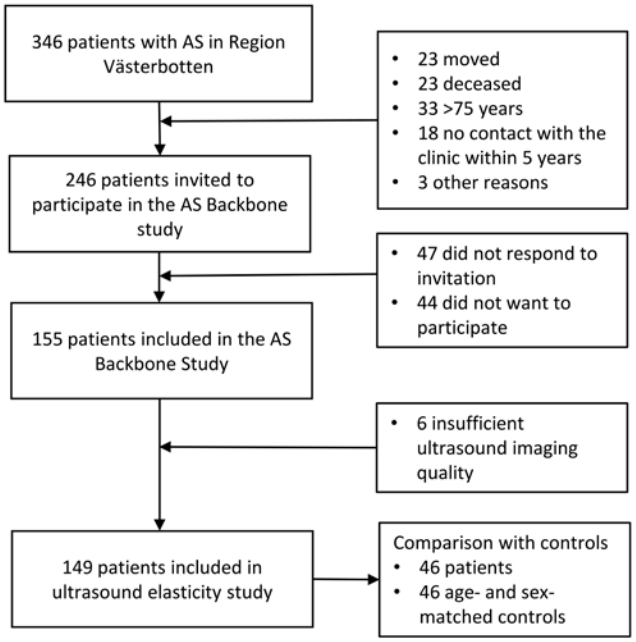

Figure 1. Flow chart of the inclusion of patients with AS into the Backbone Study. AS: ankylosing spondylitis.

assessment) was used to measure CCA 2D circumferential strain parameters from SAX (specific equation used not provided by the software company). The clip was edited to exclude significant drift or movement. An average of 3 consecutive beats was analyzed. The internal vessel wall was outlined manually at end-systole and end-diastole and the clip played to ensure accurate speckle tracking analysis. The average circumferential 2D strain value was then recorded (Figures 2A,B). A higher circumferential 2D strain value indicates more motion and deformation of the vessel wall.

β stiffness index. β stiffness index was calculated offline using the equation:

$$\beta = \ln(SBP/DBP)/((ESD-EDD)/EDD)^{29}.$$

The systolic BP (SBP) and diastolic BP (DSP) were taken at the time of the examination in a supine position, and the end-systolic diameter (ESD) and end-diastolic diameter (EDD) luminal diameters were taken from the CCA LAX 1–2 cm into the CCA from the bulb from 3 consecutive heartbeats. ESD and EDD were defined as the largest and smallest luminal diameters, respectively (Figure 2C). A higher β stiffness index indicates an increased stiffness of the vessel.

Reliability testing of circumferential 2D strain. An expert US operator (PL) analyzed the left CCA of 10 randomly selected individuals, blinded to whether the individual was a patient or a control. The delineation of the wall for tracking was done independently by the 2 operators (LL and PL) and was compared by interobserver reliability testing; the calculated coefficient of variation was 11.7%.

