Modulation of QT Interval During Autonomic Nervous System Blockade in Humans

André Diedrich, MD, PhD; Jens Jordan, MD; John R. Shannon, MD; David Robertson, MD; Italo Biaggioni, MD

Background—It is thought that the autonomic nervous system modulates QT interval, but traditional autonomic blockade combining propranolol and atropine has produced conflicting results. We used the alternative approach of interrupting neurotransmission at the level of autonomic ganglia to determine its effect on the QT interval.

Methods and Results—We infused trimethaphan at increasing doses (0.5 to 10 mg/min IV) while monitoring heart rate, heart rate variability spectra, QT interval, and blood pressure in 10 normal volunteers, 9 patients with multiple system atrophy (MSA), and 8 patients with pure autonomic failure (PAF). The QT interval was corrected for heart rate using Bazett’s formula (QTc). Patients with PAF had very low heart rate variability and a prolonged QTc at baseline (465±8 ms) compared with patients with MSA (448±6 ms) and normal subjects (432±6 ms). In normal subjects, trimethaphan dose-dependently prolonged QTc (to 469±7 ms), decreased RR interval (995±45 to 670±35 ms), and abolished heart rate variability. In MSA patients, trimethaphan also prolonged QTc (to 463±7 ms) and reduced heart rate variability but did not significantly change RR interval (from 813±38 to 801±39).

Conclusions—Autonomic blockade prolongs QT interval in normal subjects to a similar duration as in PAF patients. Furthermore, blocking residual autonomic tone in PAF patients is associated with a further increase in QT interval length. Patients with MSA have greater residual sympathetic tone and greater prolongation of the QT interval during ganglionic blockade than PAF patients. (Circulation. 2002;106:2238-2243.)

Key Words: nervous system, autonomic ■ trimethaphan ■ spectrum analysis

Increased duration of the QT interval on the surface ECG is associated with increased mortality in patients with cardiac disease\(^1\) and in apparently healthy populations.\(^2,3\) Accordingly, determination of QT interval length in the surface ECG corrected for heart rate (QTc) is commonly used for risk stratification in clinical studies. The QT interval reflects depolarization and repolarization of myocardial cells. Factors that augment depolarization or delay repolarization of myocardial cells can increase QT interval length. Genetic factors\(^4\) and nongenetic factors such as electrolyte disturbances and drugs\(^5\) influence the QTc. There is indirect evidence that autonomic nervous system activity also influences QTc. QTc is prolonged in patients with diabetic autonomic neuropathy\(^6\) and in patients with familial dysautonomia.\(^7\) Similarly, QTc is increased in patients with primary autonomic failure due to pure autonomic failure (PAF) or multiple system atrophy (MSA).\(^8\) However, studies using pharmacological blockade of \(\beta\)-adrenergic receptors alone or in combination with atropine have not consistently shown a similar increase in QT interval length.\(^9\)-\(^10\) The difference between chronic autonomic failure and acute pharmacological blockade might suggest that short-term loss of autonomic input is not sufficient to increase QT interval duration. An alternative explanation for the phenomenon is that pathways that are not affected by blockade of muscarinic receptors or \(\beta\)-adrenergic receptors, such as \(\alpha\)-adrenergic receptors, or cotransmitter release are important in QT interval prolongation.

Blockade of autonomic ganglia using the \(N\nabla\)-cholinergic antagonist trimethaphan may provide a better approach to assess the contribution of the autonomic nervous system\(^11\) because trimethaphan interrupts sympathetic and parasympathetic nerve traffic to postganglionic autonomic neurons, thus decreasing neurotransmitter release.\(^12\) In the present study, we tested the hypothesis that interrupting sympathetic and parasympathetic nerve traffic by ganglionic blockade results in QTc prolongation. For this purpose, we studied 3 groups of subjects: healthy young volunteers, patients with autonomic failure with MSA (Shy-Drager syndrome) who have residual sympathetic tone, and patients with PAF who have very low sympathetic tone.\(^13\) We used spectral analysis of heart rate interval to quantify autonomic input to the heart in the different patient populations and in response to ganglionic blockade. We reasoned that if autonomic function modulates QT interval, then baseline QT interval would be prolonged in...
PAF patients, and removal of autonomic activity with trimethaphan would prolong QT interval in healthy individuals and in MSA patients to levels found in PAF patients.

