Electrocardiographic changes in spondyloarthritis and use of anti-TNF-α drugs: a retrospective study with 100 patients

Alterações eletrocardiográficas em espondiloartrites e uso de anti-TNF-α: estudo retrospectivo em 100 pacientes

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ABSTRACT

Objective: To investigate the prevalence of electrocardiographic changes in patients with spondyloarthritis and to correlate these changes with use of anti-tumor necrosis factor-alpha (TNF-α) drugs and HLA-B27 positivity.

Methods: Retrospective study including 100 patients diagnosed with spondyloarthritis according to Assessment of SpondyloArthritis International Society (ASAS) criteria and 50 controls. Epidemiological and clinical features, results of inflammatory activity tests, HLA-B27 positivity, and medication use data were extracted from medical records. Disease activity was assessed using the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI). All participants were submitted to electrocardiogram performed using a 12-lead device; rhythm, heart rate, conduction disorders and QT interval corrected using the Bazett formula were analyzed.

Results: Of 100 patients with spondyloarthritis, 51 were on anti-TNF-α drugs and 49 were not. HLA-B27 was detected in 53.1% of patients in the sample. Patients with spondyloarthritis had lower heart rate (p=0.06), longer QT interval (p<0.0001) and higher prevalence of right bundle branch block (p=0.014) compared to controls. Duration of disease was weakly correlated with heart rate (Rho=0.26; 95%CI: 0.06-0.44; p=0.008). The prevalence of right bundle branch block was positively correlated with HLA-B27 positivity. Use of Anti-TNF-α drugs did not interfere with electrocardiographic parameters.

Conclusion: Patients with spondyloarthritis had lower heart rate, longer QT interval and a higher prevalence of right bundle branch block compared to controls. HLA-B27 positivity was associated with the prevalence of right bundle branch block. Anti-TNF-α drugs had no impact on electrocardiographic findings.

Keywords: Spondylarthropathies; Electrocardiography; Bundle-branch block; HLA B27 antigen; Anti TNF-α; Tumor necrosis factor-alpha

RESUMO

Objetivo: Avaliar a prevalência de alterações eletrocardiográficas em pacientes com espondiloartrites, correlacionando-as com o uso de medicações antifator de necrose tumoral alfa (TNF-α) e presença do HLA-B27. Métodos: Estudo retrospectivo com 100 pacientes com diagnóstico de espondiloartrites pelo critério Assessment of SpondyloArthritis International Society (ASAS) e 50 controles. Foram coletados nos prontuários dos pacientes, dados epidemiológicos, clínicos, exames de atividade inflamatória, presença do HLA-B27, e uso de medicamentos. A atividade de doença foi avaliada pelo Bath Ankylosing Spondylitis Disease Activity Index (BASDAI). Todos
INTRODUCTION

Spondyloarthritis (SpA) comprise a group of chronic diseases including ankylosing spondylitis (AS), psoriatic arthritis (PsA), reactive arthritis (ReA), juvenile SpA, inflammatory bowel disease-related SpA and undifferentiated spondyloarthritis. Major complaints associated with SpA are of musculoskeletal origin; however, several extra-articular manifestations have been reported, including cardiac conditions such as aortitis, aortic insufficiency, conduction disorders and atrioventricular blocks, which are thought to affect approximately 10% of patients. Cardiac involvement is often subclinical, associated with longstanding disease and unrelated to articular disease activity. Pacemaker implantation and valve replacement may be required in severe cases. Ankylosing spondylitis is the best understood SpA in terms of cardiac manifestations, which also include atrioventricular blocks (AVBs), arrhythmias and ventricular dysfunction due to fibrosis. First-degree AVBs are associated with an increased risk of atrial fibrillation (AF), which in turn is associated with stroke, heart failure and increased mortality.

Supraventricular arrhythmias were the most common findings in an European study with AS patients. In that study, prolonged P wave duration and dispersion were associated with inflammatory activity, as measured using the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI).

OBJECTIVE

To investigate the prevalence of electrocardiographic changes in patients with spondyloarthritis and correlations between electrocardiographic changes, use of anti-TNF-α drugs and HLA-B27 positivity.

METHODS

Retrospective study based on a convenience sample comprising patients seen at the outpatient rheumatology service of Hospital Universitário Evangélico de Curitiba between 2016 and 2017. Patients aged over 18 years and diagnosed with SpA according to Assessment of SpondyloArthritis International Society (ASAS) criteria were included. This study was approved by the Ethics and Research Committee of Sociedade Evangélica Beneficente de Curitiba, opinion No. 1.779.523, CAAE: 60727616.9.0000.0103, and was exempt from informed consent.

