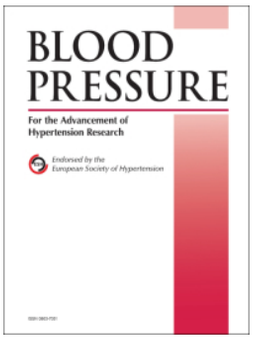

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Cardiovascular organ damage in relation to hypertension status in patients with ankylosing spondylitis

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ABSTRACT

Purpose: Hypertension is a major cardiovascular (CV) risk factor in ankylosing spondylitis (AS) patients. Less is known about the prevalence of CV organ damage in relation to hypertension status in AS patients.

Materials and Methods: CV organ damage was assessed by echocardiography, carotid ultrasound and pulse wave velocity (PWV) by applanation tonometry in 126 AS patients (mean age 49 ± 12 years, 39% women) and 71 normotensive controls (mean age 47 ± 11 years, 52% women). CV organ damage was defined as presence of abnormal left ventricular (LV) geometry, LV diastolic dysfunction, left atrial (LA) dilatation, carotid plaque or high pulse wave velocity (PWV).

Results: Thirty-four percent of AS patients had hypertension. AS patients with hypertension were older and had higher C-reactive protein (CRP) levels compared to AS patients without hypertension and controls ($p < 0.05$). The prevalence of CV organ damage was 84% in AS patients with hypertension, 29% in AS patients without hypertension and 30% in controls ($p < 0.001$). In multivariable logistic regression analyses, having hypertension was associated with a fourfold increased risk of CV organ damage independent of age, presence of AS, gender, body mass index, CRP, and cholesterol (odds ratio (OR) 4.57, 95% confidence interval (CI) 1.53 to 13.61, $p = 0.006$). In AS patients, presence of hypertension was the only covariable significantly associated with presence of CV organ damage (OR 4.40, 95% CI 1.40 to 13.84, $p = 0.011$).

Conclusions: CV organ damage in AS was strongly associated with hypertension, pointing to the importance of guideline-based hypertension management in AS patients.

PLAIN LANGUAGE SUMMARY

- **What is the context?** Ankylosing spondylitis (AS) is an inflammatory disease primarily affecting the spine. Patients with AS have increased risk for cardiovascular disease. High blood pressure (hypertension) is both very common in AS patients, and a major risk factor for developing cardiovascular disease. Hypertension leads to structural and functional changes in the heart and arteries, referred to as cardiovascular organ damage. However, little is known about the prevalence of cardiovascular organ damage in AS patients with hypertension.
- **What is new?** Using ultrasound and tonometry, we assessed organ damage in the heart and arteries in AS patients with hypertension and compared them to AS patients with normal blood pressure as well as a group of healthy controls. We found that 84% of the AS patients with hypertension had cardiovascular organ damage, compared to 29% of AS patients with normal blood pressure and 30% of controls. Independent of other

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Ankylosing spondylitis; cardiovascular organ damage; hypertension; echocardiography; arterial stiffness; carotid ultrasound

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risk factors, hypertension was associated with a fourfold increased risk of cardiovascular organ damage in AS patients.
- **What is the impact?** These findings are important because cardiovascular organ damage is potentially reversible with treatment. Our results underline the significance of guideline-directed hypertension management in AS patients to reduce cardiovascular disease.

Introduction

Ankylosing spondylitis (AS) is an inflammatory joint disease primarily affecting the sacroiliac joints. AS and other inflammatory joint diseases have been associated with increased risk of cardiovascular (CV) disease, in particular premature atherosclerosis [1–3]. However, previous research has demonstrated cardiac involvement in AS beyond atherosclerosis, including increased prevalence of aortic valve regurgitation, conduction disturbances and increased prevalence of left ventricular (LV) hypertrophy [4,5].

