Abnormal autonomic cardiovascular control in ankylosing spondylitis

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Abstract

***Objective*—This study was aimed at assessing the contribution of the autonomic nervous system to adjustments of cardiovascular function in patients with ankylosing spondylitis (AS).**

***Methods*—In 18 AS patients (mean age: 34.9; mean disease duration: 6.4 years) and 13 healthy controls (mean age: 31.7) the changes of heart rate (HR) with deep breathing (E/I ratio) and standing up (30/15 ratio) were recorded. The slope of cardiac baroreflex, the times series of blood pressure and HR values upon lying and standing, and venous plasma concentrations of catecholamines were also analysed. Erythrocyte sedimentation rate (ESR), plasma C reactive protein (CRP) concentration and a clinical index (BASDAI score) were used to assess the degree of disease activity in patients.**

***Results*—In the standing patients, blood pressure was found to decrease progressively ($p< 0.001$). Furthermore, the patients with a BASDAI score > 5 had a higher heart rate than patients with a BASDAI score < 5 ($p<0.02$), and there was a trend for a similar difference when patients were classified according to their ESR and CRP. Plasma catecholamine concentrations and the E/I ratio were not different in patients from controls. The 30/15 ratio and the slope of the spontaneous baroreflex during standing were both lower in AS patients than controls ($p< 0.01$).**

***Conclusions*—This study demonstrated a change in autonomic nervous system function of AS patients, with a decreased parasympathetic activity, as evidenced by higher HR and lower baroreflex slope. As these significant deviances were mainly observed in patients with more active (or more inflammatory) disease, the autonomic nervous system involvement could be related to the inflammatory process. This autonomic strain may be related to the cardiac involvement in AS patients.**

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Ankylosing spondylitis (AS) is an inflammatory rheumatic disease involving spine and sacroiliac joints. A peripheral disease with asymetrical oligoarthritis may also occur in some cases. Some extra-articular manifestations may be observed in AS such as a neurological involvement[1 2] and a heart disease.[3] This latter is a well recognised complication of AS, often featuring aortic regurgitation, conduction defects and more rarely arrhythmias.[3] The cauda equina syndrome is a rare neurological complication of longstanding AS and peripheral sensory neuropathy is uncommon in AS. Additionally, thoracic spine fracture or cervical spine subluxation in AS patients may be responsible for spinal cord compression.[2]

Abnormalities of both the central and the peripheral nervous system are described in inflammatory rheumatic diseases and autoimmune diseases such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), systemic scleroderma (SSc) or Sjögren's syndrome (SS).[4 5] Autonomic neuropathy is a third form of neurological involvement also observed in these diseases. For instance, autonomic dysfunction has been found in 30–50% of RA patients.[6 7]

The status of the autonomic nervous system (ANS) in these conditions has been defined by assessing autonomic controlled cardiovascular adjustments. Several non-invasive tests based on cardiovascular reflexes can be used for a simple assessment of generalised autonomic nerve function.[8] These tests reflect both sympathetic and parasympathetic activities. The parasympathetic pathway is a major contributor to continuous rapid adjustment of heart rate, and measuring baroreflex sensitivity provides a reliable, non-invasive assessment of human vagal tone.[9 10] Determination of the spontaneous baroreflex sensitivity has proved to be effective in detecting patients with high risk of arrhythmias and sudden death after myocardial infarction.[10] Finally, plasma catecholamine concentrations bear indications on both the activity of orthosympathetic efferent fibres (noradrenaline spillover) and the sympathetic adrenomedullary secretion (adrenaline).[11 12]

Activity of the ANS has not been previously assessed in AS. In this study, we aimed at determining whether any sign of a modified autonomic control of cardiovascular function might be observed in AS patients. We also examined the relations between the indices of AS activity and indicators of autonomic activity. To improve our ANS examination, we combined standard cardiovascular reflex tests, plasma catecholamines and baroreflex sensitivity.

Methods

PATIENTS

A cross sectionnal study was conducted. Eighteen AS patients satisfying the modified New York criteria for AS[13] were included. All subjects were fully informed about the purpose of the study and gave their informed consent to

Table 1 Clinical, biological, and radiological characteristics of 18 patients with ankylosing spondylitis

	mean	*SEM*	*median*	*range*
age (y)	34.9		30	23–56
sex	5 women 13 men	—	—	—
disease duration (y)	6.4		4.5	0.5–22
Schober's test (cm)	3.4	0.25	3	1.5–5
sacroiliitis (n) (%)	14 (78)	—	—	—
ESR mm 1st h	19.9	4.54	18	2–74
CRP (mg/l)	12.6	5.02	3.1	2–67
HLA B27 (%)	15 (83.3)	—	—	—
BASDAI score	4.77	0.56	5.1	0.75–8.3
axial/peripheral disease	11/7	—	—	—

ESR = erythrocyte sedimentation rate; CRP = plasma C reactive protein concentration; BASDAI = Bath Ankylosing Spondylitis Disease Activity.

