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# QT dispersion as a predictor of arrhythmic events in patients with ankylosing spondylitis

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## Abstract

*Objective*. The aim of the study was to evaluate QT dispersion (QTd), an indicator of repolarization heterogeneity, and its relation to ventricular arrhythmias in patients with ankylosing spondylitis (AS).

*Methods*. A full history, clinical examination, electrocardiograms and 24-h Holter monitoring were performed in 88 AS patients and 31 volunteers of similar age and sex. Groups were compared based on electrocardiographic abnormality, QTd, arrhythmias and heart blocks.

*Results*. QTd and corrected QTd (QTcd) were significantly greater in AS patients than controls (QTd, 52.8 $\pm$ 15.1 *vs* 35.5 $\pm$ 8.9 ms, $P < 0.0001$; QTcd, 60.3 $\pm$ 16.1 *vs* 39.4 $\pm$ 10.7 ms, $P < 0.0001$). The magnitudes of these parameters were associated with the duration of the disease (QTd, $r = 0.56$, $P < 0.01$; QTcd, $r = 0.60$, $P < 0.001$). The frequency of ventricular extrasystoles was found to be correlated with QTd ($r = 0.35$, $P < 0.01$) and QTcd ($r = 0.33$, $P < 0.01$).

*Conclusion*. Involvement of the heart may be seen in AS during the early clinical course of the disease. QTd may give clues about the presence of arrhythmias and can be used as a new technique for the evaluation of asymptomatic patients. Earlier detection of cardiac involvement could alter the prognosis of the patients.

KEY WORDS: Ankylosing spondylitis, QT dispersion, Arrhythmias, Holter monitoring.

## Introduction

The cardiac manifestations seen in ankylosing spondylitis (AS) include aortitis causing aortic insufficiency, myocarditis causing conduction disturbances, and increased myocardial fibrosis causing abnormalities of left ventricular relaxation [1–4]. The literature has focused especially on the aortic insufficiency and the conduction disturbances, and less attention has been paid to the other forms of cardiac arrhythmias.

QT dispersion (QTd) is an indicator of repolarization heterogeneity and has been studied in many diseases, including coronary artery disease, post-infarct risk stratification and long QT syndrome [5–7]. Because myocardial involvement and increased myocardial fibrosis are complications of AS, we expect increased repolarization heterogeneity and arrhythmic events in this group of patients. The small amount of data on 24-h Holter examination in AS patients indicates higher frequencies of both atrial and ventricular extrasystoles and intermittent conduction disturbances [8, 9]. However, to our knowledge the occurrence of QTd and the relationship between QTd and ventricular arrhythmias in AS patients has not yet been investigated. In this study, QTd was evaluated in AS patients free of cardiac symptoms and was compared with that in healthy control subjects. Arrhythmic events and conduction disturbances in both groups were recorded using 24-h Holter monitoring, and the correlation between QTd and the frequency of ventricular extrasystoles was evaluated.

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## Patients and methods

### *Patients*

Eighty-eight consecutive patients, all fulfilling the New York criteria for AS [10], were included in the study. Patients with a history or symptoms relevant to cardiac disease, systemic hypertension, diabetes or other rheumatic diseases were excluded. Thirty-one volunteers with no previous history of cardiac disease or hypertension served as a control group, and were similar to the patients in age and sex. The control subjects had either soft-tissue or degenerative rheumatic disorder. None of the patients and control subjects had symptoms that might be related to cardiac arrhythmias, such as palpitations, hypotension, syncope and chest pain.

A full history, clinical examination, standard 12-lead electrocardiographs and 24-h Holter examination were

performed in all subjects. Patients with conduction disorders on Holter examination were evaluated by echocardiography for the presence of valvular involvement. Blood samples for HLA typing were obtained in patients with AS.