Methods

Study Subjects
We studied a total of 27 subjects: 9 had MSA (4 men and 5 women aged 67±2 years with a body mass index of 25.0±0.4 kg/m²), 8 had PAF (2 men and 6 women aged 70±4 years with a body mass index of 23.4±1.0 kg/m²), and 10 were healthy volunteers (6 men and 4 women aged 27±2 years with a body mass index of 23.3±1.0 kg/m²). Criteria used in the diagnosis of MSA and PAF have been reported previously.13 In short, patients with PAF have profound orthostatic hypotension and severely impaired autonomic reflexes with a very low sinus arrhythmia ratio, low heart rate response to the Valsalva maneuver, exaggerated blood pressure decrease during phase II of Valsalva, and an absence of blood pressure overshoot during phase IV. No other neurological features are present. Patients with MSA, in addition to autonomic impairment, have Parkinsonism or cerebellar signs.14 Written, informed consent was obtained before study entry. All studies were approved by the institutional review board.

Protocol
Patients were admitted to the General Clinical Research Center at Vanderbilt University Medical Center. Vasoactive medications and fludrocortisone were discontinued for at least 5 half-lives before testing. Three days before the study, patients and control subjects were placed on a 150-mEq sodium and 70-mEq potassium diet, free of substances that could interfere with catecholamine determinations. Studies were conducted at least 2.5 hours after breakfast or lunch. Baseline measurements of heart rate and blood pressure were taken after the subject had been supine for at least 20 minutes. Then, ganglionic blockade was induced by a continuous infusion of trimethaphan (trimethaphan camsylate, Cambridge Laboratories). The infusion was begun at 0.5 or 1 mg/min and increased at 6-minute intervals. The infusion rate was increased until one of the following endpoints was reached: symptoms of excessive hypotension, no further decrease in blood pressure with increased infusion rates, or an infusion rate of 12 mg/min. In control subjects, the completeness of the blockade was assessed by bolus application of phenylephrine. We defined complete ganglionic blockade as a <1 bpm decrease in heart rate with an increase in systolic blood pressure of 25 mm Hg. Blood samples were obtained at baseline and at the end of the trimethaphan infusion from an antecubital heparin lock placed at least 30 minutes before the first blood draw. Plasma was analyzed for catecholamines by a modification of a high-pressure liquid chromatographic method previously described.15

Data Acquisition
The ECG lead II, where the U-waves are less prominent and the T-wave is often best seen, was chosen for recording. The surface ECG was amplified, and no additional filters were applied (Gould). Blood pressure was measured either by intraarterial or by volume-clamp plethysmography (Finapres, Ohmeda). Brachial blood pressure was measured manually at 1-minute intervals. The biological signals were digitized with 14-bit resolution and 500-Hz sample frequency and recorded using the WINDAQ data acquisition system (DATAQ). Data were analyzed off-line with a customized program for data analysis (PHYSIOWAVE by André Diedrich, MD, PhD, Nashville, Tenn), which was written in PV-Wave (VNI).

QT Measurements
QT measurements were visually verified using a waveform browser program (DATAQ) on a high-resolution monitor. The QT interval was averaged over 1 minute using segments uninterrupted by arrhythmias, and it was corrected for heart rate using Bazett’s formula.16

Heart Rate Variability
A QRS detection algorithm17 was used to generate beat-to-beat values. The nonequidistant event time series of RR intervals was interpolated, low-pass filtered (cutoff 2 Hz), and resampled at 4 Hz. Power-spectral density was estimated using the Welch method.18 Intervals of 128 seconds were detrended by linear regression method. The Hanning window was applied before estimation of the power spectral density. The power in the frequency ranges for low frequencies (0.04 to <0.15 Hz) and high frequencies (0.15 to <0.40 Hz) was calculated for each interval.19 The ratio between low and high frequencies was determined.

Statistics
All data are expressed as mean±SEM. Intraindividual and interindividual differences were analyzed by unpaired t tests. When appropriate, ANOVA testing or a nonparametric test for repeated measurements was used. P<0.05 was considered statistically significant.