*Table 2 Group average (SEM) values of heart rate (HR) and arterial blood pressures (SBP and DBP) for 10 minutes of supine steady state and during 10 minutes upright station. All the values recorded in standing posture were higher than supine ($p<0.001$). In the standing posture, *=$p<0.02$ between patients with BASDAI >5 and patients with BASDAI <5 as well as controls*

		HR (beat/min)	*SBP (mm Hg)*	*DBP (mm Hg)*
Control subjects	Supine	64.1 (2.2)	118.0 (3.9)	63.2 (2.2)
	Upright	81.9 (3.8)	126.6 (4.5)	79.5 (2.6)
Patients with AS	Supine	66.2 (3.3)	120.2 (3.5)	64.9 (2.2)
(n=18)	Upright	89.6 (4.7)	131.4 (4.4)	77.4 (2.2)
BASDAI	Supine	68.4 (5.3)	119.5 (7.6)	63.4 (2.7)
score >5 (n=10)	Upright	96.6 (6.3)*	135 (8.6)	75.7 (2.6)
BASDAI	Supine	63.5 (4.3)	120.7 (3)	66.9 (4)
score <5 (n=8)	Upright	78.1 (5.6)	128.5 (5)	71.3 (4.2)
ESR>20 and	Supine	71.6 (6.2)	121.4 (4.1)	65.4 (3.1)
CRP>20 (n=8)	Upright	93.3 (8.1)	133.6 (5.7)	77.6 (2.4)
ESR<20 and	Supine	61.9 (3.5)	119.2 (6.1)	64.6 (3.50)
CRP<20 (n=10)	Upright	86.6 (6.3)	129.7 (7.2)	77.2 (3.8)

participate. This group included 13 men and five women. The mean age was 34.9 (range: 23–56) and the mean disease duration was 6.4 (range: 0.5–22). Fifteen patients had the HLA B27 antigen. All the patients took non-steroidal anti-inflammatory drugs (NSAID) and five were treated with sulfasalazine. No patient had corticosteroid treatment during the study and those who were taking corticosteroids until three months before the inclusion were not included. Seven patients had a peripheral disease (as defined by involvement of peripheral joint such as knee, hip, wrist, elbow, ankle, carpal and/or metacarpal joints with evidence of arthritis: swollen joint or joint effusion). The patients were assessed by two physicians (ET, DW) for the Schober's test. Neurological examination of patients included peripheral reflexes and distal sensation in the legs (vibration and discrimination perception, warm and cold detection). The patients were questioned about autonomic symptoms including dizziness during standing, postural hypotension, abnormal sweating, disturbed bowel function. Cardiac manifestations were also recorded: dyspnea, palpitations, chest pain or syncope. A clinical index of disease activity (Bath Ankylosing Spondylitis Disease Activity Index-BASDAI) was also evaluated.[14] In all patients we also analysed the radiological sacroiliac changes (sacroiliitis) and the dorsolumbar radiographs (for the presence of syndesmophytes). Patients with raised erythrocyte sedimentation rate (ESR) and high C reactive protein (CRP) concentration (> 20 mm 1st h and 20 mg/l, respectively) or with high BASDAI score (> 5) were considered to have active disease.

