Myocardial dysfunction in ankylosing spondylitis

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Abstract

Echocardiographic evidence has suggested abnormalities of the myocardial function in patients with ankylosing spondylitis. In this work the cardiac function in patients with ankylosing spondylitis and in normal volunteers was evaluated. Twenty four normal volunteers and 21 patients with ankylosing spondylitis aged 18-45 were studied. None had overt cardiac disease. Cardiac function was assessed at rest with echocardiography, at rest and during supine bicycle exercise using radionuclide angiography in the left anterior oblique position following equilibration with 740 MBq of technetium-99. The subjects undertook supine bicycle exercise with 30 W increments every three minutes to the point of fatigue. Comparison of data from normal volunteers and patients with ankylosing spondylitis were made using Student's *t* test for independent samples or the Mann-Whitney non-parametric technique, as appropriate.

Subjects were matched for age, sex, height, and weight. There were no echocardiographic differences; however, global nuclide left ventricular function showed several differences between normal volunteers and patients with ankylosing spondylitis. The peak filling rate during exercise was significantly lower in patients with ankylosing spondylitis: normal volunteers 6.5 (SD 1.2); patients with ankylosing spondylitis 5.7 (1.2). The time to reach peak filling during exercise was significantly lower in patients with ankylosing spondylitis: normal volunteers 102 (22); patients with ankylosing spondylitis 120 (23). Regional analysis also showed differences between patients with ankylosing spondylitis and normal volunteers both at rest and during exercise. In the anteroapical region the filling fraction and peak filling rate were significantly lower in patients with ankylosing spondylitis. Most of the differences (although not all) were in the variables of diastolic function. This study shows that there are subtle abnormalities in cardiac function in patients with ankylosing spondylitis. The major abnormalities are in the diastolic function, suggesting a decrease in left ventricular compliance.

There have been many studies linking ankylosing spondylitis with cardiac abnormalities. The abnormalities described include aortitis,¹⁻³ aortic aneurysms,⁴ and a variety of aortic root abnormalities of which aortic incompetence is

most frequently observed.⁵⁻⁷ Cardiomyopathy,⁸ electrocardiographic abnormalities,⁹ and complete atrioventricular block^{5, 9, 10-12} have been recorded. One study has shown that men have a higher death rate than women and their risk of death relative to the general population was 40% in excess for cardiovascular diseases, with cerebrovascular disease excluded, although cardiac deaths were not specifically implicated.¹³ Abnormalities of the diastolic function have been recorded by echocardiographic techniques.¹⁴ Our study sought to detect abnormalities of the myocardial function in young patients with mild ankylosing spondylitis.

Patients and methods

Twenty four normal subjects were recruited from a variety of para-medical and medical staff. Twenty one patients undergoing long term follow up in a rheumatology clinic with definite ankylosing spondylitis (AS) who satisfied the New York criteria for AS¹⁵ were recruited. All patients had typical radiographic features in the axial skeleton. All participants were aged 18-45 years and had no evidence of cardiac disease, particularly no clinical nor echocardiographic evidence of aortic incompetence nor electrocardiographic abnormalities. All patients were non-smokers and had the physical capability of undertaking supine bicycle exercise testing. None of the participants was receiving drugs which might affect their myocardial function and all were normotensive. The severity in activity of ankylosing spondylitis as judged by spinal deformity, mobility, and duration of stiffness was generally mild, with only four patients being classed as having moderate disease and two as having severe disease. The normal subjects had no history of cardiac disease, were normotensive, and had normal electrocardiograms and echocardiograms.

The subjects underwent a detailed history and clinical examination, assessment of severity of ankylosing spondylitis, routine lung function tests, and haematological and biochemical profiles. All patients underwent a chest radiograph and all of the these investigations listed gave normal results. The groups were of similar age, weight, and height with no significant differences between them (table 1), except for the maximum heart rate at peak exercise. Exercise times for each group were similar. Each patient underwent a gated nuclide angiogram and echocardiographic examination with two dimensional and M mode recordings.

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Table 1 Clinical data for normal subjects and patients with ankylosing spondylitis

Subjects	Normal subjects (n=24)	Patients with ankylosing spondylitis (n=21)
Mean (SD) age (years)	35.7 (6)	33 (6)
No of women	4	4
Mean (SD) height (cm)	174 (8)	172.6 (10)
Mean (SD) weight (kg)	70.8 (11.5)	69.9 (12.1)
Mean (SD) heart rate during peak exercise (beats/min)	161 (18)	153 (15)*
Mean (SD) exercise time (min)	15.8 (4.0)	14.1 (4.5)

*No significant difference was seen between the two groups except for heart rate at peak exercise, which was significantly lower in patients with ankylosing spondylitis ($p=0.044$).

