Electrocardiographic criteria for vagotonia—validation with pharmacological parasympathetic blockade in healthy subjects

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Abstract

Background: The importance of vagal tone on cardiac function and cardiovascular mortality is well established. Although the presence of an enhanced cardiac vagal tone (CVT) is frequently diagnosed using the 12-lead resting electrocardiogram (ECG) in daily practice, most of the proposed criteria have been determined on an empirical basis. Our objective was to evaluate the effects of pharmacological blockade of the parasympathetic component of the autonomic nervous system on resting ECG tracings.

Methods: Nine healthy young adults (24±5 year-old) underwent parasympathetic blockade with atropine sulfate i.v. (0.04 mg kg⁻¹) and resting ECGs were obtained before and 15 min thereafter. CVT was assessed by a dimensionless index, which measures the RR interval reduction caused by the vagal withdrawal induced by a 4-s exercise test performed on a cycle ergometer where the subjects pedal as fast as possible with no added resistance.

Results: This index was 1.63±0.24 and 1.03±0.03, before and after atropine, respectively (P<0.0001). Atropine reduced the R–R intervals (P<0.0001), and the amplitude of T-waves in several leads (DII: P=0.03; V4: P=0.04; V5: P=0.03; V6: P=0.01), and abolished the appication of T-waves, J-point and ST-segment elevations (P<0.05), and U-waves (P<0.05), which were present in baseline ECG in all subjects in at least two leads. The R-wave amplitude in leads V4, V5, and V6 (all P≥0.10) was not modified by atropine infusion.

Conclusion: The duration of the R-R intervals and the amplitude of T-waves in leads DII, V4, V5, and V6, and the presence of T-wave appication, U-waves, and elevation of J-point and ST-segment should be used to detect enhanced cardiac vagal tone in healthy subjects.

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1. Introduction

Diminished cardiac vagal tone (CVT), associated with an enhanced sympathetic drive in the presence of induced myocardial ischemia, reduces the ventricular fibrillation threshold, thus facilitating the occurrence of life-threatening arrhythmias [1–3]. On the other hand, enhanced vagal activity produced by pharmacological means [4,5] or by direct electrical neurostimulation [6,7] reduces the occurrence of arrhythmias. In the clinical setting, a preserved CVT is a positive prognostic factor in patients with coronary heart disease [8–10] and with heart failure [11].

In daily cardiology practice, the diagnosis of vagotonia is based on the 12-lead resting electrocardiogram (ECG). However, there has been no study determining the experimental basis for detecting enhanced CVT in the ECG. Actually, a previous study [12] has demonstrated the lack of consensus

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among specialists in electrocardiography and cardiac arrhythmias on the ECG variables to be considered for the diagnosis of vagotonia.

Acute controlled interventions that inhibit the end-organ effects of vagal tone, such as pharmacological blockade, may provide a single opportunity to evaluate the influence of CVT on ECG. In this study, we have analyzed the ECG modifications caused by the pharmacological suppression of CVT by atropine infusion in healthy volunteers.

2. Materials and methods

2.1. Subjects

Asymptomatic healthy young adults (six male; three female; age = 24 ± 5 years old) underwent a pharmacological blockade of the parasympathetic component of autonomic nervous system. All subjects were considered healthy on basis of clinical examination, blood testing (hemogram, biochemistry and electrolytes), maximal exercise testing, and Doppler echocardiogram. Also, none of them had taken any medications in the 7 days preceding the study. All subjects signed an informed consent after detailed explanation of the procedures and potential discomforts. The study had been approved by the Institutional Review Board.

2.2. Procedures

Following a 5-min rest period on the supine position after a 3-h fast, a standard 12-lead ECG was performed, and the subjects sat on a cyclergometer and had the ECG monitored by one single lead (CC5) in order to perform the 4-s exercise test (4-sET), to estimate CVT. In each occasion, two maneuvers were performed, and the highest CVT index (see below) was considered for analysis. The 4-sET is a validated procedure [13,14], which consists in pedaling as fast as possible a cycle ergometer without added resistance (with ‘zero load’), between the fourth and the eighth second of a 12-s long maximal inspiratory apnea. From the ECG tracing (lead CC5), two specific R–R intervals were measured in milliseconds: the one immediately before exercise or the shortest one during exercise. Thus, we obtained a dimensionless index, the CVT index, which reflects the heart rate (HR) response at the onset of the exercise, which mechanism has been demonstrated to correspond predominantly to a vagal withdrawal, without sympathetic influence [13,14]. In addition, this chronotropic response is not changed if an eventual non-voluntary Valsalva maneuver is performed [15]. A CVT index equal to 1.00 indicates the absence of heart rate response and would theoretically correspond to the absence of CVT. This procedure has also been used to evaluate CVT in different experimental approaches [16].

