SYMPATHETIC OVERACTIVITY AND ARRHYTHMIAS IN TETANUS: 
ELECTROCARDIOGRAPHIC ANALYSIS

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SUMMARY

As a result of the advances in the control of pulmonary insufficiency in tetanus, the cardiovascular system has increasingly been shown to be a determining factor in morbidity and mortality but detailed knowledge of the cardiovascular complications in tetanus is scanty. The 24h-Holter was carried out in order to detect arrhythmias and sympathetic overactivity in 38 tetanus patients admitted to an ICU. The SDNN Index (standard deviation from the normal R-to-R intervals), was useful in detecting adrenergic tonus, and ranged from 64.1 ± 27 in the more severe forms of tetanus to 125 ± 69 in the milder ones. Sympathetic overactivity occurred in 86.2% of the more severe forms of the disease, but was also detected in 33% of the milder forms. Half the patients had their sympathetic overactivity detected only by the Holter. The most frequent arrhythmias were isolated supraventricular (55.2%) and ventricular (39.4%) extrasystoles. There was no association of the arrhythmias with the clinical form of tetanus or with the presence of sympathetic overactivity. The present study demonstrated that major cardiovascular dysfunction, particularly sympathetic overactivity, occurs in all forms of tetanus, even in the milder ones. This has not been effectively detected with traditional monitoring in ICU and may not be properly treated.

KEYWORDS: Tetanus; Cardiovascular system; Arrhythmias; Sympathetic overactivity.

INTRODUCTION

It is estimated that 1,000,000 cases of tetanus per year occur throughout the world4. A higher incidence occurs in countries with poor social, economic and educational indicators14,30.

Mortality was around 85% before the introduction of treatment with antitetanus immunoglobulin; with immunoglobulin, mortality remains between 10 and 60%3,9,13,14,18,30. This variation depends mainly on the facilities of the health unit where the treatment is conducted18,21,25,30, on the patient’s age2,14,17 and on the severity of the disease14,30.

Recently, with the advent of more effective control and prophylaxis of respiratory complications in intensive care units (ICU), formerly the main cause of death (61 to 80%)1,3,4, the effects of tetanus on the cardiovascular system have been observed and seem to cause increasing morbidity and mortality in these patients3,7,18,21,26.

The cardiovascular manifestations of tetanus consist of disturbances of heart rate and rhythm, blood pressure instability, arrhythmias, myocardial dysfunction and sympathetic overactivity10,15,20,30. They may be due to the direct action of the tetanus toxin on the heart, to the drugs used to control rigidity and spasms, and to the hypersympathetic state induced by the failure to inhibit adrenal release of catecholamines3,8,23,29.

One study shows that this dysautonomia is responsible for nearly 30% of deaths and that only 26% of the tetanus patients who survived the disease showed a clinical manifestation of sympathetic overactivity28.

Current literature on the topic is scanty and states that patients who develop more severe clinical conditions more frequently present hemodynamic, myocardial or electrocardiographic abnormalities than those with the milder forms of tetanus3,4,10,25,30.

The literature reinforces the idea that the sympathetic overactive syndrome occurs only in very severe tetanus17,14,30, and fails to take into account the possibility of hypercatecholaminemia without any obvious clinical manifestation in patients with the less severe forms of the disease.

These complications remain a challenge and have motivated the authors to study the association between the presence of arrhythmias and sympathetic nervous system hyperactivity and the severity of the disease.
clinical form of tetanus, for a better knowledge of this relationship could contribute to more prompt and effective treatment of these patients.

MATERIALS AND METHODS

The study population included all patients aged 12 years or over admitted to the Intensive Care Unit of the Division of Infectious and Parasitic Diseases (ICU-IPDS) of the Oswaldo Cruz University Hospital of Pernambuco State University (OCUH-PSU) in a consecutive order between October 1998 and November 2000 with a clinical diagnosis of tetanus, and no cardiocirculatory disease at admission. The patients or a legal guardian signed a written authorization before enrolment in the study. The study was approved by the Ethics Committee of the Hospital.