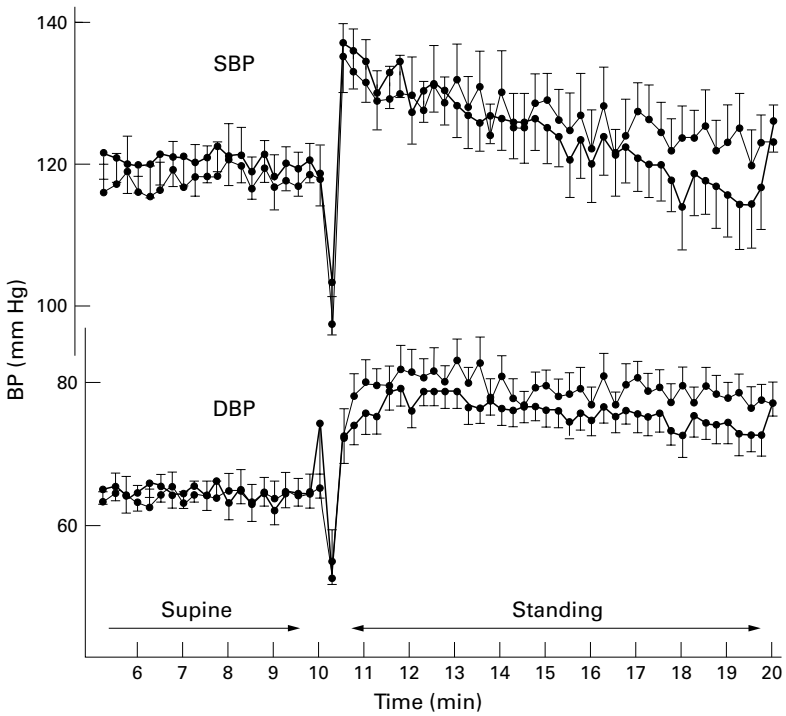

Figure 1 Time series average values of systolic (SBP, top traces) and diastolic (DBP, bottom traces) blood pressure in 13 control subjects (thin lines) and 18 patients with ankylosing spondylitis (thick lines) at the end of a supine 30 minute period and during 10 minutes after standing up. Vertical bars indicate group SEM. For clarity of the figure, only one average value has been plotted each 15 seconds, from the beat by beat individual records. BP of control and AS subjects were not different in the supine posture, but during the standing station there was a significant time decrease of systolic and diastolic pressures in the AS patients ($p<0.001$).

Exclusion criteria were: (a) age lower than 18 or higher than 65 years; (b) conditions known to affect autonomic function including hypertension, diabetes mellitus (fasting glycaemia higher than 1.2g/l or 6.7 mmol/l), neurological diseases, amyloidosis, renal failure (serum creatinine higher than 120 µmol/l); (c) concomittant treatment with drugs that act on the cardiovascular and central nervous system: diuretics, antiarrhythmics, calcium channel blockers, neuroleptics, antiepileptics and antidepressive drugs; (d) patients taking α or β adrenoceptor antagonists at the time of study.

CONTROL SUBJECTS

The control group included 13 healthy volunteers (eight men and five women; mean age: 31.7; range: 21–54) without history of conditions known to interfere with the ANS. None of these control subjects was receiving treatment at the time of evaluation.

GENERAL ORGANISATION OF THE STUDY

Study sessions were completed in the morning, at least two hours after a light breakfast (containing no caffeinated beverage), in a quiet dimly lit room and at comfortable ambient temperature (22–24°C). The subjects rested first in the supine position for 20 minutes after having been wired up with ECG electrodes. Then, they performed two 40 second bouts of deep breathing, being coached for five seconds inspiration and five seconds expiration. An intravenous catheter was then inserted in a vein of the left forearm, and then the subject rested another 15 minutes after which a venous blood sample was collected. Then, the finger cuff of a photoplethysmograph sensor for blood

pressure (BP) (Finapres, Ohmeda, Englewood Co) was placed on the third finger of the right hand and kept from then at the heart level during the following sequences of examinations to avoid the effects of changes in hydrostatic pressure. Data were collected for 10 minutes rest in the supine position, during assuming the upright standing posture (5–8 seconds duration) and during assuming 10 minutes standing. Venous blood was also collected at the end of the 10 minute standing period.