Hypertension is a major CV risk factor in AS patients [6]. In a recent prospective study of 630 AS patients with a mean age of 39 years, 19% developed hypertension during 5 years of follow-up [7]. Hypertension causes CV disease through the development of CV organ damage such as atherosclerosis, stiffening of the arteries, LV hypertrophy, LV dysfunction and left atrial (LA) dilation in the heart [8–10]. However, as opposed to clinical CV disease, treatment of CV risk factors such as hypertension can protract or reverse the development of CV organ damage [9,11,12]. Therefore, guidelines recommend assessment of CV organ damage in hypertension to improve prevention of CV disease [9]. Although hypertension is common in AS patients, little is known about the frequency of CV organ damage in AS patients with hypertension compared to their normotensive counterparts. In the current study, the aim was to assess the prevalence of CV organ damage assessed by echocardiography, carotid ultrasound and arterial stiffness in groups of AS patients with hypertension or normal blood pressure and healthy controls.

Materials and methods

Study population

AS patients were recruited from a cohort established at the Department of Rheumatology, Diakonhjemmet Hospital in 2008-2010. Details regarding this cohort have been published previously [13,14]. In short, AS patients diagnosed by the modified New York criteria [15] were recruited from the Oslo area in Norway, the gross majority Caucasians. Of the 257 AS patients invited, 159 agreed to participate (response rate 62%). Of those, 17 patients were excluded due to established CV disease (defined as previous cardiac surgery/intervention, myocardial infarction, angina pectoris, transitory ischaemic attack, cerebral ischaemic event and intermittent claudication). In this sub-study, additional 16 patients were excluded due to incomplete echocardiographic data. Thus, for the present analyses, 126 patients with AS were included.

Control subjects without inflammatory joint disease, stratified for age, sex and residential area to the participating AS patients, were randomly selected by Statistics Norway. Of the 329 invited control subjects, 132 (40%) agreed to participate. Sixty-one control subjects were excluded because of established CV disease or hypertension, leaving a control group of 71 subjects. All patients and controls signed an informed consent according to the Declaration of Helsinki, and the study protocol was approved by the South Eastern Norwegian Regional Committee for Medical and Health Research Ethics, approval number S-02059.

Ankylosing spondylitis disease characteristics

Duration of disease was defined from the onset of symptoms as previously recommended in AS [16]. Disease activity was calculated by the Bath Ankylosing Disease Activity Index (BASDAI) [17] and the Ankylosing Spondylitis Disease Activity Score (ASDAS)-C-reactive protein (CRP) [18].

Health status and cardiovascular risk factors

Self-reported information about the participants' medical history, smoking status and current medical therapy were collected on a standardised questionnaire. The information was later quality assured by the consultant cardiologist (AGS) during the consultation. Brachial blood pressure was measured in accordance with the European Society of Hypertension guidelines using an OMRON M7 apparatus (Kyoto, Japan) [9]. The average of the two last measurements was reported as the office blood pressure. Hypertension was defined as use of antihypertensive medication, a

history of hypertension, or elevated office blood pressure (≥140/90 mmHg). Serum total cholesterol and CRP were analysed in fasting blood samples by the COBAS 6000 (Roche diagnostics, Basel, Switzerland) machine. Low-density lipoprotein cholesterol (LDL) was calculated with the Friedewald equation [19].

Cardiovascular organ damage

Cardiac organ damage

Standardised transthoracic echocardiograms were recorded on a Vivid 7 (General Electrics Vingmed Ultrasound, Horten, Norway) scanner at the Preventive Cardio-Rheuma Clinic, Department of Rheumatology, Diakonhjemmet Hospital, Oslo, Norway. Off-line image analyses were done at the Echocardiography Core Laboratory at the University of Bergen, (Bergen, Norway) as previously described [4]. Readings were done by the same reader (HM) and then proofread by the same highly experienced reader (EG) on digital workstations equipped with Image Arena software version 4.1 (TomTec Imaging Systems GmbH, Unterschleissheim, Germany). Quantitative echocardiographic analyses were performed following the joint guidelines from the European Association of Cardiovascular Imaging and American Society of Echocardiography [20]. Echocardiographic parameters of cardiac organ damage in hypertension and corresponding cut-off values were assessed as recommended in a consensus paper from the European Association of Cardiovascular Imaging/the European Society of Cardiology Council on Hypertension and the European Society of Hypertension [21]. LV mass was indexed for height$^{2.7}$, and LV hypertrophy was considered present if LV mass index >49.2 g/m$^{2.7}$ in men and >46.7 g/m$^{2.7}$ in women [22, 23]. Relative wall thickness was defined as 2 x LV posterior wall thickness/internal LV diameter ratio in end-diastole and considered high if ≥0.43 (concentric geometry) [21]. Left atrial (LA) dilatation was defined as LA volume in apical 4-chamber >34 ml/m^2 [21]. LV diastolic function was assessed from early mitral annulus velocities (e') in septal and lateral positions, and considered abnormal if septal annular e'<7 cm/s and lateral annular e' velocity <10 cm/s. The ratio of early mitral filling (E) to the average annular e' velocity (E/e') was considered abnormal if >14 [21].