A superficial venous access was then obtained, and parasympathetic blockade was performed with the infusion of atropine sulfate (0.04 mg kg⁻¹) within 5 min [17]. After atropine administration, we performed a resting 12-lead ECG followed by two 4-sET, both repeated at intervals thereafter (5, 15, 30, 60, 90 and 120 min after atropine infusion).

We selected two ECG tracings for analysis: the baseline ECG, performed immediately before venous puncture; and the ECG tracing obtained 15 min after the end of the atropine infusion, occasion in which the CVT index would tend to be 1.00, meaning absence of CVT.

2.3. Data analysis

The following ECG variables were measured (mean of three complexes or waves without interference and with a stable baseline): R-wave amplitude in leads V4 (RV4), V5 (RV5), and V6 (RV6); T-wave amplitude in leads DII (TDII), V4 (TV4), V5 (TV5), and V6 (TV6); sum of the amplitudes of R-waves in leads V4, V5, and V6 (Rtot); sum of the amplitudes of T-waves in leads V4, V5, and V6 (Ttot); duration of R–R interval (R–R), presence of U-waves (U), and presence of ST-segment elevation (STelev). The amplitudes were measured in millimeters, the R–R duration was measured in milliseconds, and the presence of U-waves and STelev was registered as to the number of leads in which these characteristics were observed.

This ECG analysis was performed twice by one of the authors, with a 30-day interval, and the analysis was based on the mean results. The Student paired t-test or the Wilcoxon test for discrete variables was
Table 1
Results of the correlation analyses between the ECG variables and the CVT index, before the venous infusion of atropine sulfate

<table>
<thead>
<tr>
<th>ECG variable</th>
<th>$r$ or $rs$</th>
<th>$P$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RV4</td>
<td>0.70*</td>
<td>0.036</td>
</tr>
<tr>
<td>RV5</td>
<td>0.58</td>
<td>0.104</td>
</tr>
<tr>
<td>RV6</td>
<td>0.52</td>
<td>0.153</td>
</tr>
<tr>
<td>TV4</td>
<td>0.69*</td>
<td>0.040</td>
</tr>
<tr>
<td>TV5</td>
<td>0.70*</td>
<td>0.037</td>
</tr>
<tr>
<td>TV6</td>
<td>0.74*</td>
<td>0.022</td>
</tr>
<tr>
<td>U</td>
<td>0.48</td>
<td>0.191</td>
</tr>
<tr>
<td>R-R</td>
<td>0.81*</td>
<td>0.008</td>
</tr>
<tr>
<td>TDII</td>
<td>0.67*</td>
<td>0.048</td>
</tr>
<tr>
<td>Stelev</td>
<td>0.55</td>
<td>0.125</td>
</tr>
<tr>
<td>Rtot</td>
<td>0.65</td>
<td>0.057</td>
</tr>
<tr>
<td>Ttot</td>
<td>0.74*</td>
<td>0.022</td>
</tr>
</tbody>
</table>

$r$ = Pearson correlation coefficient; $rs$ = Spearman-rank correlation coefficient; * significant correlations.

applied to compare the pre- and post-atropine values. We also calculated the correlation between baseline CVT index values and each of the variables of baseline ECG with the Pearson or the Spearman-Rank procedure, when appropriate. A 5% probability level was accepted for statistical significance.

Table 2
Values of the ECG variables before (PRE) and after (POST) the venous infusion of atropine sulfate

<table>
<thead>
<tr>
<th>ECG variable</th>
<th>PRE</th>
<th>POST</th>
<th>$P$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RV4</td>
<td>17.0±2.6</td>
<td>17.3±2.9</td>
<td>0.781</td>
</tr>
<tr>
<td>RV5</td>
<td>16.2±2.3</td>
<td>15.0±2.3</td>
<td>0.098</td>
</tr>
<tr>
<td>RV6</td>
<td>12.0±1.3</td>
<td>11.2±1.3</td>
<td>0.097</td>
</tr>
<tr>
<td>TV4</td>
<td>5.6±0.9</td>
<td>4.1±0.7*</td>
<td>0.040</td>
</tr>
<tr>
<td>TV5</td>
<td>5.0±1.0</td>
<td>3.1±0.5*</td>
<td>0.027</td>
</tr>
<tr>
<td>TV6</td>
<td>3.7±0.6</td>
<td>2.2±0.4*</td>
<td>0.010</td>
</tr>
<tr>
<td>U</td>
<td>5±1</td>
<td>0±0*</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>R-R</td>
<td>1070±73</td>
<td>487±40*</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>TDII</td>
<td>3.2±0.3</td>
<td>1.8±0.2*</td>
<td>0.003</td>
</tr>
<tr>
<td>Stelev</td>
<td>3±1</td>
<td>0±0*</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Rtot</td>
<td>45.2±5.9</td>
<td>43.4±6.2</td>
<td>0.372</td>
</tr>
<tr>
<td>Ttot</td>
<td>14.3±2.3</td>
<td>9.5±1.6*</td>
<td>0.015</td>
</tr>
</tbody>
</table>