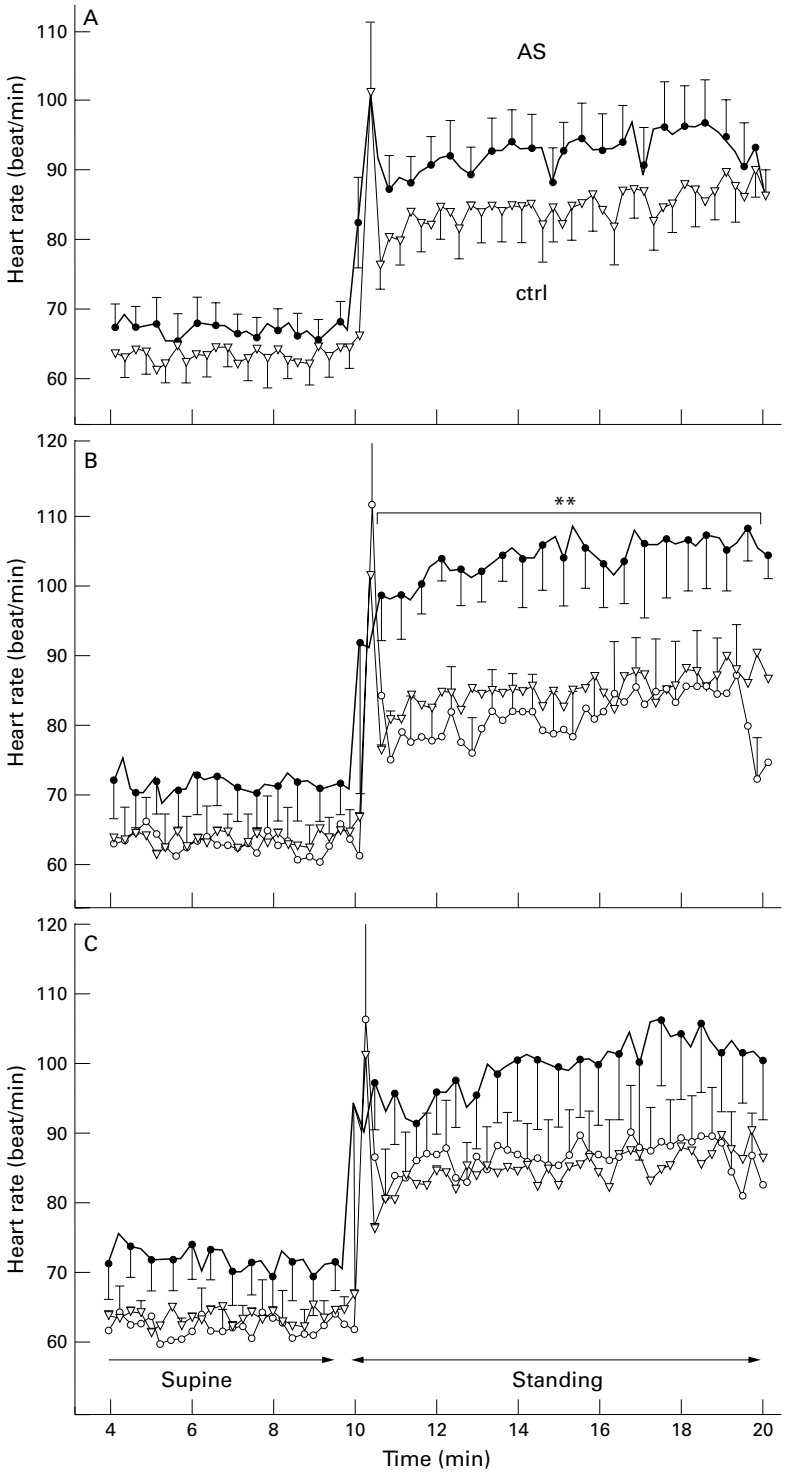

Figure 2 Time series average values of heart rate in 13 control subjects (control, light triangles and thin lines) and 18 patients with ankylosing spondylitis (AS, thick lines in the A panel) at the end of a supine 30 minute period and during 10 minutes after standing up. Vertical bars indicate group SEM. For clarity of the figure, only one average value has been plotted each 15 seconds, from the beat by beat individual records. In panels B and C thick lines are for average HR values of AS patients with BASDAI score > 5 (n = 10) and ESR > 20 mm 1st h with CRP > 20 mg/l (n = 8), whereas thin lines and light empty circles represent average values for AS patients with BASDAI score lower than 5 (panel B) and patients with ESR < 20 mm 1st h and CRP < 20 mg/l (panel C). Patients with lower criteria of inflammatory disease have clearly HR values values similar to control subjects, and during standing the average values of patients with BASDAI score > 5 were higher than their counterparts with BASDAI < 5 and the controls (panel B, p < 0.02).

COLLECTION OF VALUES OF R-R INTERVALS AND BP

The R-R intervals were measured after processing the QRS complexes from an electrocardiograph with a peak detection circuit. Finger arterial BP and R-R intervals collected for each cardiac cycle during 10 minutes supine and during 10 minutes standing were stored on a microcomputer via an analogue to digital converter (Metrabyte DAS-16) for later analysis.

DATA ANALYSIS

The activity of the ANS was assessed by calculating the standardised indices of changes in heart rate as responses to deep breathing (E/I ratio) and standing up (30/15 ratio)[8] and the slope of cardiac baroreflex from identifying spontaneaous baroreflex sequences.[15 16] We also considered times series of BP and heart rate (HR) values supine and standing, and venous plasma concentration of catecholamines.

E/I ratio was calculated from supine deep breathing at a rate of 6/mn. The ratio of the longest RR interval (recorded during expiration) over the shortest (occurring during inspiration) is defined as E/I.

30/15 ratio was calculated from the shortest RR interval occurring after the begining of standing up (around the 15th second) and the longest occurring about 30 seconds after quitting the supine posture.