RADIONUCLIDE ANGIOGRAPHY

Autologous red cells were labelled with 740 MBq technetium-99m using an established semi in vitro technique. Following re-injection of the labelled cells, the patient was placed in a supine position on a bicycle exercise couch for imaging with an IGE 400T camera in the left anterior oblique 45° position with 10–15° of caudal tilt to improve chamber separation. A gated angiogram was acquired at rest at 24 frames per cycle using a 64×64 frame mode acquisition with centre field of view zoom. A minimum of 5×10^6 counts was recorded, equivalent to 20 000 counts per frame. Computing was undertaken on a Gamma II system. The patient then exercised at a starting load of 30 W, with 30 W increments every three minutes until the point of fatigue was reached. An exercise angiogram using the same parameters was then recorded for up to two minutes without a further increase of workload. The total counts recorded were in the range $(2.5-5) \times 10^6$, depending on the patient's exercise tolerance. The gate tolerance was set at 3% at rest and 10% on exercise.

For beat rejection the computer compared the last acquired beat with the previously computed average and if this was outside the gate tolerance (typically ± 100 ms) acquisition was suspended until a beat within the tolerance was sampled. Acquisition then restarted on the next beat. Processing was based on a package using an automatic moving ventricular region of interest with an automatic background region of interest. Manual drawings of the regions of interest were also undertaken. The data were smoothed temporally before processing.

The angiograms were computed globally and for four regions. The following parameters were calculated from the time-activity curve^{16 17} (fig 1): ejection fraction, peak ejection rate, time to peak ejection rate and to peak filling rate, and filling fraction. In addition, the angiograms were scored region by region. The angiograms were scored by two independent observers, who were not blinded for logistical reasons. (There were only two experienced staff members in the department and both knew the patients well. It was not possible to obliterate their names from the computer screen, and therefore it was not possible to report blinded.) Normal function

Figure 1 Left ventricular (LV) time-activity curve illustrating the deviation of peak ejection rate (PER) and time to peak ejection rate (TTPER), peak filling rate (PFR) and time to peak filling rate (TTPFR), and first third filling fraction (FF) $(A-B)/A$. EDV=end diastolic volume; SV=stroke volume; and ESV=end stroke volume.

scored 0, hypokinesia 1, akinesia 2, and dyskinesia 3.

ECHOCARDIOGRAPHIC MEASUREMENTS

Echocardiography was undertaken by an experienced observer with two dimensional and M mode recordings. The echocardiogram images were obtained with an Aloka Ultrasound Instrument (Sector Scanner SSD/710, Aloka, Tokyo, Japan). Standard measurements of end systolic and end diastolic septal thickness, left ventricular internal diameter, and posterior wall thickness were derived. In addition, the left ventricular ejection time, circumferential fibre shortening, and ejection fraction were calculated. We also used the M mode to calculate the minimum left ventricular dimension to mitral valve opening in milliseconds (MD-MVO) and the interval from aortic valve closure to mitral valve opening in milliseconds (IVR).

STATISTICAL ANALYSIS

This was performed using the statistical graphics program, Statgraphics, run on a TRS-809 1000 HD computer. Data were tested for normality using the χ^2 test. Comparisons of normal subjects and patients with ankylosing spondylitis were made using Student's *t* test for independent samples or the Mann-Whitney non-parametric technique, as appropriate. Data were derived for each parameter (gated nuclide scan) at rest and on exercise. The change in each parameter due to exercise was calculated (e.g. ejection fraction (EF) $EF_{rest} - EF_{exercise}$; p_{diff}). The proportional changes in each parameter due to exercise was also calculated (e.g. $EF_p = (EF_r - EF_{ex})/EF_r$) — the proportional change in ejection fraction due to exercise ($\times 100$ to convert to a percentage; p_{prop}).

The group of normal subjects studied defined the range of normal values for our laboratory in patients aged 18–45 years.

Figure 2 Global peak filling rate (PFR) in normal subjects (N) and patients with ankylosing spondylitis (AS) at rest and during exercise (Exc.). *p=0.026. EDV=end diastolic volume.

Figure 3 Global time to peak filling rate (TTPFR) in normal subjects (N) and patients with ankylosing spondylitis (AS) at rest and during exercise (Exc.). *p=0.012.