Results

Clinical Characteristics
PAF and MSA patients exhibited profound orthostatic hypotension, with a fall in systolic blood pressure of 99±12 and 86±12 mm Hg, respectively. This was associated with a modest increase in heart rate (15±1 and 15±4 bpm, respectively), which was inadequate considering the profound decrease in blood pressure. In both groups, respiratory sinus arrhythmia was markedly attenuated, blood pressure decreased profoundly during phase II of the Valsalva maneuver, and the blood pressure overshoot during phase IV was markedly reduced or absent. The Valsalva heart rate ratio was reduced in both groups. These findings are consistent with severe parasympathetic and sympathetic dysfunction in both groups of patients. Supine blood pressure was elevated in both groups of patients with autonomic failure; supine hypertension is a recognized complication of this disorder.20 No differences in serum potassium levels were found between PAF patients, MSA patients, and normal volunteers (4.25±0.13, 4.15±0.09, and 4.45±0.16 mEq/L, respectively).

Hemodynamic Effects of Ganglionic Blockade
Control subjects had a moderate decrease in blood pressure with the incremental infusion of trimethaphan (Figure 1 and Table). In contrast, MSA patients had a profound depressor response to relatively low infusion rates of trimethaphan (Figure 1 and Table). Even though much larger trimethaphan doses were used, PAF patients exhibited a smaller depressor response to trimethaphan than MSA patients. Some PAF patients did not respond at all to trimethaphan. At baseline, the RR interval was shorter in MSA patients than in control subjects (P<0.05; Figure 1 and Table). A similar trend was observed for RR interval in PAF patients. RR interval decreased in control subjects during trimethaphan, but it did not change in PAF or MSA patients (Figure 1 and Table).

Heart Rate Variability
Data on heart rate variability at baseline and during ganglionic blockade in control subjects and in MSA and PAF patients are given in the Table. Heart rate variability could be analyzed in only 4 PAF patients because of frequent atrial and
ventricular premature beats, an abnormality that was not observed in MSA patients. Resting heart rate variability was markedly reduced in patients with MSA and PAF compared with control subjects (P<0.01 for the low frequency component and P<0.05 for the high frequency component). In control subjects, incremental trimethaphan infusion caused a progressive decrease in the low frequency component (P<0.001) and in the high frequency component (P<0.001) of heart rate variability to values as low as those seen in severe autonomic failure (Figure 2). Although baseline heart rate variability was low in MSA patients, trimethaphan elicited a further reduction (P<0.01 for both low frequency and high frequency RR variability; Figure 2). This effect was less pronounced in PAF patients (P<0.05 for low frequency RR variability, P=NS for high frequency RR variability; Figure 2).

Plasma Catecholamines
Before trimethaphan infusion, plasma norepinephrine concentration was significantly lower in PAF patients than in MSA patients or in control subjects. With trimethaphan infusion, plasma norepinephrine concentration decreased in all 3 groups (Table).

### Baseline Characteristics and Response to Ganglionic Blockade

<table>
<thead>
<tr>
<th></th>
<th>PAF</th>
<th>MSA</th>
<th>Controls</th>
<th>PAF (8 mg/min)</th>
<th>MSA (2 mg/min)</th>
<th>Controls (8 mg/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Systolic BP, mm Hg</td>
<td>186±6</td>
<td>203±9</td>
<td>134±4</td>
<td>157±7</td>
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<td>101±5</td>
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<td>Diastolic BP, mm Hg</td>
<td>82±8</td>
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<td>69±2</td>
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<tr>
<td>Heart rate, bpm</td>
<td>69±3</td>
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<td>69±3</td>
<td>76±4</td>
<td>91±4</td>
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<tr>
<td>RR interval, ms</td>
<td>883±38</td>
<td>813±38</td>
<td>995±45</td>
<td>878±31</td>
<td>801±39</td>
<td>670±35</td>
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<td>QT interval, ms</td>
<td>437±13</td>
<td>404±12</td>
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<td>444±10</td>
<td>414±14</td>
<td>383±8</td>
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<td>QTc, ms</td>
<td>465±8</td>
<td>448±6</td>
<td>432±3</td>
<td>475±9</td>
<td>463±7</td>
<td>469±7</td>
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<tr>
<td>LF RRI, ms²</td>
<td>11±1.3</td>
<td>59±26</td>
<td>480±65</td>
<td>2.1±1.7</td>
<td>4.3±0.9</td>
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<tr>
<td>HF RRI, ms²</td>
<td>22±5.4</td>
<td>30±12</td>
<td>674±186</td>
<td>14±5.4</td>
<td>9.1±3.4</td>
<td>2.9±0.92</td>
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<tr>
<td>LF:HF ratio</td>
<td>0.60±0.10</td>
<td>2.1±0.78</td>
<td>1.4±0.41</td>
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<tr>
<td>Plasma NE, nmol/L</td>
<td>138±43</td>
<td>363±55</td>
<td>180±16</td>
<td>44±18</td>
<td>191±56</td>
<td>100±23</td>
</tr>
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</table>