Spontaneous baroreflex slope (SBRs): sequences of three or more beats in which the systolic BP and the following R-R interval changed in the same direction (either increasing or decreasing), which reflect the HR response to spontaneous variation in BP, were computer searched and considered as spontaneous baroreflex events.[15–18] These events were counted and a linear regression was calculated for all the sequences detected during one steady state epoch. The slope of this regression was taken as a quantitative index of the cardiac spontaneous baroreflex sensitivity (ms/mm Hg).[15–19]

Determination of plasma catecholamine: in each sample, plasma concentrations of noradrenaline, adrenaline and dopamine were determined by a sensitive and specific radioenzymatic method.[20]

STASTISTICAL ANALYSIS

The results were expressed as means (SEM). Changes with active standing were evaluated by analysis of variance (ANOVA) for repeated measurements followed by post hoc Fisher's protected least square difference. Differences between different groups were assessed by the Kruskall-Wallis one way ANOVA and the Mann-Whitney U test. Difference between postures in either group were assessed by the Wilcoxon paired signed rank test. Correlations were analysed by the Spearman rank correlation coefficient.

Results

Table 1 shows the details on the clinical, radiological and biological features of the AS patients. No symptom or physical sign of neurological abnormality and/or peripheral neuropathy was found at interview or physical examination. No patient had any history of cervical subluxation and/or complained of neck pain at the time of assessment. There was no arrythmia or conduction disturbances on any ECG recording and no cardiac symptom was found. No symptom suggestive of ANS impairement was recorded and only one patient had postural hypotension (that is, a lowered diastolic pressure by 10 mm Hg and systolic by 20 mm Hg in the standing posture). In this patient group, 14 had radiological evidences of sacroiliitis but the four patients without radiographic changes in the sacroiliac joints also satisfied the New York criteria for AS. Dorsolumbar syndesmophytes were observed in five subjects. Seven patients had AS with peripheral involvement, eight had a raised ESR and high CRP concentrations (> 20 mm 1st h and 20 mg/l, respectively) and 10 had a BASDAI score higher than 5.

BP AND HR

The supine and standing values of each subject were first averaged over 10 minutes of steady state in either posture, and the group means then calculated (table 2). There was no significant difference in mean BP (systolic BP and diastolic BP) between controls and AS patients, in either posture. Systolic BP, diastolic BP and HR were significantly higher in the standing posture than supine in all the control and AS subjects (ANOVA; $p<0.001$). We then analysed the patterns of times series of BP and HR (beat by beat recordings): in the standing posture, systolic BP and diastolic BP were steady in the control subjects, but in patients with AS there was an obvious downshift of BP with elapsing time (ANOVA; $p<0.001$; fig 1). HR was significantly higher in patients with high BASDAI score (> 5) than in patients with lower score (< 5) and controls (ANOVA; $p< 0.02$) (table 2 and fig 2). A similar trend was seen between patients with ESR > 20 mm 1st h and CRP > 20 mg/l, and the other AS patients and control subjects, but did not reach statistical significance.

PLASMA CATECHOLAMINES

During supine rest the venous concentrations of plasma noradrenaline were in the normal physiological range in control subjects and in AS patients (270 (21) *v* 263 (17) pg/ml, respectively; Mann-Whitney U; NS). After 10 minutes standing, plasma noradrenaline had increased significantly and similarly in both control subjects and AS patients (table 3). Concentrations of plasma adrenaline were also normal and similar in either control and AS subjects in each of the two postures. The concentration of plasma dopamine was not different between controls and patients, and did not change with posture (table 3).

CHANGES IN RR INTERVAL WITH DEEP BREATHING AND DURING STANDING

The values of the E/I ratio were not different between control subjects and AS patients (Mann-Whitney U test; table 3). Conversely, values of the 30/15 ratio were lower in patients with either a BASDAI score higher than 5 or an ESR higher than 20 mm 1st h and CRP> 20 mg/l than in the alternate patient groups and the control subjects (Kruskal-Wallis test, Mann-Whitney U; table 3).

SPONTANEOUS BAROREFLEX SLOPE

The number of spontaneous baroreflex sequences during 10 minutes in either posture were not different in controls and AS patients or in any subgroup of patients (table 3). In the supine posture, the slope of cardiac baroreflex (SBR) was in the usual range (19, 22, 23) in every group of subjects (table 3, fig 3; NS), and this value had significantly decreased after assuming the standing posture (Wilcoxon's paired rank test; $p<0.001$) (table 3, fig 3). However, in this upright posture, SBR was significantly lower in the whole of the AS patients than controls subjects (Mann-Whitney U; $p<0.01$; table 3, fig 3). Furthermore, SBR

Table 3 Effect of standing on group average values of heart rate (ratio 30/15; E/I measured supine), slope of the spontaneous baroreflex (SBR), and plasma catecholamines

