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## Ankylosing spondylitis and heart abnormalities: do cardiac conduction disorders, valve regurgitation and diastolic dysfunction occur more often in male patients with diagnosed ankylosing spondylitis for over 15 years than in the normal population?

Received: 25 October 2004 / Revised: 14 February 2004 / Accepted: 14 February 2005 / Published online: 25 October 2005  
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**Abstract** The objective of this study was to determine the rate of selected cardiac pathologies (conduction disorders, valve regurgitation and diastolic dysfunction) in patients with long-standing ankylosing spondylitis (AS) and compare the results with the prevalence in the normal population. A rheumatologic (structured questionnaire interview) and cardiac evaluation (resting electrocardiography and echocardiography) was performed in 100 male subjects with AS and a disease duration of more than 15 years. The rates for conduction disorders, aortic and mitral valve regurgitation and diastolic dysfunction were compared with the corresponding results in the literature among the normal population. In patients with long-standing AS there was no increased rate for valve regurgitation (mitral and aortic valve) and for arrhythmia. Diastolic dysfunction occurred more often in patients with long-standing AS. However, this might be caused by the presence of other cardiovascular risk factors such as age and hypertension. According to these results, a cardiologic evaluation with echocardiography should not be recommended routinely in patients with long-standing AS. To confirm these results, a large prospective study with patients with long-standing AS and with a matched control group should be performed in the future.

**Keywords** Ankylosing spondylitis · Conduction disorder · Diastolic dysfunction · Heart affection · Valve regurgitation

### Introduction

Ankylosing spondylitis (AS) is a chronic systemic inflammatory rheumatic disorder that primarily affects the axial skeleton and mainly involves young male subjects [1]. Peripheral joints, tendons and ligaments may also be affected. Uveitis is the most common extraskelatal manifestation; less frequently cardiovascular and pulmonary involvement occurs [1].

Based on the findings in the literature the prevalence of heart pathologies in patients with AS can reach up to 64% [2]. Various studies indicate a higher rate of conduction disturbances, valvular heart diseases and cardiomyopathies in patients with AS when compared with the normal population [3–6]. Conduction disturbances of the heart, such as atrioventricular blocks (AVB), bundle-branch blocks and intraventricular blocks have been observed regularly [3, 5, 7–12]. Screening for a prolonged QT time has been recommended since it might be associated with HLA-B27 [12]. Various pathologies may affect the heart valves, mainly the aortic valve [13]. The spectrum of these structural changes is wide and can range from only minor thickening of the valves or nodules on the valves to severe regurgitation requiring surgical replacement of the affected valve. Clinical signs of cardiomyopathy were often associated with diastolic and/or systolic dysfunction of the ventricles [2, 4, 5, 14–20].

As a consequence of these pathologies, heart insufficiency and stroke were found to be increased in patients with AS [2, 11, 21, 22]. This is associated with a decreased life expectancy in this population [23, 24].

In daily clinical practice symptoms of heart involvement are rarely seen. However, the importance of these pathologies might be underestimated. The aim of this study was to determine the rate of heart abnormalities in patients suffering from AS for more than 15 years compared to the rate in the normal population.

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## Materials and methods

### Subjects

One hundred men (32–86 years,  $54.9 \pm 10.1$  years) with AS diagnosed for more than 15 years participated in this cross-sectional study. The first 100 volunteers who responded to an advertisement in the newsletter of the Ankylosing Spondylitis Society of Switzerland in July 2001 were included in the study. The Ankylosing Spondylitis Society of Switzerland is a self-help organization run by patients afflicted with the disease. The study design has been approved by the Ethics Committee of Balgrist University Hospital (Spezialisierte Unterkommission für Orthopädie der Kantonalen Ethikkommission, Zurich, Switzerland) and informed consent was obtained from all participants.

Included were male patients with a diagnosis of AS and a disease duration of more than 15 years. The diagnosis of AS was based on a clinical examination performed by a physiatrist or a rheumatologist with experience in treating patients with AS. In a few cases, the diagnosis needed to be confirmed by reading previous X-rays. Since the majority of the patients were treated for AS for over 15 years by board certified rheumatologists, no complete work-up was performed to confirm the diagnosis.

Exclusion criteria were a disease duration of less than 15 years, female gender, manifest psoriasis or psoriatic arthritis and Reiter's syndrome.