RV4, R-wave amplitude in lead V4; RV5, R-wave amplitude in lead V5; RV6, R-wave amplitude in lead V6; TV4, T-wave amplitude in lead V4; TV5, T-wave amplitude in lead V5; TV6, T-wave amplitude in lead V6; U, presence of U-waves; R-R, R–R interval duration, em milliseconds; TDII, T-wave amplitude in lead DII; Stelev, presence of ST-segment elevation; Rtot, sum of the R-wave amplitudes in leads V4, V5, and V6; Ttot, sum of the T-wave amplitudes in leads V4, V5, and V6. The amplitudes were measured in millimeters and the presence of U-waves and Stelev were registered as to the number of leads where the characteristic was present. Values are mean±standard error. * Significant differences vs. PRE.

3. Results

The atropine infusions were performed without any unexpected complication. All subjects reported dry mouth and mild visual disturbances after atropine infusion. However, no subject reported a major discomfort that would cause the interruption of the procedure. All symptoms were absent 6 h after the onset of the procedure.

As expected and according to previously published results [13,14], the results of the CVT index tended to 1.00 in the 4-sET performed 15 min after atropine administration (mean and S.D.: 1.03±0.03), with values differing from baseline (1.63±0.24; $P<0.0001$). Table 1 shows the results of the linear correlation analysis between CVT measures and ECG variables and Table 2 shows the ECG variables and the respective levels of probability.

4. Discussion

In the present study, the selective pharmacological parasympathetic blockade was produced to determine how the presence of this component influences the resting ECG. The results demonstrate a significant reduction in the R–R interval; a reduction in T-wave amplitude in leads DII, V4, V5, and V6; and the consistent disappearance of U-waves, and ST-segment elevations. In the baseline ECG we also observed a significant association between CVT index and the following ECG variables: amplitude of R-waves in lead V4; amplitude of T-waves in leads DII, V4, V5, and V6; and the R–R interval; with the exception of R-waves in lead V4, the same variables were significantly modified with the parasympathetic blockade.

The internal control of the study was the use of the 4-sET to evaluate CVT. It has been shown that CVT index reflects CVT without any measurable sympathetic influence [13,14]. Our data confirm this concept, since the acceleration of the HR with dynamic exercise was abolished in the subjects after atropine infusion.

CVT has been also studied extensively by different measures of HR variability, which carries prognostic value in coronary artery disease [18] and in heart failure patients [19]. Wennerblom et al. [20] has
investigated a particular aspect of HR variability, the rate and velocity of change in HR during Holter 24-h recordings, as a measure of vagal withdrawal and sympathetic activation.

The CVT index used in the present study is analogous to this strategy as it also measures the HR increase caused by vagal withdrawal [13,14]. Although HR variability has been used to assess CVT, there are many controversial issues to be resolved, related to methodological aspects as well as to physiological interpretations [21]. Therefore, there is still a place for determination of CVT by means of simple, low-cost, widely available and established methods, such as the standard ECG.

An important methodological concept in the present study is the use of pharmacological blockade to study the ECG changes. This strategy must consider the theoretical features of Rosenblueth and Simeone model [22], which validity depends on a series of factors: first, on its applicability in humans, because it was proposed from experimental studies on cats. This evaluation is sometimes difficult, since various studies performed pharmacological blockade in anesthetized animals, and it is known that anesthesia modifies the activity of the parasympathetic component [23]. Second, the doses of atropine sulfate must block completely the parasympathetic component of the autonomic nervous system. Third, it is assumed that the blockade of one component does not interfere with the activity of the other one.

The dose of atropine sulfate was the same as suggested by Jose [17], and further demonstrated by Jose and Taylor [24] as adequate to promote a complete blockade of the parasympathetic efference to the heart. This dose—and even lower doses of atropine—have been frequently used in studies on HR control by autonomic nervous system [25–30].