	E / I	*30 / 15*	*Number of spontaneous BR sequences*	*SBR slope (ms/mm Hg)*	*noradrenaline (pg/ml)*	*adrenaline (pg/ml)*	*dopamine (pg/ml)*
Controls							
Supine	1.46 (0.05)	1.38 (0.05)	30 (6.6)	19.7 (3.2)***	270 (21)	49 (6)	62 (4)
Upright			62 (9.3)***	8.8 (1.1)	557 (38)***	78 (13)***	62 (3.8)
AS patients							
Supine	1.39 (0.04)	1.29 (0.05)	34 (4.8)	16.7 (2.8)***	262 (17)	50 (5.5)	58 (3.6)
Upright			54 (8.9)***	5.4 (0.6)§§	525 (41)***	85 (10)***	57 (4.7)
BASDAI > 5	1.37 (0.06)	1.21 (0.06)‡					
Supine			35 (6.3)	15.4 (3.2)***	260 (27)	57 (10)	57 (5)
Upright			49 (12)***	4.3 (0.46) §§	† 580 (62)***	101 (21)***	57 (8)
BASDAI < 5	1.42 (0.06)	1.39 (0.09)					
Supine			32 (8.8)	18.4 (5.6)***	265 (23)	41 (7)	58 (5)
Upright			61 (14)***	6.9 (1.2)	447 (47)***	70 (13)***	58 (5)
ERS>20 and CRP>20	1.37 (0.06)	1.19 (0.07)‡					
Supine			31 (7.4)	12.8 (4.1)***	287 (26)	51 (10)	53 (6)
Upright			42 (13)***	4.7 (0.7) §	540 (75)***	84 (22)***	54 (9)
ERS<20 and CRP<20	1.41 (0.05)	1.37 (0.08)					
Supine			36 (7.3)	19.8 (4.1)***	240 (24)	50 (6)	62 (4.3)
Upright			64 (12)***	6.03 (1)	512 (53)***	88 (11)***	60 (5)

‡ = $p<0.05$ between these patients and both the control subjects and the other patient groups; * = $p<0.05$ and *** = $p<0.001$ between supine and standing; § and §§, respectively for $p<0.03$ and $p<0.01$ between patients and control subjects in the standing posture. † = $p<0.07$ between patients with BASDAI >5 and <5. Data shown as mean (SEM). Abbreviations as in table 1.

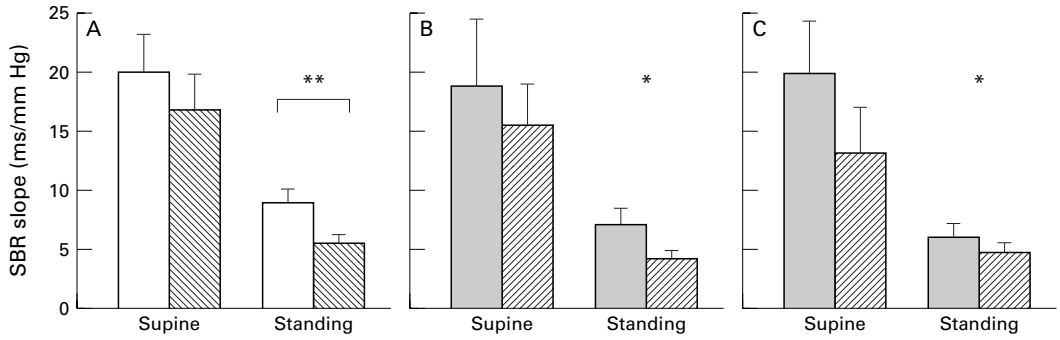

*Figure 3 Group average values (and SEM) of the slope of spontaneous baroreflex (SBR) in the supine (left columns of each panel) and standing postures (right columns of each panel). Panel A: white bars = 13 control subjects; hatched bars = 18 AS patients. Panel B: lightly dotted bars = AS patients with BASDAI score < 5; hatched bars = patients with BASDAI score > 5. Panel C: lightly dotted bars = AS patients with ESR < 20 mm 1st h and CRP < 20 mg/l; hatched bars = patients with ESR > 20 mm 1st h and CRP > 20 mg/l. ** = p < 0.01, * = p <0.05 as compared with control subjects in the same standing posture.*