Ethics. The Regional Ethical Review Board at Umeå University, Sweden,

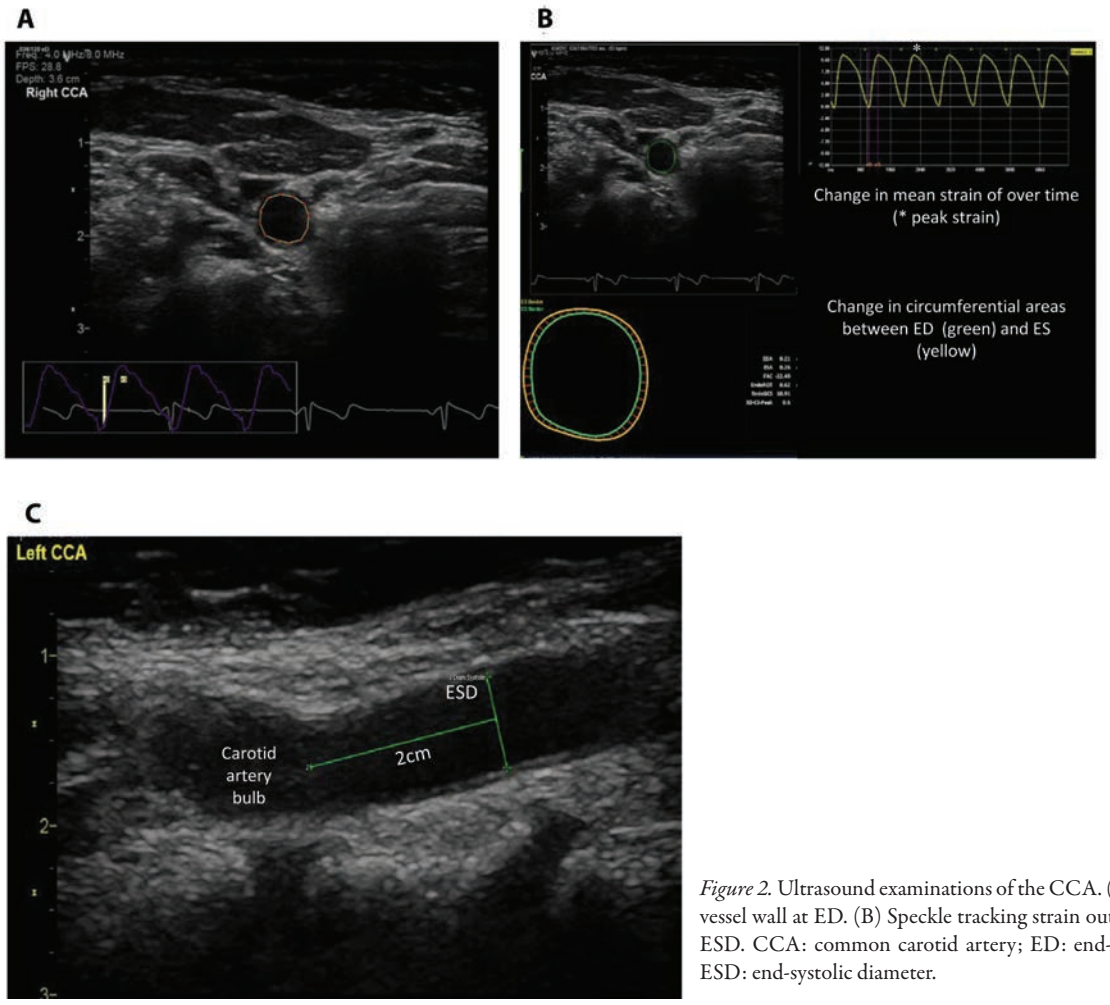

Figure 2. Ultrasound examinations of the CCA. (A) Outline of the internal vessel wall at ED. (B) Speckle tracking strain output. (C) Measurement of ESD. CCA: common carotid artery; ED: end-diastole; ES: end-systole; ESD: end-systolic diameter.

approved the study (patients dnr 2015/352-31, 2016/208-31, controls dnr 2010-21-21, 2014/198-32M), which was performed in accordance with the Declaration of Helsinki. All patients included in the Backbone Study gave written informed consent.

Statistics. Continuous variables are presented as mean (SD) or median (IQR) and categorical variables are shown as numbers and percentages. An independent *t*-test or the Mann-Whitney U test was used to compare continuous variables as appropriate. and the chi-square test was used for categorical comparisons. Correlations between variables were calculated using Pearson bivariate correlation test. Univariable and multivariable linear regression analyses were used to analyze factors associated with mean bilateral CCA circumferential 2D strain and mean bilateral β stiffness index. The dependent variables, mean bilateral CCA circumferential 2D strain and mean bilateral β stiffness index, were normally distributed. Independent variables with a univariable *P* value ≤ 0.1 were considered for the multivariable models. Also, correlations between independent variables in the models were analyzed and the limit was set to r < 0.7 and the variable with the best prediction in the univariable analysis was selected for the multivariable analysis. Residual plots were assessed for assumptions of linearity to be confirmed. To have a characteristic was coded 1 and to not have a characteristic was coded 0 in the dichotomous variables. Female sex was coded 1 and male sex 0. Statistics were performed using SPSS version 24 (SPSS Inc., IBM Corp.). $P < 0.05$ was considered statistically significant.