Results

GLOBAL SCAN DATA

Several significant differences were observed between the two groups for the global scan data. The peak filling rate during exercise was significantly lower in the patients with ankylosing spondylitis than in the normal subjects, and the change in this parameter due to exercise was significantly less in the patients with ankylosing spondylitis than in the normal subjects (fig 2 and table 2). The time to peak filling rate was significantly higher in the patients with ankylosing spondylitis than in the normal subjects during exercise, although the extent of the decrease observed in this parameter due to exercise was comparable between the groups (fig 3 and table 2). Angiographic scores during both rest and exercise were significantly higher in the patients with ankylosing spondylitis than in the normal subjects (fig 4 and table 2).

ANTERIOR-SEPTAL SCAN DATA

Several differences were observed between

Figure 4 Global angiographic scoring in normal subjects (N) and patients with ankylosing spondylitis (AS) at rest and during exercise (Exc.). *p=0.00001.

Table 2 Global scan data

Variable*	Normal subjects				Patients with ankylosing spondylitis				p Value	p _{diff}	p _{prep}
	Mean (SD)	Maximum	Minimum	Range	Mean (SD)	Maximum	Minimum	Range			
EFr (%)	64 (6)	75	48	27	62 (6)	74	53	21	0.474	0.296	0.307
EFex (%)	71 (5)	80	60	20	71 (8)	87	56	31	0.765		
FFr (%)	44 (9)	61	17	44	42 (8)	56	25	31	0.487		
FFex (%)	26 (10)	45	10	35	28 (10)	48	11	37	0.611	0.370	0.292
PERr (vol/s)	3.3 (0.8)	5.4	2.0	3.4	3.3 (1.1)	5.8	2.2	3.6	0.665		
PERex (vol/s)	7.6 (1.9)	12.6	4.2	8.4	7.3 (1.7)	10.3	4.4	5.9	0.794		
PFRr (EDV/s)	2.7 (0.5)	3.6	1.9	1.7	2.7 (0.5)	3.5	1.9	1.6	1.00	0.022*	0.066
PFRex (EDV/s)	6.5 (1.2)	9.6	4.3	5.3	5.7 (1.2)	7.7	3.7	4.0	0.026*		
TTPERr (ms)	320 (29)	378	266	112	319 (33)	378	270	108	0.964		
TTPERex (ms)	230 (74)	378	125	243	210 (36)	275	150	125	0.873	0.724	0.811
TTPFRr (ms)	138 (27)	205	84	121	142 (26)	192	99	93	0.683		
TTPFRex (ms)	102 (22)	161	68	93	120 (23)	168	75	93	0.012*		
Angio _r	0.04 (0.20)	1	0	1	0.81 (0.81)	3	0	3	0.00004*	0.631	—
Angio _{ex}	0.04 (0.20)	1	0	1	0.86 (0.79)	3	0	3	0.00001*		

*EFr=ejection fraction (rest); EFex=ejection fraction (exercise); FFr=filling fraction (rest); FFex=filling fraction (exercise); PERr=peak ejection rate (rest); PERex=peak ejection rate (exercise); PFRr=peak filling rate (rest); PFRex=peak filling rate (exercise); TTPERr=time to peak ejection rate (rest); TTPERex=time to peak ejection rate (exercise); TTPFRr=time to peak filling rate (rest); TTPFRex=time to peak filling rate (exercise); Angio_r=angiogram (rest); Angio_{ex}=angiogram (exercise); EDV=end diastolic volume.

normal subjects and patients with ankylosing spondylitis in this region.

The filling fraction at rest was significantly lower in the patients than in normal subjects, but this was not apparent during exercise. The decrease in filling fraction during exercise was comparable in the two groups (fig 5 and table 3).

The peak filling rate during exercise was significantly less in the patients than in the normal subjects, but the change in this variable due to exercise was increased to the same extent in both groups (although this just failed to be significant, $p_{diff}=0.061$; fig 6 and table 3). The time to peak filling rate was higher in the patients with ankylosing spondylitis during both rest and exercise, but the change in these parameters was consistent between the two groups (fig 7 and table 3).

APICAL SCAN DATA

There was no difference between normal subjects and patients with ankylosing spondylitis with respect to parameters recorded during rest and exercise, except for angiographic scoring which was significantly higher in the patients with ankylosing spondylitis during both rest and exercise. The time to peak ejection rate was the only parameter to show a significantly greater percentage decrease in normal subjects than in patients with ankylosing spondylitis (43 v 34%, respectively).

Figure 5 Anteroseptal filling fraction (FF) in normal subjects (N) and patients with ankylosing spondylitis (AS) at rest and during exercise (Exc.). * $p=0.044$.