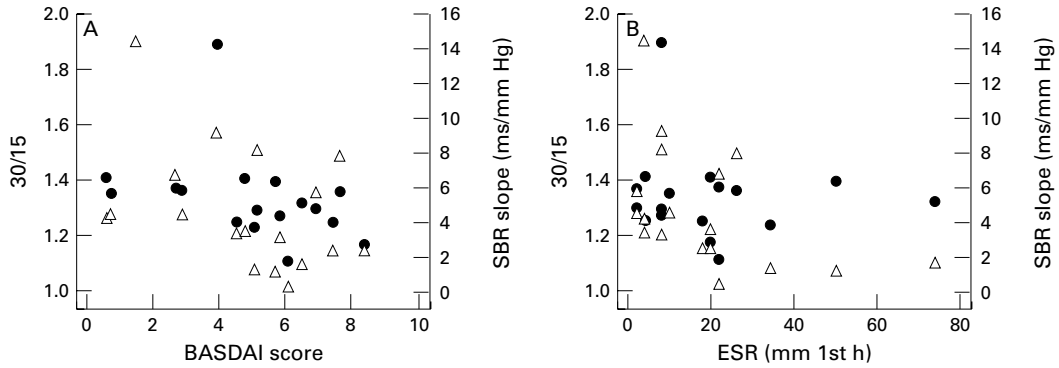

Figure 4 Scatter plots of individual values of RR interval 30/15 ratio (left vertical axis; empty triangles) and standing measured slope of spontaneous cardiac baroreflex (SBR; right vertical axis; black circles) against BASDAI score (panel A) and ESR (panel B) on horizontal axis. Spearman rank correlation coefficients were significant between SBR and BASDAI score ($r = -0.56$, $p < 0.03$), and between 30/15 index and ESR ($r = -0.55$; $p < 0.03$).

upon standing was significantly lower in AS patients with increased BASDAI score (> 5), with raised ESR and increased CRP (> 20 mm 1st h and 20 mg/l) than in control subjects (Mann-Whitney U; p<0.05) (table 3, fig 3).

CORRELATIONS BETWEEN PARASYMPATHETIC INDICATORS AND MARKERS OF DISEASE ACTIVITY AND INFLAMMATION

Individual 30/15 values were significantly correlated with the ESR (Spearman rank correlation coefficient $r = -0.55$; $p < 0.03$; fig 4) and SBR values correlated with BASDAI score ($r = -0.56$; $p < 0.03$; fig 4).

Discussion

Our study unveiled significant differences in values of HR, arterial BP and ANS indicators between patients with AS and control subjects. Our patients had no clinical autonomic symptoms and only one postural hypotension was observed at the time of examination. The neurological examination was normal for each patient suggesting that changes in autonomic control were not associated with peripheral or central nervous system involvement.

Indeed, several results pointed for differences in autonomic control of circulatory status between patients with AS and healthy control subjects. Firstly, analysis of time series during quiet standing provided significant evidence that in AS patients arterial BP was not maintained steady. Also, standing HR was higher in patients than controls, essentially a feature of patients with clinical signs of more active disease (increased ESR and CRP values or high BASDAI score). The standing SBR was significantly lower in than controls, also mainly in subgroups of patients with active disease.

Although BP values averaged over the standing epochs were not significantly different between AS patients and controls, over time maintenance of BP was achieved in our control subjects but not in our AS patients. Indeed, while averaging successive values may conceal conspicuous changes, taking into account numerous repeated measures increases the power of trend analysis. The lack of significant difference between AS and control subjects in plasma catecholamines in either supine and or standing postures argue against any marked abnormality of the orthosympathetic control of vascular tone. However, the significantly higher HR during standing in patients with AS would be consistent with the struggle for maintaining haemodynamic balance when arterial BP was shifting down. Indeed in the same posture, the SBR was significantly lower in AS patients, a feature mainly present in the patients who had clinical and biological signs of more active disease. The SBR has been found a sensitive indicator of parasympathetic tone.[16 21] Thus a lower setting of SBR during standing posture in AS patients than control subjects probably reflected a decreased parasympathetic braking of heart rate, consistent with the significantly higher HR in the same patients. SBR has been recently reported to unveil small abnormalities

in cardiovascular control of diabetic patients with no conspicuous clinical cardiac or vascular signs.[22] Although in our study the classic E/I index of parasympathetic activity was not different in AS patients and controls, values of the 30/15 ratio were lower in patients with indicators of more active or more inflammatory disease, consistent with SBRs values. A previous study in healthy subjects had also provided evidence that SBR and 30/15 are two closely related indicators of ANS activity.[23]

Our data demonstrated for the first time some deviant balance of the ANS in AS patients, mainly a decreased parasympathetic tone. Progressively decreasing systolic BP were recorded during standing, in association with the lower parasympathetic tone.

Vasomotor and baroreflex deconditioning as they result from prolonged bed rest or microgravity may lead to circulatory disorders similar to those observed in our subjects with high BASDAI scores or high ESR.[18 24] However, despite their stiffness and pain, our patients with more active disease were not confined to bed or chair. Rather, on each day they were exercising through everyday activities. More than half of them (including patients with high BASDAI or ESR) were at work with their professional activities, as were the healthy controls. It is thus difficult to consider that the circulatory abnormalities we found resulted from physical deconditioning as it occurs after several weeks of lying down with a complete absence of physical exercising.