RESULTS

Altogether, 149 patients (68.5 % men) were included with a mean age of 55.3 ± 11.2 years and a mean symptom duration of 31.5 ± 11.6 years. HLA-B27 was present in 146 (98.0%) patients. Sixty-seven (45.0%) of the patients were ever smokers and 8 (5.4%) smoked regularly. The median mSASSS value was 8.0 (1.0–30.0) and 82 (55.0%). Patients with AS had at least 1 syndesmophyte. In total, 36 (24.2%) patients were treated with a conventional synthetic disease-modifying antirheumatic drug (csDMARD) and/or a biologic DMARD (bDMARD). Sixty-five (43.6%) of the patients had hypertensive disease and 21 (14.1%) were on medication against dyslipidemia (Table 1).

Comparisons between patients with AS and controls. The patients with AS had significantly lower CCA strain and higher stiffness identified by a lower circumferential 2D strain and higher β stiffness index compared to the controls (Table 2). Significant difference was found neither in circumferential 2D strain (8.3 ± 2.5% vs 7.0 ± 2.8%, $P = 0.12$) nor in β stiffness index, between men and women with AS (13.1 ± 1.3 mmHg/mm vs 13.2 ± 2.2 mmHg/mm, $P = 0.95$). Concerning controls, no significant difference was found in circumferential 2D strain between men and women (10.2 ± 1.9% vs 10.4 ± 2.1%, $P = 0.73$) or in β stiffness index between control men and women (12.5 ± 1.45 mmHg/mm vs 12.15 ± 1.15 mmHg/mm, $P = 0.39$). Three (6.5%) of the patients with AS smoked regularly and 23 (50.0%) had ever been smokers. No information about smoking was available for controls.

Linear regression analyses demonstrating factors associated with mean bilateral CCA circumferential 2D strain (all AS patients). In the univariable analysis, CCA circumferential 2D strain was associated significantly with age, symptom duration, ESR, hsCRP, history of anterior uveitis or peripheral arthritis, BASMI, severe spinal radiographic changes, SBP, DBP, and heart rate (Table 3). In the multivariable analysis, the mean circumferential 2D strain

Table 1. Descriptive characteristics of 149 patients with ankylosing spondylitis.

	Values
Sex	
Women	47 (31.5)
Men	102 (68.5)
Age, yrs	55.3 ± 11.2
BMI, kg/m^2	27.8 ± 5.2
Ever smoker	67 (45.0)
Current smoker, regular frequency	8 (5.4)
SF-36 PCS[a]	39.8 ± 8.8
SF-36 MCS[a]	45.2 ± 11.6
AS-related variables	
Duration of symptoms, yrs	31.5 ± 11.6
HLA-B27–positive	146 (98.0)
ESR, mm/h	10.0 (5–20) 13.7 ± 11.9
CRP, mg/L	2.6 (1.0–6.0) 4.6 ± 6.1
History of anterior uveitis	77 (51.7)
History of peripheral arthritis	80 (53.7)
BASDAI	3.7 ± 1.9
ASDAS-CRP	1.8 ± 0.7
BASFI	2.9 ± 2.0
BASMI	4.1 ± 1.5
NSAID, regular use	94 (63.1)
csDMARD	19 (12.8)
bDMARD	25 (16.8)
csDMARD and/or bDMARD	36 (24.2)
mSASSS[b]	8.0 (1.0–30.0) 17.5 ± 20.4
≥ 1 syndesmophyte[b]	82 (55.0)
Severe spinal radiographic changes[b,c]	30 (20.3)
Comorbidity and CV-related variables	
Systolic BP, mmHg	133 ±17
Diastolic BP, mmHg	77 ± 10
Pulse pressure, mmHg	56 ± 13
Heart rate, bpm	68 ± 11
Right CCA circumferential strain, %	7.9 ± 3.1
Left CCA circumferential strain, %	7.9 ± 3.3
Mean CCA circumferential strain, %	7.9 ± 2.9
Right CCA β stiffness, mmHg/mm[a]	13.3± 2.0
Left CCA β stiffness, mmHg/mm[a]	13.4± 2.0
Mean CCA β stiffness, mmHg/mm[a]	13.3 ± 1.5
MI, surgical myocardial revascularization, or stroke	9 (6)
Hypertensive disease	65 (43.6)
Diabetes mellitus	8 (5.4)
Taking dyslipidemia medication	21 (14.1)
Cholesterol, mmol/L	5.4 ± 1.1
HDL, mmol/L	1.6 ± 0.5
LDL[b], mmol/L	3.3 ± 0.9
Cholesterol/HDL	3.7 ± 1.2
Triglycerides, mmol/L	1.3 ± 0.6