*Methods*

*QT analysis.* All patients had a rest 12-lead ECG recorded at 25 mm/s paper speed. None of the patients was taking any anti-arrhythmics or drugs that may alter the results of QT analysis. The QT interval was measured manually from the onset of QRS to end of the T wave, defined as a return to the T–P baseline. If U waves were present, the QT interval was measured to the nadir of the curve between the T and U waves. Four consecutive cycles were measured in each of the 12 leads. All measurements were made by two blinded, experienced cardiologists. From the four cycles, mean QT, maximum QT and minimum QT were calculated. Dispersion parameters were calculated as the difference between the maximal and minimal values of QT, and the corrected QT interval was calculated using Bazett's formula. Blinded inter- and intra-observer variability of QT measurements were both $<5\%$.

*Holter monitoring.* Twenty-four-hour Holter monitoring was performed in all patients and control subjects with a CardioCoder (Delmar Avionics, Irvine, CA, USA) Model 459 three-channel Holter monitoring system. The types were analysed by one blinded cardiologist. The arrhythmias and heart blocks were defined using internationally accepted criteria [11, 12]. The frequencies of ventricular and supraventricular extrasystoles (VES and SVES) were noted and ventricular arrhythmias were further classified according to the Lown classification (class 0, absence of VES; class 1A, VES $<30$/h, $<1$/min; class 1B, VES $<30$/h, $>1$/min; class 2, VES $>30$/h; class 3, multiform VES; class 4A, repetitive VES couplet; class 4B, repetitive VES salvos or ventricular tachycardia; class 5, early VES-R on T) [13].

*Statistical analysis.* Values are expressed as mean $\pm$ S.D. and percentage when appropriate. Student's *t*-test of independent samples was used for the continuous variables that were distributed normally. Nonparametric variables were analysed with the Mann–Whitney *U*-test. Prevalence data were compared by group, using $\chi^2$ analysis or Fisher's exact test. Relationships between variables were analysed using correlation analysis, which was the Pearson correlation coefficient for normally distributed variables and the Spearman correlation coefficient for non-normally distributed variables. Statistical significance was set at $P < 0.05$.

## Results

The ankylosing spondylitis group included 44 male and 44 female patients and the control group included 16 male and 15 female healthy subjects. Table 1 gives data on their age and sex and, for the patients with AS, disease duration, HLA-B27 positivity and the occurrence of uveitis. The patient and control groups were similar with respect to age and sex (age, $P > 0.05$, Student's *t*-test of independent samples; sex, $P > 0.05$, $\chi^2$ test). None of the patients or control subjects had any physical findings relevant to valve disease.

TABLE 1. Clinical features of ankylosing spondylitis patients and control subjects

| | Ankylosing spondylitis ($n = 88$) | Control ($n = 31$) |
|---|---|---|
| Age (yr)[a] | $33 \pm 11$ | $33 \pm 9$ |
| Age range (yr) | 19–64 | 19–60 |
| Men/women | 44/44 | 16/15 |
| Heart rate (beats/min)[a] | $73.7 \pm 11.4$ | $72.8 \pm 9.6$ |
| Disease duration (months)[a] | $67.3 \pm 69.8$ | – |
| Range of disease duration months | 1–360 | – |
| No. of HLA-B27$^+$ subjects | 80 (91%) | – |
| No. of subjects with uveitis | 14 (16%) | – |

[a]Values are expressed as mean $\pm$ S.D.

*Electrocardiogram*

The standard 12-lead electrocardiogram was abnormal in six (6.8%) AS patients and two (6.4%) control subjects. In the AS group one patient had poor anteroseptal R wave progression, two had non-specific ST and T wave abnormalities, one had first-degree atrioventricular (AV) block (PR 0.24), one had an intraventricular conduction defect and one had right bundle branch block. One control subject had non-specific ST and T wave abnormalities and one had the juvenile pattern.