Cardiac organ damage was diagnosed if there was presence of LV hypertrophy, LV concentric geometry, abnormal septal and lateral annular e' velocities, elevated E/e' ratio and/or LA dilatation.

Arterial organ damage

Arterial stiffness was assessed by carotid-femoral pulse wave velocity (PWV) using a Sphygomocor device (AtCor, Sydney, Australia) as previously described [14]. PWV is an indirect measure of arterial stiffness where the velocity of the pulse wave through the central arteries are measured, and higher speed indicates arterial stiffening. High PWV was defined as PWV >10 m/s [24]. PWV was not available in 36 of the participants in the study.

Carotid atherosclerosis was assessed using a B-mode ultrasonography with a GE Vivid 7 ultrasound scanner (GE Vingmed Ultrasound, Horten, Norway) and a 12 (9-14)-MHz linear matrix array transducer [13,25]. Plaques in the common carotid artery, bulb, and the internal carotid artery were identified as protrusions into the lumen >1.5 mm or a protrusion >2 times the intima media thickness (IMT) [26]. Plaques were verified with a cross-sectional image from the same probe.

Arterial organ damage was defined as presence of carotid plaque and/or high PWV in accordance with current recommendations [21]. Any CV organ damage was defined as presence of cardiac and/or arterial organ damage.

Statistics

The statistical analyses were done using IBM SPSS statistics version 26.0 (IBM, Armonk, New York, USA). Categorical variables are presented as percentages and numbers. Normally distributed continuous data are expressed as mean and standard deviation (SD) and non-normally distributed continuous variables (CRP) as median and interquartile range. Non-normally distributed variables were log transformed before inclusion in uni- and multivariable analyses. Participants were grouped in three categories: AS patients with hypertension, AS patients without hypertension, and control subjects without hypertension. Comparisons between groups were performed using one-way analysis of variance with Scheffe's post hoc test, general linear model with Sidak's post hoc test, the Chi-square test or the two-sample Student's t-test as appropriate. Uni- and multivariable logistic regression analyses were used to identify covariables of CV organ damage. Results of the logistic regression analysis were reported as odds ratios (OR) and 95% confidence intervals (CI) for the individual variables. A two-tailed p-value of <0.05 was considered statistically significant in all analyses.

Table 1. Clinical characteristics of the study population.

	AS patients with hypertension ($n=43$)	AS patients with normal BP ($n=83$)	Controls with normal BP	P-value
Age (years)	58.6 ± 8.0†	44.6 ± 10.9*	47.1 ± 10.9*	<0.001
Women, n (%)	16 (37)	33 (40)	37 (52)	0.192
Body mass index (kg/m^2)	26.4 ± 3.1†	24.3 ± 3.4*	25.0 ± 3.8	0.006
LDL cholesterol (mmol/L)	3.5 ± 0.9	3.0 ± 1.0	3.5 ± 0.9†	0.003
Current smoking, n (%)	7 (16)	14 (17)	16 (23)	0.597
Diabetes, n (%)	4 (10)	2 (3)	0 (0)*	0.017
Blood pressure				
Systolic blood pressure (mmHg)	140 ± 14†	118 ± 11*	117 ± 12*	<0.001
Diastolic blood pressure (mmHg)	86 ± 9†	74 ± 7*	72 ± 7*	<0.001
Pulse pressure (mmHg)	54 ± 10†	44 ± 9*	45 ± 8*	<0.001
Medication				
Antihypertensive medication, n (%)	23 (54)†	–	–	–
Statin treatment, n (%)	6 (14)†	2 (2)*	3 (4)	0.023
s-DMARDs, n (%)	9 (21)	10 (12)	–	0.196
b-DMARDs, n (%)	7 (16)	17 (21)	–	0.548
NSAIDs, n (%)	26 (61)	60 (72)	7 (10)*†	<0.001
Prednisolone, n (%)	5 (12)	6 (7)	2 (3)	0.177
AS disease characteristics				
Disease duration (years)	30.3 ± 10.6†	20.0 ± 9.6*	–	<0.001
ASDAS score	2.4 ± 1.0	2.2 ± 1.0	–	0.211
BASDAI score	3.7 ± 2.0	3.5 ± 1.7	–	0.473
C-reactive protein (mg/l), median (IQR)	5.0 (2.0,12.0)†	3.0 (1.0,8.0)*	1.0 (1.0,2.0)*†	<0.001