Values are mean ± SD, median (IQR), or n (%). [a] Data missing for 3 patients. [b] Data missing for 1 patient. [c] ≥ 3 consecutive intervertebral bridges, cervical, and/or lumbar spine. AS: ankylosing spondylitis; ASDAS: Ankylosing Spondylitis Disease Activity Score; BASDAI: Bath Ankylosing Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; BASMI: Bath Ankylosing Spondylitis Metrology Index; bDMARD: biological disease-modifying antirheumatic drug; BP: blood pressure; bpm: beats per minute; CCA: common carotid artery; CRP: C-reactive protein; csDMARD: conventional synthetic disease-modifying antirheumatic drug; CV: cardiovascular; ESR: erythrocyte sedimentation rate; HDL: high-density lipoprotein; LDL: low-density lipoprotein; MCS: SF-36 mental component summary score; MI: myocardial infarction; mSASSS: modified Stoke Ankylosing Spondylitis Spine Score; NSAID: nonsteroidal antiinflammatory drug; PCS: SF-36 physical component summary score; SF-36: 36-item Short Form health survey.

Table 2. Comparisons between circumferential 2D strain and β stiffness index in common carotid arteries in patients with AS and age- and sex-matched controls.

	AS Patients, n = 46	Controls, n = 46	*P*
Sex			
Men	31 (64.7)	31 (64.7)	
Women	15 (32.6)	15 (32.6)	
Age, yrs	50.4 ± 8.7	49.8 ± 9.2	0.75
Systolic BP, mmHg[a]	127 ± 13	127 ± 12	0.96
Diastolic BP, mmHg[a]	75 ± 9	74 ± 8	0.53
Circumferential 2D strain, %			
Right	7.8 ± 2.8	10.1 ± 2.1	< 0.001
Left	8.0 ± 3.1	10.5 ± 2.6	< 0.001
Mean	7.9 ± 2.6	10.3 ± 1.9	< 0.001
β stiffness index, mmHg/mm			
Right[b]	13.0 ± 1.7	12.4 ± 1.4	0.05
Left[c]	13.3 ± 2.1	12.3 ± 1.8	0.02
Mean[d]	13.1 ± 1.7	12.3 ± 1.3	0.02

Values are mean ± SD or n (%). [a] Controls, n = 45. [b] AS patients, n = 44; controls, n = 45. [c] AS patients, n = 45; controls, n = 44. [d] AS patients, n = 43; controls, n = 44. 2D: 2-dimensional; AS: ankylosing spondylitis; BP: blood pressure; AS: ankylosing spondylitis.

showed inverse significant associations with age, ESR, a history of anterior uveitis, and present treatment with a csDMARD and/or a bDMARD (R^2 0.33; Table 4).

Linear regression analyses demonstrating factors associated with mean bilateral CCA β stiffness index (all AS patients). In the univariable analysis, the mean CCA β stiffness index associated significantly with age, symptom duration, BASMI, mSASSS, severe spinal radiographic changes, and hypertensive disease (Table 3). In the multivariable analyses, only age was associated with the mean β stiffness index (R^2 0.19; Table 4).