A diagnosis of tetanus was based on epidemiological data, clinical history and physical signs. The patients with a recent wound history and muscular rigidity in one or more groups of muscles, with or without muscular spasms (spontaneous or triggered by stimuli) [4,30], were included as cases of tetanus. Tetanus was classified, according to clinical parameters and clinical manifestations [29,30], into:

- mild tetanus: trismus, dysphagia and generalized rigidity;
- moderate tetanus: patients with symptoms of the mild form of the disease, with mild and occasional spasms, usually resulting from stimuli;
- severe tetanus: patients with symptoms of the moderate form of the disease, with recurrent spasms, usually triggered by minor or imperceptible stimuli;
- very severe tetanus: patients with symptoms of the severe form of the disease, with severe and repetitive spasms difficult to control with medications, with or without signs of dysautonomia (mainly sympathetic overactivity). The presence of this clinically manifested overactivity characterizes the patient’s tetanus as very severe, irrespective of the other clinical findings [31].

At admission and at 2-day intervals the severity of the tetanus was classified according to clinical parameters and clinical manifestations of sympathetic overactivity that included increased sweat; blood pressure variations; heart rate or rhythm instability; sustained tachycardia away from the spasm; adynamic ileus; hyperglycemia; hyper- or hypothermia, all without other defined causes [1,3,29,30]; and ventricular and supraventricular arrhythmias. All patients were admitted to the ICU, used a cardiac monitor and had their blood pressure and heart rate recorded every two hours.

All the patients were also submitted to 24-hour electrocardiographic monitoring (Holter). The examination was carried out in the first ten days of hospitalization. The electrocardiographic data was recorded on magnetic cassette tapes, using a two-channel Dynamis 3002 recorder. The evaluation of the electrocardiographic monitoring for the 24-hour recording period was done with the DMS system, which consists of a tape analyzer and a specific program to analyze heart rate variability (DMS-1995) through the fluctuations of the R-to-R intervals in normal QRS complexes, in five minutes cycles, estimating the mean and standard deviation of its variability. This analysis was done in every cycle for the whole registering period, estimating the mean of the standard deviation for 24 hours. The sdnn index (mean of standard deviation of HRV of the normal R-to-R intervals) was the parameter used. The existence of sympathetic overactivity was identified either by clinical signs or by the SDNN Index [11,12,22,24]. When SDNN was lower than 100 milliseconds, the presence of dysautonomia was considered [34].

For the analysis of the electrocardiographic monitoring (Holter) the patients were considered at the most severe stage of their progression. If the patient developed a more severe form of the disease after the Holter was done, a further examination was performed and the previous one was excluded from the analysis. This happened on two occasions. All the exams were performed by the same professional, at the electrocardiography service of the Chagas Disease Out-Clinic of the OCUH-PSU.

For the data analysis, the clinical conditions of the disease were regrouped into two categories, according to the clinical severity of the disease: Group A: mild and moderate forms; Group B: severe and very severe forms.

The association between groups A and B and the presence of electrocardiographic alterations was evaluated, as well as the association between the severe and very severe forms (group B) and the presence of sympathetic overactivity. These analyses were carried out by the SISA statistics program (“Simple Interactive Statistical Analysis”), estimating the relative risk, 95%-confidence interval and the Fisher Test – the latter being statistically significant when the p-value was less than 0.05 (p < 0.05) [http://home.clara.net/sisa/]. (Cited 21 Aug 2001).

The intensity of dysautonomia in patients with and without sympathetic overactivity, detected by the Holter, and its clinical manifestations were also analyzed in relation to the clinical forms of tetanus. This was carried out through the difference between the means of the standard deviation of the normal R-to-R intervals in the groups studied. The means were calculated by the “Descriptive Statistics” program [http://www.physics.csbsju.edu/stats/descriptive2.html] (cited 22 Aug 2001), and the “Online Analysis of Data” was used for the analysis [http://glass.ed.asu.edu/stats/analysis/]. (Cited 21 Aug 2001).

RESULTS

Thirty-eight patients admitted to the UCI took part in the study, of whom 89.4% were males. Mean age was 37.8 ± 15 years. Twenty-one (55.3%) patients had very severe tetanus, 8 (21%) severe, 7 (18.4%) moderate and 2 (5.3%) mild tetanus.

Table 1 shows the electrocardiographic alterations detected by the Holter, distributed by clinical form of tetanus.

Some patients were found to have more than one type of arrhythmia. Most had simple arrhythmias: 55.2% (21/38) had isolated supraventricular extrasystoles and 39.4% (15/38) had isolated ventricular ones. Others also occurred but in a smaller number of patients: supraventricular extrasystoles in 21% (6/38), tachycardia in 5.2% (2/38), ventricular extrasystoles in 10.5% (4/38) and bigeminism in 5.2% (2/38). Conduction disturbances were also uncommon, being registered in 5.2% (2/38) of patients.
Tables 2 and 3 show the abnormalities of cardiac rhythm in general and specific rhythm disturbances detected by the Holter, according to the severity of the clinical form of tetanus (Table 2) and the presence of sympathetic overactivity on Holter (Table 3). The differences were not statistically significant.