**Catecholamine measurements, vital signs, and heart rate variability at baseline and during ganglionic blockade with trimethaphan in PAF patients (n=8; n=4 for spectral results), MSA patients (n=9), and control subjects (n=10). Values are mean±SEM. BP indicates blood pressure; NE, norepinephrine, HF RRI, RR interval variability in the high frequency range; LF RRI, RR interval variability in the low frequency range; LF:HF ratio, ratio between RR variability in the low frequency range and RR variability in the high frequency range.**
Baseline QTc was prolonged in PAF patients and in MSA patients compared with control subjects (P<0.05, Figure 3, top, and Table). Trimethaphan produced a dose-dependent increase in QTc in normal subjects (P<0.001 by ANOVA; Figure 3, bottom, and Table). The uncorrected QT interval duration actually decreased with ganglionic blockade due to the decrease in RR interval. QTc also increased moderately in MSA patients in response to ganglionic blockade (P<0.001). In these patients, QTc prolongation was observed in the absence of a significant change in RR interval. In PAF patients, trimethaphan elicited a small but significant change in QTc (P<0.01). When we plotted QTc changes during ganglionic blockade against changes in heart rate variability, we found a significant nonlinear correlation between these parameters in patients and in control subjects (Figure 4).

**Discussion**

We used 3 novel and complementary approaches to examine the potential modulation of QTc interval by the autonomic nervous system. First, we studied patients with different degrees of postganglionic autonomic impairment. Second, we induced ganglionic blockade with trimethaphan to produce a gradual reduction in autonomic input to the heart. Third, we used spectral analysis of heart rate interval to quantify cardiac autonomic tone and assess its relationship with the QT interval. We found that patients with PAF, who are characterized by very low sympathetic tone, exhibited a prolonged QTc that was accompanied by markedly reduced heart rate variability in both the high and low frequency components. Autonomic blockade with trimethaphan reduced heart rate variability in MSA patients with residual sympathetic tone and in normal subjects, and this was associated with a gradual prolongation of QTc to levels observed in PAF patients. Taken together, these results provide strong evidence for modulation of ventricular repolarization by the autonomic nervous system in humans.

It is important to consider the underlying pathophysiology of these different forms of autonomic failure in the interpretation of our results. In MSA, the lesion resides within the central nervous system and involves the neural connections responsible for baroreflex modulation of autonomic tone. However, the neurons that tonically discharge sympathetic activity (eg, those residing in the rostral ventrolateral medulla or in the spinal cord) and efferent pathways distal to these centers (eg, spinal tracts and postganglionic noradrenergic fibers) seem to be conserved in MSA. Accordingly, MSA patients have normal or only slightly reduced supine plasma norepinephrine concentrations and intact noradrenergic innervation to the heart. They are not able, however, to engage and modulate sympathetic tone as required, thus they lack the ability to maintain orthostatic hemodynamics. In PAF patients, the neural damage involves more distal structures compared with MSA. The sympathetic tracts in the intermediolateral column of the spinal cord and postganglionic noradrenergic fibers are lost. This state of affairs is
evidenced by the very low plasma norepinephrine levels found in these patients.\(^{15,21}\) Profoundly reduced norepinephrine release from noradrenergic nerve terminals.\(^{24}\) and the lack of fluorodopa uptake by the heart.\(^{22}\) The difference in cardiac autonomic innervation explains the greater heart rate variability and shorter QTc observed in MSA compared with PAF patients.