DISCUSSION

In this investigation of biomechanical properties by US of the CCA in a contemporary cohort of patients with AS from northern Sweden, we demonstrated a reduced strain and increased stiffness in patients with AS compared with controls. We selected 2 methods, the recently developed speckle tracking circumferential 2D strain and the established method, β stiffness index, as we were interested in studying, for the first time in patients with AS, to our knowledge, biomechanics on the same arteries with different methods and to investigate if they were comparable. Speckle tracking circumferential 2D strain assesses arterial motion and deformation, whereas the β stiffness index assesses arterial stiffness. Further, in the multivariable analyses among patients with AS, we found that AS-related factors and age were associated with circumferential 2D strain, whereas only age was associated with β stiffness index. Thus, age was the only common contributing determinant explaining some of the variations of the 2 measurements of biomechanical properties of CCA in this cohort of patients with AS. Interestingly, the AS-related variables of ESR, history of anterior uveitis, and present treatment with a csDMARD and/or a bDMARD were also significant determinants of circumferential 2D strain. Thus, our results indicate that the circumferential 2D strain method has the capacity to capture aspects of strain related to inflammation and the severity of the AS disease. The HLA-B27–positive rate was high, 98% in this cohort of patients with AS from northern Sweden, which may be explained by the high HLA-B27 rate, 17% in the population in this area[30].

There is a growing recognition that the prevalence of CVD is increased in patients with AS, which contributes to increased mortality[7,31,32,33,34]. An elevated risk of CV and cerebrovascular diseases related to atherosclerosis has been demonstrated in patients with AS[2,4,5,6,35,36]. In addition, the prevalence of other typical AS-related cardiac manifestations such as aortic insufficiency and cardiac conduction disturbances is more common compared to the general population[3,5,37]. Together with traditional CV risk factors for atherosclerotic CVD[38], inflammation itself is considered to play a role in AS[39]. Decreased elasticity of the arterial wall may be present before the occurrence of clinical symptoms or atherosclerotic plaques. Biomechanical properties of the CCA have been investigated only in a few studies of patients with inflammatory arthritis diseases, all being cross-sectional. Kaplanoglu, *et al* recently reported no difference in β stiffness index between 38 patients with AS (mean age 39.6 yrs) and 49 healthy controls (mean age 35.5 yrs)[40]. The discrepancy with our results might be explained by the lower mean patient age in the study by Kaplanoglu, *et al*[40] compared to our study. In other investigations assessing vessel biomechanics, the results showed that pulse wave velocity used to assess aortic stiffness, augmentation index (AIx) measuring arterial stiffness, and echocardiographic evaluation of aortic distensibility were impaired in AS patients compared with controls[41,42,43]; these results are in line with our findings. Moreover, in a study on patients with rheumatoid arthritis, both β stiffness index and speckle tracking 2D strain showed results in the same direction as ours: The β stiffness index was increased and the strain reduced compared to controls[44]. Likewise, in patients with psoriasis, of which approximately 20% had psoriatic arthritis, the β stiffness index was increased compared to controls[45].

We did not find a significant association between strain and stiffness in all patients with AS (r = –0.13, *P* = 0.11; data not shown). Such an association has been displayed in persons without inflammatory rheumatic disease[19,46]. This discrepancy might be explained by our findings that AS-related factors were associated with biomechanical properties measured by circumferential 2D strain but not with the β stiffness index. Concerning anterior uveitis, we have previously discovered it to be independently associated with aortic regurgitation in AS, and believed to be induced by an inflammatory process in the aortic root[47]. Interestingly, we now also show anterior uveitis to be related to the strain of the CCA. Inflammation is known to accelerate atherosclerosis and in a longitudinal study on AS, CRP and ASDAS were associated with future elevated AIx[48]. However, it remains to be established if inflammation is also related to the forthcoming impairment of the biomechanical properties of CCA in AS.

Table 3. Univariable linear regression analysis in 149 patients with AS with common carotid artery biomechanical measurements as dependent variables.