Patients with severe or very severe clinical tetanus (Group B) were twice as likely to have sympathetic overactivity than patients with mild or moderate tetanus (Table 4). However, when comparing just the two categories in group B, even if the sample size is not large enough for the analysis of subgroups, the absence of a significant statistical difference and the confidence interval, which is not wide, suggest that severe tetanus cases have the same chance of developing SO as the very severe. Table 4 also shows the severity of this dysautonomia in relation to the different degrees of severity of tetanus (the SDNN value is inversely proportional to the intensity of sympathetic overactivity). The more severe patients (Group B) had a more intense adrenergic tonus (measured by SDNN values) than patients with a milder form of tetanus (Group A), the latter presenting a SDNN mean compatible with a normal sympathetic modulation (higher than 100 milliseconds). The difference was statistically significant.

The intensity of sympathetic overactivity detected by the Holter was not different between the different groups classified by severity of clinical forms of the tetanus (Table 5). Differences in the SDNN means were not found when comparing patients with sympathetic overactivity detected by Holter and clinical signs with those with no clinical signs (Table 5).
The majority of the patients had the more severe forms of tetanus. The most frequent arrhythmias were isolated supraventricular and ventricular extrasystoles. Sympathetic overactivity was two and a half times more frequent in the more severe cases, but it was also detected in the milder forms of the disease. Half the patients had their sympathetic overactivity detected only by the Holter. There was no association of the arrhythmias with the clinical form of tetanus or with the presence of sympathetic overactivity.

The study design adopted, a case series with internal controls, may limit the inference of our findings. However this design may be very useful in the early stages of the development of knowledge about a particular topic and is justified, in this case, by the rarity or absence of studies on arrhythmias and sympathetic nervous system hyperactivity in the tetanus literature. It should be emphasized that it was not intended, in this stage, to establish a cause and effect relationship, but to detect an association between these electrocardiographic alterations and the severity of tetanus. It should be further explored in more powerful controlled studies.

The function of the autonomous nervous system can be evaluated by heart rate variability analysis (HRV) and can be determined by analysis of time or frequency analysis. This study used the HRV in relation to time, as there is a strong correlation between the variables determined by both methods.

The variable used in this study was the mean of the standard deviation of the HRV from normal R-to-R intervals (SDNN) recorded by the Holter in cases of tetanus with sympathetic overactivity (SO) detected by the Holter, distributed according to the clinical forms of the disease, to the severity of tetanus, and to the presence of clinical manifestations of dysautonomia.

### Table 4

Frequency of sympathetic overactivity (SO) detected by the Holter and mean of standard deviation of HRV from normal R-to-R intervals (SDNN) in 38 cases of tetanus, distributed according to severity of the clinical form of the disease.

<table>
<thead>
<tr>
<th>Clinical forms</th>
<th>With SO</th>
<th>Total of cases</th>
<th>SDNN means</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group B*</td>
<td>25</td>
<td>29</td>
<td>64.1 ± 27.3</td>
</tr>
<tr>
<td>Very severe tetanus</td>
<td>19</td>
<td>21</td>
<td>62.9 ± 29.0</td>
</tr>
<tr>
<td>Severe tetanus</td>
<td>06</td>
<td>08</td>
<td>67.2 ± 24.0</td>
</tr>
<tr>
<td>Group A**</td>
<td>03</td>
<td>09</td>
<td>125.0 ± 69.3</td>
</tr>
<tr>
<td>Total cases</td>
<td>28</td>
<td>38</td>
<td></td>
</tr>
</tbody>
</table>

* Group B: patients with severe and very severe tetanus; ** Group A: patients with mild and moderate tetanus.

### Table 5

Mean of standard deviation of HRV from normal R-to-R intervals (SDNN) recorded by the Holter in cases of tetanus with sympathetic overactivity (SO) detected by the Holter, distributed according to the clinical forms of the disease, to the severity of tetanus, and to the presence of clinical manifestations of dysautonomia.