Figure 6 Anteroseptal peak filling rate (PFR) in normal subjects (N) and patients with ankylosing spondylitis (AS) at rest and during exercise (Exc.). * $p=0.044$.

Figure 7 Anteroseptal time to peak filling rate (TTPFR) in normal subjects (N) and patients with ankylosing spondylitis (AS) at rest and during exercise. * $p=0.004$; ** $p=0.002$.

Table 3 Anterior-septal scan data

Variable*	Normal subjects				Patients with ankylosing spondylitis				p Value	p_{diff}	p_{prep}
	Mean (SD)	Maximum	Minimum	Range	Mean (SD)	Maximum	Minimum	Range			
EFr (%)	61 (8)	82	43	39	56 (11)	75	39	36	0.098	0.866	0.585
EFex (%)	69 (12)	98	48	50	65 (14)	91	36	55	0.311		
FFr (%)	38 (11)	58	19	39	30 (13)	53	4.5	48.5	0.044*		
FFex (%)	28 (15)	68	2	66	24 (14)	68	2.9	65.1	0.361	0.514	0.249
PERr (vol/s)	3.1 (1.0)	1.7	4.9	3.2	3.1 (1.4)	7.6	1.5	6.1	0.715	0.949	0.949
PERex (vol/s)	6.7 (1.8)	11.3	4.1	7.2	6.7 (2.8)	13.8	2.7	11.1	0.890		
PFRr (EDV/s)	2.8 (0.9)	4.7	1.4	3.3	2.7 (1.0)	4.7	1.4	3.3	0.610		
PFRex (EDV/s)	6.8 (2.7)	14.9	3.1	11.8	5.3 (1.8)	8.2	2.8	5.4	0.044*	0.061	0.197
TTPERr (ms)	324 (47)	420	240	180	297 (41)	405	224	181	0.052	0.0003*	0.00
TTPERex (ms)	176 (36)	242	83	159	206 (33)	300	160	140	0.005*		
TTPFRr (ms)	132 (38)	210	70	140	165 (35)	216	108	108	0.004*		
TTPFRex (ms)	97 (24)	160	51	109	125 (33)	192	75	117	0.002*	0.703	0.91
Angio _r	0 (0)	0	0	0	0.43 (0.51)	1	0	1	0.0004*	0.535	—
Angio _{ex}	0 (0)	0	0	0	0.50 (0.51)	1	0	1	0.0001*		

*For abbreviations see table 2.

INFERIOR SCAN DATA
No difference was observed between normal subjects and patients with ankylosing spondylitis during exercise or rest. There was no difference in the degree of change of these parameters during exercise between the two groups.

POSTERIOR SCAN DATA
No difference was observed for any of the parameters studied between normal subjects and patients with ankylosing spondylitis during exercise nor at rest. The difference between parameters failed to show any effect, but when the proportionate differences were examined there was a smaller increase in peak filling rate

Figure 8 Anteroseptal time to peak ejection rate (TTPER) in normal subjects (N) and patients with ankylosing spondylitis (AS) at rest and during exercise. *p=0.005.

Table 4 Comparison of echocardiographic data in normal subjects and patients with ankylosing spondylitis

Variable*	Normal subjects		Patients with ankylosing spondylitis	
	Mean	SD	Mean	SD
EDST (cm)	1.0	0.14	1.1	0.18
ESST (cm)	1.5	0.26	1.6	0.22
EDLVID (cm)	4.9	0.49	4.8	0.51
ESLVID (cm)	3.1	0.46	3.2	0.46
EDPWT (cm)	1.0	0.14	1.1	0.12
ESPWT (cm)	1.6	0.29	1.7	0.27
LVET (ms)	408	23	405	28
FS (%)	36	6.8	34	6.9
SV (ml)	87	28.5	81	28.1
EF (%)	73	7.8	70	9.9
MD-MVO (ms)	50	14.2	46	10.1
IVR (ms)	73	15.5	74	29.9

Statistical analysis was performed using the Student's *t* test for independent samples or the Mann-Whitney test, as appropriate, adopting a 5% level of significance. p Value not significant in any instance.
*EDST=end diastolic septal thickness; ESST=end systolic septal thickness; EDLVID=end diastolic left ventricular internal diameter; ESLVID=end systolic left ventricular internal diameter; EDPWT=end diastolic posterior wall thickness; ESPWT=end systolic posterior wall thickness; LVET=left ventricular ejection time; FS=circumferential fibre shortening; SV=stroke volume; EF=ejection fraction; MD-MVO=minimum left ventricular dimension to mitral valve opening; IVR=interval from active valve closure to mitral valve opening.

during exercise in the patient group compared with normal subjects (136 v 165%, respectively).
The time to peak ejection rate during exercise was significantly higher in the patients with ankylosing spondylitis than in the normal subjects, and this parameter showed a lower decrease in the patients with ankylosing spondylitis than in the normal subjects (29 v 45%; fig 8 and table 3).
Table 3 shows that angiographic scoring was significantly higher in the patients with ankylosing spondylitis than in the normal subjects during both rest and exercise.