Medical records were screened for epidemiological and clinical data, presence of comorbidities, erythrocyte sedimentation rate (ESR) values, C-reactive protein (CRP) levels and HLA-B27 positivity. Disease activity was assessed using the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI). This instrument rates fatigue, spinal pain, peripheral arthritis, enthesitis and morning stiffness severity and duration on a zero to 10 scale; scores ≥4 are suggestive of active inflamed joint.
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The sample comprised 150 individuals, as follows: 51 diagnosed with SpA and using anti-TNF-α drugs, 49 diagnosed with SpA and not using anti-TNF-α drugs and 50 controls. Patient data are shown in table 1.

### RESULTS

The sample comprised 150 individuals, as follows: 51 diagnosed with SpA and using anti-TNF-α drugs, 49 diagnosed with SpA and not using anti-TNF-α drugs and 50 controls. Patient data are shown in table 1.

**Table 1.** Descriptive data of 100 patients diagnosed with spondyloarthritis included in the sample

| Descriptive data | n=100 |
|------------------|-------|
| SpA manifestation |       |
| Ankylosing spondylitis | 53    |
| Psoriatic arthritis | 31    |
| Undifferentiated | 7     |
| IBD-related | 4     |
| Juvenile SpA | 2     |
| Reactive arthritis | 2     |
| Non radiographic SpA | 1     |
| Involvement |       |
| Axial | 30    |
| Peripheral | 19    |
| Axial and peripheral | 51    |
| Sex |       |
| Male | 53    |
| Female | 47    |
| Age, years | 16-73; mean 48.9±11.9 |
| Duration of disease, years | 1-30; median 7; IQR=3.2-12.0 |
| HLA-B27 positive | 42*   |
| Medications |       |
| Non-steroidal anti-inflammatory drugs | 43    |
| Methotrexate | 25    |
| Leflunomide | 51    |
| Anti-TNF-α | 51    |
| Etanercept | 17    |
| Adalimumab | 20    |
| Infliximab | 14    |
| BASDAI | 0-8; median 2.0 (IQR=1.0-3.4) |
| C-reactive protein, mg/dL | 0-43; median 6.0 (IQR=2.3-6.0) |
| ESR, mm | 1-100; median 16.5 (IQR=6.2-26.7) |

* Data available in 79 medical records only. IBD: inflammatory bowel disease; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; IQR: interquartile range; ESR: erythrocyte sedimentation rate; SpA: spondyloarthritis.

Comparative analysis revealed similar findings between SpA and control patients regarding sex (male/female ratio, 57% versus 58%; p=0.90), age (mean age 48.9±11.9 versus 46.0±13.4 years; p=0.19), smoking habits (21% versus 28%; p=0.33), alcohol abuse (10% per group; p=1.0) and prevalence of hypertension (32% versus 36%; p=0.46), diabetes mellitus (10% versus 4%; p=0.21) and hypothyroidism (14% versus 8%; p=0.42).

Comparative analysis of electrocardiographic findings in patients and controls are shown in table 2. Patients suffering from SpA had lower heart rate and higher prevalence of IRBBB compared to controls. Spondyloarthritis patient had more prolonged QT intervals; QTc tended to be more prolonged in patients with SpA compared to controls.
Table 2. Comparative analysis of electrocardiographic findings in patients with spondyloarthritis and controls

| ECG                        | SpA Group (n=100) | Control Group (n=50) | p value |
|----------------------------|-------------------|----------------------|---------|
| Sinus rhythm, n (%)        | 100 (100)         | 50 (100)             |         |
| Heart rate, bpm            | 47-96, median 68 (59-76) | 51-101, median 73.5 (66.7-92.0) | 0.006   |
| Heart rate, seconds        | 0.61-1.28, mean 0.90±0.14 | 0.59-1.18, mean 0.83±0.12 | 0.009   |
| First-degree atrioventricular block, n (%) | 3 (3) | 0 | 0.55 |
| Ventricular repolarization changes, n (%) | 54 (54) | 20 (40) | 0.10 |
| Right bundle branch block, n (%) | 37 (37) | 6 (12) | 0.014* |
| QT, seconds                | 0.32-0.49, median 0.40 (0.37-0.40) | 0.32-0.48, median 0.36 (0.36-0.40) | <0.0001 |
| QTc, seconds               | 0.36-0.49, median 0.41 (0.39-0.43) | 0.34-0.49, median 0.40 (0.38-0.43) | 0.08 |

* Odds ratio: 4.3; 95% confidence interval 1.67-11. ECG: electrocardiogram; QTc: corrected QT interval (Bazett formula).