Some rare occurrence of water retaining effect has been described with NSAIDs. The patients we studied had normal renal function and none had any clinical evidence of oedema or extracellular volume disorder. If NSAID induced water retaining was to occur in some subjects, the resulting increase in plasma volume would then counteract the decrease in BP we observed. Such a bias seems unlikely in our results.

Abnormalities in the balance of the ANS have previously been found in several inflammatory rheumatic diseases such as RA[6 7] with a prevalence between 30% and 50%. A similar frequency was reported in SLE[25 26] and patients with SSc are at higher risk of developing an autonomic neuropathy.[27] For RA and the latter autoimmune diseases, it was thought that the autonomic neuropathy could result from vasculitis, amyloidosis or could be related to some therapeutic side effect. An immunological pathophysiology is thus generally envisioned.[6 7] But similar immunological mechanisms were unlikely in our patients. In fact, when vasculitis had been described in AS, it had no clinical expression such as mononeuritis caused by involvement of vasa nervorum.[2] Amyloidosis is known to complicate AS with long disease duration, while the disease of our patients had lasted for an average 6.4 years. The patient's concomitant medications cannot explain the observed autonomic deviances because treatments able to interfer with the ANS had been retained as exclusion criteria for our study. Finally, there is currently no convincing evidence of an immunological mechanism in AS, and hence no substantial grounding for the observed abormalities in autonomic control of cardiovascular function.

Conversely, the inflammatory process itself might cause some autonomic abnormalities in our AS patients. Indeed, the patients with disturbances in the balance of the ANS were those with raised ESR and increased CRP and high BASDAI score. There is numerous evidence for the contribution of the nervous system to inflammation.[28] Experimental models have revealed the influence of the unmyelinated primary afferent neurons in the inflammatory response. Substance P, a major neurotransmitter of painful stimuli by unmyelinated C fibres, is implicated as a neurogenic inflammatory mediator.[28] In RA, substance P concentrations were found increased in the synovial fluid.[29] There is other evidence that ANS interacts with inflammation: sympathectomy or guanethidine, a sympathetic blocker agent, significantly decreased the severity of joint injury in experimental arthritis.[28] In RA, treatment with guanethidine led to clinical improvements.[30] It has also been suggested that the orthosympathetic nervous system could influence the immune response by stimulating the β_2 adrenoceptors of lymphocytes. A decreased density of β_2 receptors on peripheral blood mononuclears cells has been observed in patients with RA and SLE.[31] However, evidence of lymphocyte activation is still lacking to date in AS. In our study, patients with active AS had small but significant abnormalities of control of HR, BP and SBR in the standing posture—that is, when higher tuning of vascular tone and cardiac activity are required. Therefore, it may be hypothesised that the shifted ANS activity in AS might result from the inflammatory state. A shift of vascular tone toward easier vasodilatation has been described in the bronchial mucosa[32] and also in the skin of subjects with bronchial asthma,[33 34] a disease featuring an inflammatory triggered production of nitric oxide.[35] Our data would thus be consistent with an inflammatory weakening of physiological vasoconstriction—that is, able to mediate the drift of arterial BP, up regulating in turn HR through lowering of parasympathetic tone. However, it remains to establish which particular mediators of inflammation, for example, peptides, cytokines, nitric oxide, etc, finally influence the setting of ANS activity.

The consequences of the ANS involvement in rheumatic diseases are not well known. As already quoted, ANS probably modulates inflammatory responses.[36 37] We previously found that RA patients with ANS impairement had less erosive disease than patients without autonomic disturbances.[6] In diabetic patients, the involvement of autonomic cardiac nerves may be responsible for arrhythmias and sudden death, and heart disease mainly contributes to the overall prognosis of SSc. The heart disease is also a well recognised complication of AS, with disturbances of cardiac conduction in 1–33% of patients and less commonly observed arrhythmia.[3] Cardiovascular diseases have been implicated as one cause of the slightly increased mortality in AS patients.[38]

Our AS patients had a higher HR than control subjects. Thus, an imbalance in the autonomic nervous control of the heart might contribute to conduction defect and/or rhythm disturbances and therefore could influence the prognosis of the disease.

In conclusion, we observed several evidences of a shifted ANS control of cardiovascular balance in standing AS patients as increased HR, slowly decreasing BP and lowered SBR. These signs of autonomic strain were more prominent in patients with active disease, suggesting a causative role of the inflammatory process. It is tempting to speculate that this deviant cardiac autonomic control might occur earlier than the conspicuous ECG conduction abnormalities.

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