ECHOCARDIOGRAPHIC DATA
Table 4 shows that there were no differences between normal subjects and patients with ankylosing spondylitis as measured by echocardiographic techniques.

Discussion
Structural abnormalities of the heart have been well documented. These include aortitis,¹⁻³ aortic aneurysms,⁴ and various aortic root abnormalities including aortic incompetence.⁵⁻⁷ The most frequently documented abnormalities are electrocardiographic, including complete heart block.^{5 9 11-12} Of note is the paper by Radford *et al*,¹³ which showed that patients with ankylosing spondylitis have a greater risk of death relative to the general population. It was not shown, however, that this was due to heart disease. More recently, Brewerton *et al*¹⁴ reported diastolic abnormalities using echocardiographic techniques. We have examined a similar group of patients with ankylosing spondylitis aged between 18 and 45 and normal subjects in whom cardiac disease had been specifically excluded. The patients with ankylosing spondylitis did not have severe spinal deformity.

Despite the apparently mild ankylosing spondylitis, we noted several abnormalities of the cardiac function as measured by radionuclide imaging. Global assessment of left ventricular function highlighted several differences between the normal subjects and patients with ankylosing spondylitis. The peak filling rate was decreased, the time to peak filling rate was prolonged, and the change in peak filling rate due to exercise was decreased. These parameters represent abnormalities of the diastolic function compared with normal subjects. It may be argued that these parameters are affected by heart rate. As the heart rate in patients with ankylosing spondylitis was lower than in normal subjects, the results may be influenced by this discrepancy. We do not think that this is so, as we would expect a more uniform result in all regions. The data showed abnormalities, particularly in the anteroseptal region and are supported by the work of Brewerton *et al*.¹⁴

Angiographic scoring also highlighted an apparently highly significant abnormality in scoring between the two groups. These data are less reliable, as for logistic reasons we were unable to score the groups blindly, although they were scored independently by two

observers. We also found abnormalities of the diastolic function in other regions, particularly the anteroseptal region. The reason for this is uncertain. Brewerton *et al* have shown that there is a mild diffuse increase in reticulin deposition between individual muscle cells and around muscle bundles in necropsy studies of patients with ankylosing spondylitis.¹⁴ They did not report any predilection for the interventricular septum; however, this is a possibility as the major abnormalities were shown in this region. The regional abnormality in the septum might be attributed to ischaemic heart disease. This is unlikely as all the patients had normal resting and exercise electrocardiograms and none had ischaemic symptoms. In a group of 21 patients it is unlikely that they would have uniformly affected regional abnormalities. We conclude that this is a genuine finding in patients with ankylosing spondylitis.

There is considerable overlap between the findings in normal subjects and patients with ankylosing spondylitis, but the mean values are highly significantly different for several parameters. We were unable to relate this to severity of disease as only two of this group were classified as having severe disease. Many more had abnormalities, as confirmed by the statistical data.

The heart rate discrepancy between normal subjects and patients with ankylosing spondylitis might be accounted for by involvement of the sinus node in the disease process. Other studies have shown electrocardiographic abnormalities.^{5, 9, 10-12}

Echocardiographic data, unlike previously published work, failed to detect any differences between normal subjects and patients with ankylosing spondylitis. There are a number of possible explanations for the perceived echocardiographic differences in our study and that of Brewerton *et al*.¹⁴ Their echocardiograms were recorded in different centres using different staff and possibly different equipment. There may have been differences in the normal subjects and the severity of disease in the patients. Brewerton *et al*¹⁴ used the Wilcoxon rank paired test, whereas we used the Mann-Whitney test. The MD-MVO is a variable parameter with means of 9 and 56 ms recorded in normal subjects in two separate studies by the same workers.^{14, 18} Despite the lack of echocardiographic agreement between the two studies, the nuclear angiographic data in our study did

support the earlier reported echocardiographic findings by Brewerton *et al*.¹⁴

The finding of abnormal myocardial function in young patients is at first sight cause for concern, especially when linked to reports which identify an increased death rate in this group of patients. This increased death rate has not, however, been shown to be due to a cardiac cause, but further epidemiological data are clearly required.

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