*$p<0.05$ vs. AS patients with hypertension, †$p<0.05$ vs. AS patients with normal blood pressure.
AS: ankylosing spondylitis; ASDAS: ankylosing spondylitis disease activity score; BASDAI: Bath ankylosing spondylitis disease activity index; BP: blood pressure; b-DMARD; biological disease modifying antirheumatic drugs; s-DMARD; synthetic disease modifying antirheumatic drugs; IQR: interquartile range; LDL; low density lipoprotein; NSAID: non-steroidal anti-inflammatory drugs.

Results

Clinical characteristics

The clinical characteristics of the study population are presented in Table 1. Thirty-four percent of the patients had hypertension. The AS patients with hypertension were older, had higher CRP levels, and higher systolic and diastolic blood pressure compared to the AS patients with normal blood pressure and controls (all $p<0.05$, Table 1). The AS patients with hypertension also had higher BMI and a higher proportion used statin treatment compared to the AS patients with normal blood pressure. The prevalence of treated hypertension was 54% among AS patients with hypertension (Table 1).

The AS disease duration was longer in the AS patients with hypertension compared to AS patients with normal blood pressure, but there were no significant differences in other AS disease characteristics including BASDAI score and ASDAS score as well as antirheumatic medication (Table 1).

Prevalence of cardiovascular organ damage

The prevalence of any cardiac organ damage was 65% in AS patients with hypertension, 18% in AS patients with normal blood pressure and 16% in controls ($p<0.001$, Table 2). AS patients with hypertension had higher prevalence of all individual parameters of cardiac organ compared to the AS patients with normal blood pressure and controls, except for prevalence of dilated left atrium and elevated E/e' (Table 2), Figure 1). There was no difference in the prevalence of cardiac organ damage between AS patients with normal blood pressure and controls.

The prevalence of arterial organ damage was 58% in AS patients with hypertension, 11% in AS patients with normal blood pressure and 18% in control subjects ($p<0.001$, Table 2). The prevalence of carotid plaque and high PWV were both higher in AS patients with hypertension compared to AS patients with normal blood pressure and controls, while prevalence did not differ between AS patients with normal blood pressure and controls (Table 2, Figure 1).

When cardiac and arterial organ damage was considered together, the prevalence of any CV organ damage (cardiac or arterial) was 84% in AS patients with hypertension, 29% in AS patients with normal blood pressure and 30% in control subjects ($p<0.001$, Table 2, Figure 2). Forty percent of AS patients with hypertension had combined cardiac and arterial organ damage, while none of the AS patients with normal blood pressure and four percent of the control subjects had this ($p<0.001$, Table 2, Figure 2).

Factors associated with cardiovascular organ damage

Total study population. In univariable logistic regression analyses, the main covariables of any CV organ damage

Table 2. CV organ damage in AS patients with hypertension and normal blood pressure and controls.