	Mean Bilateral Circumferential 2D Strain, %		Mean Bilateral β Stiffness Index, mmHg/mm	
	B, Unstandardized	*P*	B, Unstandardized	*P*
Sex, women (vs men)	−0.67	0.18	−0.19	0.48
Age, yrs	**−0.073**	**< 0.001**	**0.052**	**< 0.001**
BMI, kg/m^2	−0.046	0.30	0.017	0.52
Ever smoker	−0.30	0.53	−0.18	0.65
SF-36, PCS	0.022	0.46	−0.011	0.44
SF-36, MCS	−0.005	0.81	−0.004	0.71
Covariates, AS-related				
Duration of symptoms, yrs	**−0.063**	**0.002**	**0.029**	**0.008**
HLA-B27–positive	−1.63	0.33	1.60	0.14
ESR, mm/h	**−0.084**	**< 0.001**	0.005	0.68
CRP, mg/L	**−0.092**	**0.016**	0.005	0.80
History of anterior uveitis	**−1.18**	**0.012**	−0.023	0.93
History of peripheral arthritis	**−1.13**	**0.016**	0.30	0.23
BASDAI	−0.039	0.75	0.020	0.77
ASDAS-CRP	−0.17	0.61	0.060	0.75
BASFI	−0.19	0.10	0.10	0.11
BASMI	**−0.49**	**0.001**	**0.32**	**< 0.001**
NSAID, regular use	0.44	0.37	0.056	0.83
csDMARD and/or bDMARD	−1.07	0.05	0.41	0.18
mSASSS, score	−0.016	0.18	**0.015**	**0.016**
≥ 1 syndesmophyte	−0.15	0.76	0.43	0.09
Severe spinal radiographic changes[a]	**−1.16**	**0.047**	**0.64**	**0.044**
Covariates, CV-related				
Systolic BP, mmHg	**−0.037**	**0.006**	0.009	0.20
Diastolic BP, mmHg	**−0.070**	**0.003**	0.00	0.98
Pulse pressure, mmHg	−0.023	0.19	0.015	0.10
Heart rate, bpm	**−0.055**	**0.008**	0.020	0.08
MI, surgical myocardial revascularization or stroke	1.15	0.24	−0.46	0.39
Hypertensive disease	−0.48	0.31	**0.53**	**0.038**
Diabetes mellitus	0.46	0.66	0.25	0.65
Dyslipidemia, medication	0.064	0.92	0.42	0.24
Cholesterol, mmol/L	−0.41	0.06	0.12	0.32
HDL, mmol/L	−0.91	0.06	0.11	0.70
LDL, mmol/L	−0.36	0.15	0.077	0.57
Triglycerides, mmol/L	−0.12	0.75	0.32	0.13

To have a characteristic was coded 1 and to not have a characteristic was coded 0. Female sex was coded 1 and male sex 0. Values in bold are statistically significant. [a] ≥ 3 consecutive intervertebral bridges, cervical, and/or lumbar spine. 2D: 2-dimensional; AS: ankylosing spondylitis; ASDAS: Ankylosing Spondylitis Disease Activity Score; BASDAI: Bath Ankylosing Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; BASMI: Bath Ankylosing Spondylitis Metrology Index; bDMARD: biologic disease-modifying antirheumatic drug; BP: blood pressure; bpm: beats per minute; CRP: C-reactive protein; csDMARD: conventional synthetic disease-modifying antirheumatic drug; CV: cardiovascular; ESR: erythrocyte sedimentation rate; HDL: high-density lipoprotein; LDL: low-density lipoprotein; MCS: SF-36 mental component summary score; MI: myocardial infarction; mSASSS: modified Stoke Ankylosing Spondylitis Spine Score; NSAID: nonsteroidal antiinflammatory drug; PCS: SF-36 physical component summary score; SF-36: 36-item Short Form health survey.

Among risk factors for CVD, we found age to be associated with circumferential 2D strain and β stiffness index in the multivariable analyses. Kaplanoglu, *et al* showed, in univariate analyses, that the β stiffness index was associated with age, symptom duration, and BMI in AS, partly in agreement with our findings[40].