*Conduction abnormalities*

Seven (7.9%) of 88 AS patients had conduction disturbances on 24-h Holter examination. Three of them (3.4%) had first-degree AV block (transient in two patients and permanent in one), i.e. P–R interval $\geqslant 0.20$ s. One patient (1.1%) had Mobitz type II second-degree AV block, one (1.1%) had transient complete AV block with nodal escape beats, one (1.1%) had right bundle branch block and one (1.1%) had intermittent left bundle branch block. None of the control subjects had any conduction disturbance other than one episode of Wenckebach type second-degree AV block during the night, seen in one person. There were no events of bradycardia ($<40$ beats/min during the day) either in the patients or in the control group. The 46-yr-old male patient with intermittent complete AV block had moderate aortic regurgitation and mild mitral regurgitation, diagnosed echocardiographically. Moderate aortic regurgitation that was silent on physical examination was also detected in another patient with Mobitz type II AV block.

*Ventricular arrhythmias*

The distribution of ventricular arrhythmias according to the Lown classification in patients with AS and control subjects is shown in Table 2. In the AS group, one patient had class 4B, three had class 4A, five had class 3, one had class 2, one had class 1B and 34 had class 1A ventricular arrhythmias, whereas no ventricular

TABLE 2. Distribution of ventricular arrhythmias according to Lown classification in patients with ankylosing spondylitis and control subjects

| | Ankylosing spondylitis | | Control subjects | |
|---|---|---|---|---|
| Class | Number | % | Number | % |
| 0 | 43 | 48.8 | 24 | 77.4 |
| 1A | 34 | 38.6 | 6 | 19.3 |
| 1B | 1 | 1.1 | 0 | 0 |
| 2 | 1 | 1.1 | 0 | 0 |
| 3 | 5 | 5.7 | 1 | 3.2 |
| 4A | 3 | 3.4 | 0 | 0 |
| 4B | 1 | 1.1 | 0 | 0 |
| 5 | 0 | 0 | 0 | 0 |

arrhythmia was seen in 43 AS patients. In the control group, one subject had class 3 and six had class 1A ventricular arrhythmias. None of the patients and control subjects had R on T phenomena (Lown class 5). Based on the 24-h Holter monitoring data, the AS patients had a significantly higher frequency of ventricular premature beats than the control subjects (Mann–Whitney *U*-test, $P = 0.003$).

*Supraventricular arrhythmias*

SVES were seen in five (5.7%) patients in the AS group. These comprised one patient with SVES in couplets, one with paroxysmal atrial fibrillation and three with episodes of supraventricular tachycardia. The recorded frequency of SVES on Holter examination was found to be higher in the AS patients than in the control subjects (Mann–Whitney *U*-test, $P = 0.0002$).

*QT dispersion*

Both QT dispersion and corrected QT dispersion were significantly greater in AS patients than in normal subjects (QTd, $52.8 \pm 15.1$ *vs* $35.5 \pm 8.9$; QTcd, $60.3 \pm 16.1$ *vs* $39.4 \pm 10.7$; Student's *t*-test of independent samples, both $P < 0.0001$) (Table 3). In patients with AS, the magnitudes of these parameters were associated with the duration of disease (Pearson correlation test, QTd, $r = 0.56$, $P < 0.01$; QTcd, $r = 0.60$, $P < 0.001$). There was a correlation between the frequency of VES and QTd (Spearman correlation test, $r = 0.35$, $P < 0.01$). A similar correlation was observed between QTcd and VES frequency (Spearman correlation test, $r = 0.33$, $P < 0.01$).

## Discussion

Heart disease is a well-recognized complication of AS. Men with AS have a 40% excess cardiovascular mortality risk relative to the general population [14]. The most characteristic lesions are aortic root disease and conduction system disturbances. Myocardial involvement with increased fibrosis has also been reported in this group of patients. The prevalences of both aortic incompetence and conduction system disorders increase with age and the duration of disease. The destructive process involving the heart results in dilatation of the aortic annulus, shortening and fibrotic degeneration of the aortic valves and ultimately destruction of the AV bundle [3, 15]. Conduction disturbances usually appear before the advent of aortic valve incompetence in the majority of causes [3, 16–18].