All participants underwent a rheumatologic and a cardiac evaluation. The examinations were performed between August 2001 and May 2002.

### Rheumatologic evaluation

The rheumatologic evaluation included a structured interview. Questions of the interview included age at onset of first symptoms of AS, age at diagnosis and presence of HLA-B27. Table 1 summarizes the results of the rheumatologic evaluation.

### Cardiac evaluation

Three board certified cardiologists carried out the cardiac evaluation. The patients were assigned equally to one of the three participating cardiologists, who performed an examination according to a prespecified protocol. Resting electrocardiography (ECG) was performed to detect arrhythmia. Doppler echocardiography revealed possible mitral or aortal valve regurgitation and abnormal ventricular diastolic function (Five Great, 1.7 MHz, General Electric, Sonos, 5500-2, 1–4 MHz, Philips and Vingmed Vivid 5, 2.5 MHz, General Electric). The resulting data were compared with the rate of

**Table 1** Summary of rheumatologic evaluation ( $n = 100$ )

Age	54.9 ( $\pm 10.1$ , range: 32–86) years
Age at first diagnosis	22 ( $\pm 6.7$ , 7–40) years
Age at diagnosis	30.4 ( $\pm 10.4$ , 12–71) years
Latency from first symptoms to diagnosis	8.4 ( $\pm 8.5$ , 0–54) years
Duration of disease	32.9 ( $\pm 10.2$ , 16–69) years
HLA-B27	Positive 47%
	Negative 5%
	Unknown 48%

the same pathologies in the normal population based on a review of the existing literature.

Standardized definitions were used to categorize the pathologies (hypertension [25], atrioventricular block [26], bundle-branch block [26] and left ventricular hypertrophy (resting ECG) [27]). A prespecified protocol for the echocardiography of the left ventricle [28, 32] and for valve regurgitation was used [29].

### Literature search

A literature search was performed in order to get corresponding data for the normal population. MEDLINE (PubMed) was screened between 1988 and 2002 for studies investigating the rate of conduction disorders, aortic and mitral valve regurgitation and ventricular diastolic dysfunction in the normal population. Population-based, cross-sectional surveys with a clearly defined clinical examination protocol (ECG and echocardiography) for determining cardiac anomalies were considered as most appropriate. The criteria for consideration included the screening for pathologies such as conduction disorders, valve regurgitation and ventricular diastolic dysfunction in a large number of asymptomatic participants and—if possible—among male subjects.

### Statistics

Descriptive statistical methods were used to calculate means and standard deviation (SD). The chi-square test was used to detect differences between the study results (conduction disturbances, aortic and mitral valve regurgitation) and the data in the literature. To calculate the  $p$  value for abnormal ventricular diastolic function the one-sample  $t$ -test was used. Statistical significance was considered with a  $p$  value of  $< 0.05$ .

## Results

### Results of rheumatologic evaluation

One hundred men were enrolled in this study. All volunteers fulfilled the inclusion criteria and there were no

exclusions or dropouts. The average age of the participants was 54.9 years (range: 32–86 years,  $\pm 10.1$  years) and first symptoms occurred at the age of 22 years (7–40,  $\pm 6.7$ ). On average, the diagnosis was made at the age of 30 years (12–71,  $\pm 10.4$ ) with a delay of 8.4 years (0–54,  $\pm 8.5$ ) after the first symptoms occurred. The mean duration of the disease was 33 years (16–69,  $\pm 10.2$ ).

## Results of cardiac evaluation

### *Conduction abnormalities*

A tachy–brady syndrome was detected in one patient. Atrial fibrillation was demonstrated in two patients. An atrioventricular block was found in nine patients. Eight suffered from a grade I atrioventricular block. One subject showed a grade III atrioventricular block treated by a pacemaker.

Incomplete left bundle-branch block was observed in 14 patients and in 5 patients a complete left bundle-branch block was present.

### *Mitral and aortic regurgitation*

Twenty-nine patients showed a mitral valve regurgitation. An aortic regurgitation was detected in ten patients. Valvular insufficiencies were of mild to moderate severity (grade I in 33 patients and grade II in 5 patients) with the exception of one grade III mitral regurgitation.