Variables	AS patients with hypertension ($n=43$)	AS patients with normal BP ($n=83$)	Controls with normal BP ($n=71$)	P-value
Cardiac organ damage				
LV mass index (g/m$^{2.7}$)	40.6 ± 10.3†	33.7 ± 7.9*	31.2 ± 7.6*	<0.001
LV hypertrophy, n (%)	10 (23)†	5 (6)*	2 (3)*	<0.001
LV relative wall thickness, ratio	0.37 ± 0.08†	0.34 ± 0.07*	0.33 ± 0.07*	0.011
Concentric geometry, n (%)	11 (26)†	5 (6)*	8 (11)	0.006
Left atrium volume index (ml/m^2)	21.0 ± 10.3	19.6 ± 7.5	17.7 ± 6.2	0.080
Dilated left atrium, n (%)	3 (7)	4 (5)	0 (0)	0.108
Septal annular e′ velocity (cm/s)	6.2 ± 1.9†	9.2 ± 2.2*	9.1 ± 2.2*	<0.001
Septal annular e′ velocity <7 cm/s, n (%)	27 (63)†	12 (15)*	8 (11)*	<0.001
Lateral annular e′ velocity (cm/s)	7.7 ± 2.5†	12.2 ± 3.3*	12.1 ± 2.8*	<0.001
Lateral annular e′ velocity <10 cm/s, n (%)	33 (77)†	13 (16)*	13 (18)*	<0.001
Reduced septal and lateral e′ velocity, n (%)	24 (56)†	4 (5)*	5 (7)*	<0.001
E/e′ average ratio >14, n (%)	3 (7)	1 (1)	0 (0)*	0.031
Any cardiac organ damage, n (%)	28 (65)†	15 (18)*	11 (16)*	<0.001
Arterial organ damage				
IMT (mm)	0.74 ± 0.13†	0.60 ± 0.10*	0.65 ± 0.12*†	<0.001
Carotid plaque, n (%)	22 (51)†	9 (11)*	13 (18)*	<0.001
PWV (m/s)	8.5 ± 1.8†	6.8 ± 1.1*	6.9 ± 1.2*	<0.001
High PWV, n (%)	6 (17)†	0 (0)*	2 (3)*	<0.001
Arterial organ damage, n (%)	25 (58)†	9 (11)*	13 (18)*	<0.001
CV organ damage				
Any cardiovascular organ damage, n (%)	36 (84)†	24 (29)*	21 (30)*	<0.001
Combined arterial and cardiac organ damage, n (%)	17 (40)†	0 (0)*	3 (4)*	<0.001

*$p < 0.05$ vs. AS patients with hypertension, †$p < 0.05$ vs. AS patients with normal blood pressure.
AS: ankylosing spondylitis; BP: blood pressure; E/e′, early mitral filling/average annular e′ velocity; IMT: intima media thickness; LV: left ventricular; PWV: pulse wave velocity.

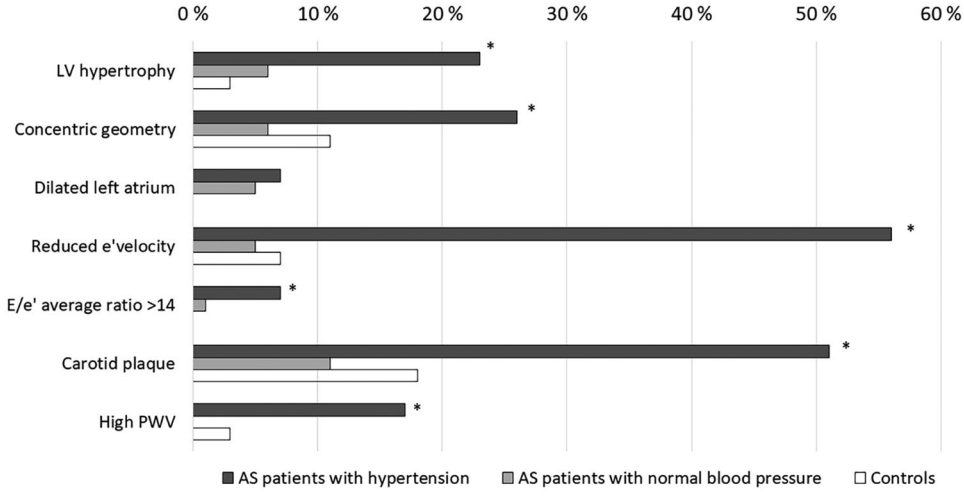

Figure 1. Cardiac and arterial organ damage according to hypertension status.
*$p<0.05$.
e′, early mitral annulus velocity; E/e′, early mitral filling/average annular e′ velocity; LV, left ventricular; PWV, pulse wave velocity.

were presence of AS, hypertension, higher age, systolic and diastolic blood pressure, BMI, CRP, LDL, and use of antihypertensive medication (Table 3).