TABLE 3. Results of QTd and QTcd analysis in ankylosing spondylitis patients and control subjects

| | Ankylosing spondylitis | Control subjects | *P* |
|---|---|---|---|
| QTd (ms) | $52.8 \pm 15.1$ | $35.5 \pm 8.9$ | $< 0.0001$ |
| QTcd (ms) | $60.3 \pm 16.1$ | $39.4 \pm 10.7$ | $< 0.0001$ |

The destructive process of AS involves not only the AV nodal tissue but the entire conduction system and even the myocardium. Our finding of increased frequency of atrial and ventricular arrhythmias in AS patients, some even potentially dangerous forms (ventricular tachycardia and multifocal VES), may be due to this diffuse involvement in the disease process.

In the present study, different degrees of AV block were recorded in five (5.7%) of the 88 patients with AS. Three had first-degree (transient in two patients, permanent in one), one had second-degree and one had intermittent complete AV block. Additionally, one case of right-bundle branch block and one of intermittent left-bundle branch block were also seen in the AS group. The reported prevalence of AV block in AS patients varies between 1 and 33%, and has a mean of 9.5% [7, 19, 20]. However, the mean age of the patients in most of these studies was considerably greater than in our study group. One thing that should be kept in mind is that this prevalence is much lower in studies that take into account only the standard electrocardiogram. This is because conduction system disorders in HLA-B27-associated diseases tend to occur intermittently, as seen in four of our patients [2, 21–24]. Intermittent complete AV heart block, recorded in one of our patients, never occurs in normal adults. In two of five patients with conduction system disturbances, a moderate aortic regurgitation was detected on echocardiographic examination. This is an expected finding, as such patients share a common pathophysiology in which conduction system disorders are associated with aortic valvular abnormalities in this disease.

The dispersion of repolarization may be assessed invasively using endocardial or epicardial mapping, or non-invasively by multilead body-surface mapping. However, in clinical practice, neither of these methods is practicable for extensive use. The dispersion of ventricular repolarization from the surface electrocardiogram has recently been proposed as a simple non-invasive marker of susceptibility to arrhythmias [25–27]. Zaidi *et al.* [28] reported that dispersion values in patients with dilated cardiomyopathy who have ventricular conduction defects are higher than in patients who do not have ventricular conduction defects, and are also higher than in normal subjects. In the present study, AS patients without any cardiac symptoms had significantly greater QT dispersion than control subjects. Thus, these patients might have inhomogeneity in ventricular repolarization

and intraventricular conduction defects. Supporting this hypothesis is the fact that, in 24-h Holter monitoring, patients with higher frequency of ventricular arrhythmias had higher QT dispersion values. However, to the best of our knowledge the literature contains no study of QT dispersion in patients with AS that can be compared with our findings.

In our study, we observed only asymptomatic patients with respect to cardiac involvement. The mean age of our study population was considerably younger than that in most other studies. Since cardiac involvement in AS is related to age and the duration of disease, if older age groups and symptomatic patients had been included, more severe arrhythmias and conduction blocks might have been detected. However, the detection of cardiac involvement during the asymptomatic period is important. Townend *et al.* [29] reported that immunosuppressive therapy could prevent or delay valvular replacement in rheumatic patients with aortic regurgitation. Other types of cardiac disease, if detected early, may also be delayed by extensive medical therapy.

In conclusion, involvement of the heart may be seen in AS patients even in the absence of clinical cardiac manifestations. However, there seems to be no reason to subject patients without any symptoms to Holter monitoring as a routine. We need some simple and cheap techniques to diagnose this involvement. Especially in outpatient clinics with a high patient load, the calculation of QTd on the standard electrocardiogram may give clues about the presence of arrhythmia and can be used as an easy and cheap non-invasive technique for the evaluation of asymptomatic patients. Patients with increased QTd can be further evaluated for asymptomatic cardiac involvement by the use of other, more expensive and complicated techniques, including echocardiography and 24-h Holter examination. This enables earlier detection of cardiac disease and more aggressive treatment, which can alter the prognosis of patients with AS.

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