### *Left ventricular dysfunction*

Left ventricular diastolic dysfunction was found in 29 subjects. The severity of this impaired function was mild in 11 patients and moderate in 18 subjects. The ratio of the early diastolic mitral inflow velocity and the late diastolic mitral inflow velocity (E/A ratio) was 1.113. Sixty-nine percent of the patients with left ventricular diastolic dysfunction suffered from arterial hypertension, whereas only 23.8% of the participants without diastolic dysfunction showed hypertensive blood pressure values. The results are summarized in Table 2.

Results compared with the findings of heart affections in the normal population

The results are summarized in Table 3

### *Conduction disorders*

To be able to compare our data with corresponding results in the literature, the following pathologies were considered as an arrhythmia: atrial fibrillation, supra-

ventricular and ventricular tachycardias, atrioventricular rhythm, ectopic atrial and ventricular beats and atrioventricular blocks. According to this definition, four participants were diagnosed with an arrhythmia: atrial fibrillation was found in two cases, grade III atrioventricular block and tachy–brady syndrome were found in one patient each.

Three articles fulfilled the prespecified selection criteria and were used to compare our data [30–32]. In our study the prevalence of cardiac blocks (atrioventricular blocks, complete and incomplete left bundle-branch block) was 5 and 7% for arrhythmia. The calculated prevalence in the literature among the normal population was 12.1% for conduction blocks and 8.4% for arrhythmia. The resulting *p* value of 0.03 even indicates a lower prevalence for conduction blocks in our population with long-standing AS. There was no statistical difference for arrhythmia with a *p* value of 0.72.

### *Mitral and aortic valve regurgitation*

The frequency of aortic or mitral valve regurgitation in our study was compared with the results of eight articles in the literature [33–40].

In our study, the prevalence for mitral regurgitation (MR, 29%) and aortic regurgitation (AR, 10%) was slightly increased when compared to the calculated prevalence in the literature (MR 21.8%, AR 6.78%). The *p* values of 0.09 for MR and 0.22 for AR did not reach statistical significance.

### *Diastolic dysfunction*

The prevalence of left ventricular diastolic dysfunction in our study was compared with the results of three published studies performed in asymptomatic volunteers [41–43]. The mean E/A ratio of these studies among the normal population was 1.28. In our study population with long-standing AS the E/A ratio was 1.13 and

**Table 2** Summary of cardiac evaluation (*n* = 100)

Pathology	<i>n</i>	Severity
Tachy–brady syndrome	1	
Atrial fibrillation	2	
Atrioventricular block	9	Grade I: 8 Grade II: 0 Grade III: 1
Left bundle-branch block	19	Incomplete 14 Complete: 5
Mitral regurgitation	29	Grade I: 26 Grade II: 2 Grade III: 1
Aortic regurgitation	10	Grade I: 7 Grade II: 3 Grade III: 0
E/A ratio <sup>a</sup>	29	Grade I: 11 Grade II: 18

<sup>a</sup>Early diastolic inflow velocity/late diastolic inflow velocity

**Table 3** Summary: comparison with corresponding results from the literature in the normal population

Pathology	Prevalence in this study	Prevalence in the literature	<i>p</i> value
Arrhythmia <sup>a</sup>	7%	8.4%	0.72
Conduction abnormalities	5%	12.1%	0.03*
Mitral regurgitation	29%	21.8%	0.09
Aortic regurgitation	10%	6.78%	0.22
Diastolic dysfunction (E/A ratio <sup>b</sup> )	1.113	1.28	<0.0001*

\*Statistically significant ( $p < 0.05$ )

<sup>a</sup>The following pathologies were considered as “arrhythmia”: atrial fibrillation, supraventricular and ventricular tachycardias, atrioventricular rhythm, ectopic atrial and ventricular beats and atrioventricular blocks

<sup>b</sup>Early diastolic mitral inflow velocity/late diastolic mitral inflow velocity

reached statistical significance ( $p < 0.001$ ) when compared with the data in the literature.

## Discussion

Heart pathologies such as conduction disorders, valve regurgitation and diastolic ventricular dysfunction have a direct impact on management and treatment. They are associated with an increased risk for complications (endocarditis and arrhythmia).

The goal of this study was to determine whether there was a higher rate of specific cardiac pathologies in male patients with long-standing AS for more than 15 years compared to the normal population.