Table 3. Electrocardiographic characteristics and HLA-B27 positivity in the group of patients with spondyloarthritis

| Characteristic               | HLA-B27 positive (n=42) | HLA-B27 negative (n=37) | p value |
|------------------------------|--------------------------|-------------------------|---------|
| Heart rate, bpm              | 47-94, mean 67.5±12.4    | 50-97, mean 69.2±10.0   | 0.52    |
| Heart rate, duration in seconds | 0.64-1.28, mean 0.91±0.16 | 0.62-1.2, mean 0.98±0.12 | 0.33    |
| QT, seconds                  | 0.32-0.49, mean 0.39±0.03 | 0.32-0.44, mean 0.36±0.02 | 0.70    |
| QTc, seconds                 | 0.38-0.49, median 0.41 (0.38-0.42) | 0.36-0.48, median 0.42 (0.40-0.43) | 0.12    |

QTc: corrected QT interval (Bazett formula).

Table 4. Comparative analysis of electrocardiographic data from patients with spondyloarthritis treated or not treated with anti-TNF-α drugs

| Characteristic               | Treated with anti-TNF-α (n=51) | Not treated with anti-TNF-α (n=49) | p value |
|------------------------------|---------------------------------|-------------------------------------|---------|
| Heart rate, bpm              | 47-98, median 68 (53-77)        | 47-97, median 68 (60-75)            | 0.77    |
| Heart rate, duration in seconds | 0.61-1.28, mean 0.90±0.15       | 0.62-1.28, mean 0.89±0.14           | 0.71    |
| QT, seconds                  | 0.32-0.49, median 0.40 (0.37-0.40) | 0.32-0.46, median 0.40 (0.37-0.40) | 0.62    |
| QTc, seconds                 | 0.36-0.48, mean 0.41±0.02        | 0.36-0.49, mean 0.41±0.025           | 0.53    |
| Incomplete right bundle branch block, n/n total | 20/51 | 17/49 | 0.63 |

QTc: corrected QT interval (Bazett formula).

**DISCUSSION**

This study revealed lower heart rates, increased prevalence of IRBBB, and higher QTc values in patients suffering from SpA compared to controls. Normal or above normal QTc intervals were detected in three patients. With the exception of IRBBB prevalence, these changes were not associated with HLA-B27 positivity. Use of anti-TNF-α drugs had no impact on the frequency of these findings.

The sample in this study has some particularities. Firstly, patients suffering from different forms of SpA were included, while most other studies are limited to patients with AS. Spondyloarthritis is associated with higher prevalence of HLA-B27 positivity; therefore lower prevalence of this histocompatibility antigen in this sample may explain the lack of associations with...
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A second explanation, also related to lower prevalence of HLA-B27 positivity, is the fact that this study was based on a Brazilian population. The prevalence of HLA-B27 positivity is lower in the Brazilian compared to Caucasian populations due to the high levels of local racial miscegenation.\(^1\)

Anti-TNF-α drugs did not interfere with electrocardiographic findings, including IRBBB. Two anecdotal theories may explain conduction disorders in the context of this study: atrioventricular node abnormalities and intraventricular septal inflammation.\(^3\)

Endarteritis of small vessels supplying the aortic valve and atrioventricular node and resulting obliteration by inflammatory process (very similar to that observed in joints) has been described.\(^4\) Had electrocardiographic changes resulted from the inflammatory process, it would be reasonable to assume such changes would be reverted by anti-TNF-α drugs. Findings of this study do not support this hypothesis. However, given the relatively long duration of disease in this sample, inflammatory changes may have progressed to irreversible, fibrotic changes. Weak as they may be, correlations between duration of disease and IRBBB have been detected in this study. Investigations with recently diagnosed patients treated with anti-TNF-α drugs may help to clarify this issue.

Lower heart rates were recorded in SpA patients in this study. Similar findings have been reported by Dik et al.,\(^14\) who detected bradycardia in 30% of 130 patients suffering from AS. Autonomic dysfunctions, particularly parasympathetic, have been described in patients with psoriatic arthritis\(^15\) and may explain this finding. Bradycardia may also reflect other conduction disorders.\(^12\)

This study also revealed a tendency towards longer QTc intervals regardless of anti-TNF-α drug use. In contrast, DI Franco et al.,\(^16\) reported asymptotically increased QT interval and dispersion in patients suffering from inflammatory polyarthritis treated with anti-TNF-α drugs. Among patients with SpA in this sample, three had above normal QTc intervals, which has been associated with increased risks of torsade de pointes type tachycardia.\(^12\) Of these, only one was on anti-TNF-α drugs.

This study has several limitations, such as lack of HLA-B27 data in control individuals and small sample size. Retrospective design introduced yet another limitation, as duration of anti-TNF-α treatment could not be accounted for. Prospective studies are warranted to further investigate the matter. Still, findings of this study emphasize the high prevalence of electrocardiographic changes in patients suffering from SpA, who are already prone to cardiovascular problems given the chronic, inflammatory nature of the disease,\(^17\) and therefore deserve closer medical attention.

### CONCLUSION

Patients suffering from spondyloarthritis had lower heart rate, longer corrected QT interval and higher prevalence of incomplete right bundle branch block compared to controls. Anti-TNF-α medication had no impact on electrocardiographic findings.

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