In multivariable logistic regression analyses, hypertension was the main covariable of any CV organ damage, associated with a fourfold increased risk after adjusting for presence of AS, age, sex, BMI, LDL and CRP (Table 3, $p = 0.006$), independent of significant associations with higher age and higher BMI ($p < 0.05$, Table 3).

As patients. In univariable logistic regression analyses, having hypertension, older age, higher systolic and diastolic blood pressure, and higher BMI were the main covariables of presence of any CV organ damage among AS patients ($p < 0.05$, Table 4). In multivariable logistic regression analyses among AS patients, having hypertension remained associated with a fourfold increased risk of presence of any CV organ damage after adjusting for sex, age, LDL level and BMI ($p = 0.01$, Table 4).

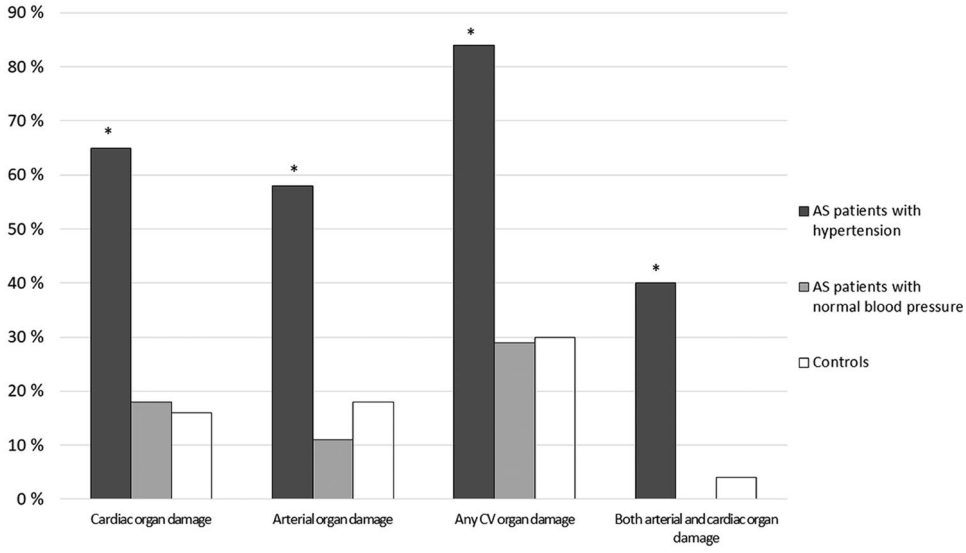

Figure 2. CV organ damage in AS patients with hypertension and normal blood pressure and controls.
*p < 0.001.
CV, cardiovascular.

Table 3. Multivariable associations of CV organ damage in total study population.

	Any CV organ damage					
	Univariable			Multivariable		
	OR	95% CI	p	OR	95% CI	p
Ankylosing spondylitis	2.17	1.17 to 4.02	0.014	1.30	0.55 to 3.11	0.553
Age (years)	1.09	1.06 to 1.13	<0.001	1.06	1.02 to 1.10	0.002
Male sex	0.80	0.45 to 1.42	0.441	0.67	0.32 to 1.40	0.283
BMI (kg/m^2)	1.16	1.06 to 1.26	0.001	1.12	1.01 to 1.25	0.034
CRP (mg/l)	1.45	1.12 to 1.89	0.006	1.08	0.74 to 1.58	0.700
Cardiovascular risk factors						
Hypertension	12.46	5.16 to 30.06	<0.001	4.57	1.53 to 13.61	0.006
Systolic BP (mmHg)	1.04	1.02 to 1.07	<0.001	–	–	–
Diastolic BP (mmHg)	1.06	1.03 to 1.10	<0.001	–	–	–
Pulse pressure (mmHg)	1.05	1.02 to 1.09	0.002	–	–	–
LDL (mmol/L)	1.43	1.04 to 1.97	0.029	1.27	0.88 to 1.84	0.210
Diabetes	2.99	0.53 to 16.72	0.213	–	–	–
Current smoking	0.97	0.47 to 2.01	0.937	–	–	–
Medication				–	–	–
Antihypertensive treatment	8.58	2.79 to 26.35	<0.001	–	–	–
Statin treatment	1.78	0.52 to 6.03	0.357	–	–	–
NSAIDs	1.37	0.78 to 2.43	0.276	–	–	–
Prednisolone	2.43	0.77 to 7.73	0.132	–	–	–
b-DMARDs	1.23	0.52 to 2.01	0.633	–	–	–
s-DMARDs	2.10	0.81 to 4.49	0.129	–	–	–