There are some limitations to the current study. It is cross-sectional; thus, we cannot draw any conclusions about causality. The R^2 values in the multivariable models are rather low, meaning that other unknown factors contribute to explaining the variation of circumferential 2D strain and β stiffness index. The number of AS patients was somewhat limited (n = 149), as was the number of controls. Mostly White men and women were included and the results cannot be generalized to other ethnicities. Further, the proportion of men was lower compared to nonparticipants. However, we do not think that the difference has influenced the results considerably since there were no significant differences in circumferential 2D strain (men 8.1 ± 2.8% vs women 7.5 ± 3.0%, $P = 0.18$; data not shown) or β stiffness index (men 13.4 ± 1.4 mmHg/mm vs women 13.2 ± 1.8 mmHg/mm, $P = 0.5$; data not shown) between the examined men and women with AS. Additionally, we did not have data on smoking habits, BMI, and dyslipidemia in the controls, who were recruited from hospital staff, which is a major

Table 4. Multivariable linear regression analysis in 149 patients with AS with mean bilateral common carotid artery circumferential 2D strain and β stiffness index as dependent variables.

Circumferential 2D Strain	Mean Bilateral Circumferential 2D Strain, %		
	B, Unstandardized	B, Standardized	*P*
Age, yrs	−0.054	−0.21	**0.02**
ESR, mm/h	−0.070	−0.29	**< 0.001**
Anterior uveitis	−0.95	−0.17	**0.03**
Peripheral arthritis ever	−0.71	−0.12	0.10
BASFI	0.036	0.026	0.76
BASMI	0.057	0.031	0.78
csDMARD and/or bDMARD	−1.06	−0.16	**0.04**
Severe spinal radiographic changes[a]	−0.78	−0.11	0.22
Diastolic BP, mmHg	−0.035	−0.12	0.10
Heart rate, bpm	−0.038	−0.15	0.06
Cholesterol, mmol/L	−0.070	−0.027	0.72
HDL, mmol/L	−0.58	−0.096	0.21
	R^2 0.33		
β stiffness index	Mean Bilateral β Stiffness Index, mmHg/mm		
	B, Unstandardized	B, Standardized	*P*
Age, yrs	0.043	0.32	**0.003**
BASMI	0.13	0.13	0.27
Syndesmophyte	−0.23	−0.077	0.43
Severe spinal radiographic changes[a]	0.12	0.034	0.74
Pulse pressure, mmHg	−0.002	−0.022	0.80
Heart rate, bpm	0.018	0.14	0.10
Hypertensive disease	0.17	0.057	0.50
	R^2 0.19		

To have a characteristic was coded 1 and to not have a characteristic was coded 0. [a] ≥ 3 consecutive intervertebral bridges, cervical, and/or lumbar spine. Values in bold are statistically significant. 2D: 2-dimensional; AS: ankylosing spondylitis; BASFI: Bath Ankylosing Spondylitis Functional Index; BASMI: Bath Ankylosing Spondylitis Metrology Index; bDMARD: biologic disease-modifying antirheumatic drug; BP: blood pressure; bpm: beats per minute; csDMARD: conventional synthetic disease-modifying antirheumatic drug; ESR: erythrocyte sedimentation rate; HDL: high-density lipoprotein.

limitation. However, the number of smokers among the patients with AS who smoked regularly was low. The well-characterized cohort of AS patients with matched controls and the usage of appropriate US methods are some of the notable strengths of this study.

In conclusion, the circumferential 2D strain was reduced and the β stiffness index increased in patients with AS compared to matched controls, indicating impaired biomechanical properties of CCA in patients with AS. Strain was associated with factors related to AS-disease severity, which was not observed for stiffness. This could imply that the process leading to impaired strain is more dependent on the course of the AS disease than is the development of stiffness. Larger and longitudinal studies are required to investigate the clinical importance of the markers of arteriosclerosis and subclinical atherosclerosis in AS and whether they add predictive value in addition to already identified risk factors for CVD.

ACKNOWLEDGMENT

We wish to thank all the patients who participated in the study. We also wish to thank the research nurses at the University Hospital of Umeå, Viktoria von Zweigbergk and Jeanette Beckman Rehnman, for assisting with the project.

DATA AVAILABILITY

The datasets generated and/or analyzed during the current study are not publicly available due to the General Data Protection Regulation (GDPR), but a limited and fully anonymized data set that supports the main analyses is available from the corresponding author on request.

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