Our major finding was a trend (without reaching statistical significance) towards an increased rate for mild to moderate aortic and mitral regurgitation compared to the normal population. The rate of conduction disorders in long-standing AS was comparable to the normal population. Left ventricular diastolic dysfunction occurred statistically more often in patients with long-standing AS than in the normal population. However, since 69% of the patients with a left ventricular diastolic dysfunction also suffered from hypertension, it may be assumed that this dysfunction is related to hypertension or age and is not caused by inflammatory changes in the myocardium of patients with long-standing AS. It has been shown that age and hypertension are two important risk factors for diastolic dysfunction [28].

We compared our data with the results of previous studies examining heart pathologies in long-standing AS. The rate of conduction disorders in the literature varied between 3 [9] and 23% [44]. A wide range was observed for atrioventricular blocks from 3 [9] to 33% [44] as well as for bundle-branch blocks from 1.1 [9] to 33% [45]. In our study the prevalence for conduction disorders was 5% and was even lower than the rate in the normal population (12.1%). The rate of valvular dysfunction in long-standing AS in the literature rapidly changed with the progress of examination techniques. Between 1970 and 1983 the average prevalence of aortic valve regurgitation was 6.9% in the reviewed literature. These studies were based on clinical examination and autopsy studies. Because of a better sensitivity and

specificity this rate increased to an average of 10.8% (range: 1.8 [2] to 16% [22]) with the introduction of (colour Doppler) echocardiography and transoesophageal echocardiography between 1987 and 2001. In this study the rate for aortic valve regurgitation was 10%. Seventy percent of these patients showed a grade I and 30% a grade II regurgitation. The rate of mitral valve regurgitation in long-standing AS was examined in only two previous studies and varied from 32 [22] to 40% [15]. The authors did not differentiate the severity of these pathologies. The rate for mitral valve regurgitation in our study was 29%, of which 26 patients showed grade I, 2 subjects grade II and 1 patient grade III regurgitation.

In the literature after 1987 the rate of diastolic dysfunction in patients with long-standing AS showed a wide range from 1.4 [14] to 63.7% [2] with a calculated mean of 26.3%. This is comparable the results of our study with a calculated mean of 29%.

The strength of this study is the examination of a homogeneous population of only male patients with long-standing AS for over 15 years. To the best of our knowledge, no previous study examined such a large number of patients with such a long mean disease duration of 32.2 years.

A number of restrictions concerning this study should be mentioned. First, the diagnosis of long-standing AS has not been verified formally. We assumed a correct diagnosis by the fact that the patients were treated by board certified rheumatologists, had a disease duration of more than 15 years and showed typical signs of AS in our own clinical examination. Second, no epidemiological studies on the prevalence of these selected heart pathologies have been conducted in Switzerland. Therefore, the comparison of our data with the corresponding results from the normal population relied on studies from other countries (Belgium, France, Germany, Italy, Sweden and the United States of America). A third concern relates to the selection of our control group. We compared our results of 100 patients with long-standing AS with the results of the normal population in the existing literature for two main reasons. Due to a limited budget, we decided to examine as many patients with long-standing AS as possible rather than having a small AS patient sample and recruiting a small control group of asymptomatic volunteers without AS

at the same time. We assumed that large epidemiological studies in normal populations provide more reliable results than a small control group. However, our findings might also reflect important differences in clinical, demographic, social or environmental factors influencing outcome between our study population and that reported in the literature. Furthermore, since the samples of the participants of our study were recruited from the Ankylosing Spondylitis Society of Switzerland the study population might not be representative for a larger population.

The results of this study suggest that the impact of cardiac abnormalities in patients with long-standing AS might have been overestimated in the past. The major finding was a statistically not significant difference of mitral and aortic valve regurgitation in patients with long-standing AS. According to these results, a cardiologic evaluation with echocardiography should not be recommended routinely in patients with long-standing AS. To confirm these results, a large prospective study with patients with long-standing AS and with a matched control group should be performed in the future.

### Take home message

The impact of cardiac abnormalities in patients with long-standing AS might have been overestimated in the past. According to the results of this study, a cardiologic evaluation with echocardiography should not be recommended routinely in patients with long-standing AS. To confirm these results, a large prospective study with patients with long-standing AS and a matched control group should be performed in the future.

**Acknowledgements** This study has been supported by a grant of the Ankylosing Spondylitis Society of Switzerland. The authors would like to thank Urs Duerst, M.D., Gerhard Junga, M.D. and Michel Troesch, M.D. for the cardiac evaluations and PD Burkhardt Seifert, Ph.D., Department for Biostatistics, University of Zurich, for his support in statistical analysis.

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