Another methodological issue refers to the pharmacokinetics of the autonomic blocking agent we employed. It has been demonstrated that 2–3 min after the atropine infusion the HR reaches a stable value [17,24]. Maciel et al. [31] demonstrated that the dose of 0.04 mg kg⁻¹ was enough to completely block, for 1 h, the acceleration of the HR induced by a static upper limbs exercise of maximal intensity, sustained by 10 s. Although the authors have employed an inhibitory parasympathetic stimulus, we have no reason to believe that during this study there has been an attenuation of the parasympathetic blocking capacity of atropine in the 15 min after the end of venous infusion. Actually, the CVT index values tended to 1.00, 5 min after the end of atropine infusion, and thus continued until 90 min after the infusion. Therefore, the moment we decided to analyze the ECG seemed adequate. Nevertheless, even considering the dose and the duration of atropine action, it is not possible to warrant a complete blocking effect, because atropine sulfate is a competitive blocking agent. From a pharmacological point of view, the competitive inhibitors only reduce the possibility of the natural agonist to interact with the receptor in the cell membrane, but once there is a determined concentration of the natural agonist in the synapses, one cannot discard the possibility of some degree of post-synaptic stimulation [32].

In spite of these difficulties, atropine sulfate produces definite effects on parasympathetic activity and on sinus node, and its use as a single agent is still the best non-invasive method to study the parasympathetic control on HR [33], on the heart, and consequently on ECG. Even considering the number of factors that interfere on the heart electrical activity, and influence its surface ECG registration, we found in this study some considerably consistent data.

First, we observed a consistent and somewhat presumable reduction of the R–R intervals. This finding is according to the literature [34], and to a previous study from our group [12] that pointed out sinus bradycardia as the preferred criterion by specialists in electrocardiography and cardiac arrhythmias.

The lack of consistent modifications on R-waves in leads V4, V5, and V6 is not surprising, as a number of cardiac and extra-cardiac factors influence their amplitude. Although a significant association between the CVT index and RV4 has been observed, we have not observed consistent changes in R-waves amplitudes with the parasympathetic blockade. In fact, the behavior of the R-waves was inconsistent: the RV4 was taller in six subjects and lower in three; the RV5 was taller in three subjects and lower in six; and the RV6 was taller in three subjects, lower in five, and remained unmodified in one. These data suggest that other uncontrolled factors may be responsible for these variations.

A relevant finding was the consistent reduction of
T-waves in leads DII, V4, V5, and V6, that was observed in eight of the nine subjects. Another interesting observation was the consistent disappearance of the appication of T-waves in all subjects who had the T-waves with this characteristic. Also, T-wave amplitude in these leads had a significant association with CVT index. This is also in accordance with the literature [34–36], that empirically consider tall and peaked T-waves as a criterion for vagotonia.

Seven subjects had a J-point elevation with at least 0.1 mV of amplitude, accompanied by a ST-segment elevation with superior concavity, in at least 2 leads. This pattern completely disappeared in six of the seven subjects (83%), having remained in only one lead of the seventh subject, who presented this pattern in 6 leads in the baseline tracing.

All subjects presented U-waves in the baseline ECG in at least 2 leads, and the subject with the higher CVT indexes had U-waves in eight leads. The U waves consistently disappeared in all subjects, in all leads, with the atropine infusion. In the ECG tracings after atropine infusion, one may observe the horizontal T–P interval showing very clearly the absence of the U-wave where it was present before.

The present results should be interpreted in light of some limitations. This study cannot distinguish if these changes were consequence of the CVT blockade; if they were consequence of the HR acceleration that accompanied the CVT suppression; or if they were due to both. The CVT reduction is generally accompanied by HR acceleration, as in the situation of the pharmacological blockade performed in this study, and in the physiological situation observed during dynamic exercise, with a concomitant stimulation of the sympathetic tone. In physiological situations, these two phenomena are tightly connected. Experimentally, even the induction of a HR acceleration with a pacemaker, without any type of autonomic handling or without any type of dynamic or static exercise, would not warrant that the efferent impulses of the parasympathetic component to the heart would be unchanged. An experimental study, in unanesthetized animals, inducing HR acceleration with a pacemaker, with the monitoring of the efference by parasympathetic and sympathetic nerves to the heart could elucidate this question. Even with these limitations, our approach seemed to be the most appropriate strategy so far to study the influences of CVT in the resting ECG.

In conclusion, the blockade of cardiac vagal tone reduced the R–R intervals and the amplitude of T-waves in leads DII, V4, V5, and V6, with disappearance of T-wave appiculation, J-point and ST-segment elevations, and U-waves, suggesting that these criteria should be used to detect vagotonia on the ECG.

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