<table>
<thead>
<tr>
<th>Clinical forms of tetanus</th>
<th>Number of cases</th>
<th>SDNN means</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group B*</td>
<td>25</td>
<td>57.3 ± 18.1</td>
</tr>
<tr>
<td>Very severe tetanus</td>
<td>19</td>
<td>56.5 ± 20.4</td>
</tr>
<tr>
<td>Severe tetanus</td>
<td>06</td>
<td>59.7 ± 8.04</td>
</tr>
<tr>
<td>Group A**</td>
<td>03</td>
<td>66.0 ± 13.1</td>
</tr>
</tbody>
</table>

* Group B: patients with severe and very severe tetanus; ** Group A: patients with mild and moderate tetanus.

### DISCUSSION

The majority of the patients had the more severe forms of tetanus. The most frequent arrhythmias were isolated supraventricular and ventricular extrasystoles. Sympathetic overactivity was two and a half times more frequent in the more severe cases, but it was also detected in the milder forms of the disease. Half the patients had their sympathetic overactivity detected only by the Holter. There was no association of the arrhythmias with the clinical form of tetanus or with the presence of sympathetic overactivity.

The study design adopted, a case series with internal controls, may limit the inference of our findings. However this design may be very useful in the early stages of the development of knowledge about a particular topic and is justified, in this case, by the rarity or absence of studies on arrhythmias and sympathetic nervous system hyperactivity in the tetanus literature. It should be emphasized that it was not intended, in this stage, to establish a cause and effect relationship, but to detect an association between these electrocardiographic alterations and the severity of tetanus. It should be further explored in more powerful controlled studies.

The function of the autonomous nervous system can be evaluated by heart rate variability analysis (HRV) and can be determined by analysis of time or frequency. This study used the HRV in relation to time, as there is a strong correlation between the variables determined by both methods.

The variable used in this study was the mean of the standard deviation of the HRV from normal R-to-R intervals (SDNN), as there is a consensus that the combination of other markers of a 24-h analysis (Holter) is not necessary.

The study showed that patients with severe clinical conditions have nearly two and a half times as much sympathetic overactivity than those with less severe conditions, which is to be expected. However, some with a moderate (28.5%) or even a mild (50%) form of the disease present an increase in sympathetic tonus. In these conditions tetanosamin is probably less implicated in the etiology, while pain, starvation, anxiety, medications (specially curares) and infection may play a major role.

The data also showed that patients with severe tetanus had the same risk of having sympathetic overactivity than the very severe group. This result could be questioned, as there could be a problem of power for the subgroup analysis. However, a relative risk close to one and a narrow confidence interval does not suggest that a larger sample would change this conclusion. This apparent similarity is clinically relevant as the patients with severe tetanus have no indication for treatment of sympathetic overactivity but, as shown by this study, may have this condition with its potentially damaging effects on the cardiovascular system.

The study showed that the intensity of sympathetic overactivity is different between Groups A and B. However when we compared the SDNN means of just those patients who had sympathetic overactivity detected by the Holter, no statistically significant difference was found either between Groups A and B or between the two categories in Group B. Interestingly, there was no difference when we compared the SDNN means of patients who presented clinical sympathetic overactivity with those of patients in whom the condition was detected only by the Holter. In other words, all patients with clinical evidence of sympathetic overactivity had it also detected by the Holter; on the other hand, there were also patients for whom there was no clinical manifestation of dysautonomia but the holter detected sympathetic overactivity and it occurred even in those with mild and moderate forms of tetanus. These results suggest that the intensity of increase in the tonus of the sympathetic nervous system was similar in all groups of patients with this condition, irrespective of the clinical form or the presence of clinical manifestations. If these results are confirmed by other studies with a larger sample it could be suggested that the intensity of the dysautonomia is not the main determinant of the clinical manifestation of adrenergic hyperactivity and that other factors, besides the tetanus...
Hiperatividade simpática e arritmias no tétano: análise eletrocardiográfica

Com os avanços no controle da insuficiência respiratória no tétano, o sistema cardiovascular tem participado de forma crescente na morbidade e mortalidade da doença, mas o conhecimento dessas complicações é escasso. No intuito de detectar arritmias e hiperatividade simpática, o holter de 24 h foi utilizado em 38 pacientes com tétano admitidos numa UTI de doenças infecciosas. O índice SDNN (desvio padrão dos intervalos normais R-a-R), foi útil na detecção do tônus simpático. O presente estudo demonstrou que importantes alterações cardiovasculares, particularmente uma hiperatividade simpática, ocorrem em todas as formas de tétano, mesmo as mais leves. Estas alterações não estão sendo detectadas pelos métodos tradicionais de monitorização em UTI, podendo resultar em falhas na abordagem terapêutica.

REFERENCES


Received: 28 March 2006
Accepted: 4 August 2006