AS, ankylosing spondylitis; BMI, body mass index; CI, confidence interval; CRP, C-reactive protein; CV, cardiovascular; b-DMARD; biological disease modifying antirheumatic drugs; s-DMARD; synthetic disease modifying antirheumatic drugs; LDL, low-density lipoprotein; NSAID, non-steroidal anti-inflammatory drugs; OR, odds ratio.

Discussion

This study clearly demonstrates that the presence of CV organ damage is common among AS patients, and highly associated with hypertension status. Having hypertension was associated with a fourfold increased risk of CV organ damage in AS patients. Of note, AS patients with normal blood pressure had comparable prevalence of CV organ damage as the control subjects, highlighting the importance of blood pressure control for the CV health in AS patients.

It is well known from studies in patients with hypertension that hypertension causes CV organ damage [8,9]. In AS patients, several previous studies have demonstrated increased prevalence of CV organ damage such as structural and functional changes in the left ventricle, subclinical atherosclerosis and increased arterial stiffness [4,5,27–30]. However, these previous studies have not focussed on the association of hypertension with CV organ damage in AS. Our results are in line with a previous study in 137 patients with inflammatory joint disease, which demonstrated that

Table 4. Multivariable associations of CV organ damage in AS patients.

	Any CV organ damage					
	Univariable			Multivariable		
	OR	95% CI	p	OR	95% CI	p
Age (years)	1.10	1.06 to 1.14	<0.001	1.06	1.01 to 1.11	0.024
Male sex	1.20	0.58 to 2.45	0.626	1.19	0.46 to 3.12	0.718
BMI (kg/m^2)	1.20	1.06 to 1.34	0.003	1.13	0.98 to 1.31	0.100
CRP (mg/L)	1.23	0.91 to 1.68	0.179			
Cardiovascular risk factors						
Hypertension	12.64	4.95 to 32.32	<0.001	4.40	1.40 to 13.84	0.011
Systolic BP (mmHg)	1.06	1.03 to 1.09	<0.001	–	–	–
Diastolic BP (mmHg)	1.07	1.03 to 1.11	0.001	–	–	–
Pulse pressure (mmHg)	1.08	1.04 to 1.12	<0.001	–	–	–
LDL (mmol/L)	1.71	1.13 to 2.59	0.012	1.22	0.76 to 1.98	0.414
Diabetes	2.33	0.41 to 13.24	0.339	–	–	–
Current smoking	0.63	0.24 to 1.64	0.341	–	–	–
Medication						
Antihypertensive treatment	7.18	2.28 to 22.64	0.001	–	–	–
Statin treatment	1.91	0.44 to 8.36	0.391	–	–	–
NSAIDs	1.01	0.48 to 2.13	0.985	–	–	–
Prednisolone	2.05	0.57 to 7.38	0.273	–	–	–
b-DMARDs	0.90	0.37 to 2.20	0.813	–	–	–
s-DMARDs	1.60	0.60 to 4.30	0.351	–	–	–
AS disease characteristics				–	–	–
BASDAI score	1.09	0.89 to 1.33	0.403	–	–	–
ASDAS score	1.21	0.83 to 1.77	0.326	–	–	–

AS, ankylosing spondylitis; ASDAS, ankylosing spondylitis disease activity score; BASDAI, Bath ankylosing spondylitis disease activity index; BP, blood pressure; BMI, body mass index; CI, confidence interval; CV, cardiovascular; b-DMARD; biological disease modifying antirheumatic drugs; s-DMARD; synthetic disease modifying antirheumatic drugs; LDL, low-density lipoprotein; NSAID, non-steroidal anti-inflammatory drugs; OR, odds ratio.

hypertension was associated with increased intima media thickness [29]. Furthermore, in a systematic review of 82 articles, hypertension was reported to accelerate arterial stiffness in inflammatory joint disease [28]. In contrast, in a Swedish study involving 149 AS patients, increased arterial stiffness was only associated with older age [31]. We have previously demonstrated that presence of AS is associated with LV hypertrophy and atherosclerosis [4,13]. However, the current study expands this previous knowledge by demonstrating that a focussed approach on hypertension, reveals the strong relationship between hypertension and CV organ damage in AS patients. Further, the association between hypertension status and CV organ damage was strengthened when we combined different types of cardiac and arterial organ damage to assess the total influence of hypertension on CV organ damage.

The relationship between hypertension and clinical CV disease in AS patients is somewhat more studied than CV organ damage. In a large Israeli register study involving 4,076 AS patients and 20,290 control subjects, AS patients had a higher risk of ischaemic heart disease, attributed to a higher burden of CV risk factors, including hypertension [1]. In the registry based Spanish CARMA project involving 2595 patients with inflammatory joint disease, higher systolic blood pressure was the only CV risk factor associated with development of CV disease [2]. This contrast a much smaller retrospective study of 133 Italian AS patients that found CRP to be a more important risk factor than systolic blood pressure for CV disease [32]. The present study adds to current knowledge by demonstrating the pivotal role of hypertension for the presence of CV organ damage in AS patients. These findings have clinical implication as CV organ damage is associated with adverse prognosis [22, 23] such as increased risk of CV death, stroke and myocardial infarction independent of CV risk factors [11]. Treatment of hypertension is well documented to lower CV risk and hypertension is a major modifiable risk factor for CV mortality and morbidity [9]. Our findings underline the importance of identifying hypertension in AS patients. Of note, the use of antihypertensive medication was associated with presence of CV organ damage in the current study, reflecting more advanced disease among the treated hypertensive patients. Although randomised clinical trials have demonstrated regression of CV organ damage with antihypertensive treatment, real word studies have shown that many patients retain CV organ damage despite antihypertensive treatment, especially when obesity is present [33]. Thus, treatment of hypertension in AS should follow established guidelines, but preferably be initiated before CV organ damage is already established

Higher BMI was also associated with presence of CV organ damage in the current study. This is in line with a previous study in 84 patients with inflammatory joint disease, where higher BMI was one of the main covariables of CV organ damage [34]. Higher body mass contributes to the development of CV organ damage through several mechanisms, including increased hemodynamic load on the LV and chronic inflammation [35, 36]. Furthermore, higher BMI is associated with development of hypertension, and unfavourable changes in glucose and lipid metabolism [37]. High BMI can also affect CV organ damage by contributing to AS disease severity as demonstrated in a recent American study of 183 AS patients [38]. However, in the present study, we did not find significant associations between AS disease activity and CV organ damage. Taken together, our findings underline the importance of retaining a healthy body weight to lower the CV risk in AS patients.

Limitations and strengths

The cross-sectional design is unsuited for demonstration of any causality between hypertension and CV organ damage. Whether the burden of CV organ damage is higher in hypertensive AS patients compared to other hypertensive populations cannot be determined from this study. AS patients with hypertension were older than the patients with normal blood pressure and controls, which could have contributed to the higher prevalence of CV organ damage in patients with hypertension. However, adjustment for age in multivariable analyses did not change the results. PWV was not available in all patients. Lastly, we cannot exclude a selection bias due to the low response rate among invited controls. The study strengths include use of a core laboratory for analysis of echocardiographic images, as recommended for echocardiographic studies [39], and the use of validated and recommended cut-off values for identification of CV organ damage [21].

Conclusion

This study demonstrates that the presence of CV organ damage is closely associated with hypertension status in AS patients, and underlines the importance of management of hypertension in AS patients to reduce the risk of future CV disease.

Disclosure statement

AGS has received speaker honoraria and/or consulting fees from AbbVie, Bayer, Eli Lilly, Novartis, Amgen and Sanofi. EG has received speaker honoraria from Bayer and Novo Nordisk.

Data availability statement

Participants of this study have not agreed for their data to be publicly shared, so supporting data is not available.

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