The differences in heart rate variability and QTc interval between patient groups and normal volunteers were removed by trimethaphan, with convergence of QTc interval to PAF levels (“intrinsic QT interval”). The dose of trimethaphan used in this study leads to an almost complete loss of sympathetic and parasympathetic function\(^{11}\) by blocking \(\text{N}_\text{cholinergic receptors in autonomic ganglia. This is demonstrated by a decrease in plasma norepinephrine concentration to levels as low as those seen in patients with severe PAF.}\(^{11}\) Furthermore, trimethaphan abolishes muscle sympathetic nerve activity even during nitroprusside injections.\(^{20,25}\) QTc increased progressively with an incremental infusion of trimethaphan in healthy subjects. In the present study, we complemented these findings by showing a dose-dependent decrease in the spectral power of the high and low frequency components of heart rate modulation. The association of progressive loss of autonomic function and prolongation in QTc strongly supports the hypothesis that autonomic innervation of the heart contributes to the regulation of QT interval length.

Previous studies on autonomic regulation of QT interval length have yielded conflicting results. Supportive studies have found that QT interval length is longer during sleep, when sympathetic tone is low, than during wakefulness\(^{26}\) and that parasympathetic blockade with atropine increases QTc.\(^{27}\) In contrast, in studies using atrial pacing to keep heart rate at a constant level, \(\beta\)-blockade alone or in combination with atropine did not result in prolongation of the QTc interval.\(^{10,27-28}\) suggesting that results obtained by atropine were confounded by heart rate changes. In the present study, trimethaphan prolonged QTc in MSA patients, in whom heart rate interval did not change. This clearly indicates that autonomic withdrawal prolongs QTc even in the absence of heart rate changes. One possible explanation for the discrepancy with previous studies is that atrial pacing may have an unphysiological effect on cardiac autonomic tone and repolarization.

Responses to trimethaphan may differ from those obtained by the commonly used “autonomic blockade” that combines atropine and a \(\beta\)-blocker. This traditional approach only decreases stimulation of cardiac \(\beta\)-adrenergic and muscarinic cholinergic receptors and does not prevent the activation of reflex mechanisms in response to these changes. In contrast, trimethaphan also decreases the stimulation of cardiac \(\alpha\)-adrenoreceptors and eliminates baroreflex-mediated mechanisms. By interrupting neuronal traffic, it also decreases the release of cotransmitters (eg, ATP and neuropeptide \(Y\)) from autonomic neurons. The contribution of the latter to the modulation of QT interval is not known.

We cannot completely exclude the possibility that trimethaphan has some direct effect on the myocardium that leads to prolongation of the QT interval. In vitro studies have shown that trimethaphan at high concentrations has a direct vasodilatory effect and at even higher doses blocks \(\alpha\)-adrenoreceptors.\(^{29,30}\) However, it has been estimated that the concentration of trimethaphan that is required to achieve ganglionic blockade is \(\approx 10\) to 100 times smaller than the concentrations needed for direct vasodilation and blockade of \(\alpha\)-adrenoreceptors.\(^{29}\) Further evidence against a direct effect of trimethaphan on the myocardium is that QTc did not change in patients with severe PAF, even with high doses of trimethaphan, arguing against a direct effect of the drug unrelated to autonomic blockade.

QT duration also depends on heart rate. A potential limitation of our study is that we assumed that the relation between QT interval and heart rate is the same in patients versus controls and that the Bazette correction appropriately takes into account this relation. We used the Bazette correction because previous studies have shown that QTc, calculated in this manner, is a predictor of cardiovascular mortality, indicating the clinical usefulness of this measurement. Also, ganglionic blockade prolonged QT interval significantly in PAF and MSA patients without changing heart rate, implicating that the changes in QT interval were caused by the elimination of residual cardiac autonomic tone and not by heart rate changes. One possible implication of this study is that PAF patients with nearly complete loss of autonomic function might represent an ideal opportunity to study the effect of medications on QT interval duration. In these unique patients, the direct effects of medications on the myocardium are not confounded by reflex-mediated changes in sympathetic and parasympathetic tone or in changes in heart rate. Similarly, ganglionic blockade with trimethaphan can be used to study the direct effects of drugs in normal subjects in the absence of autonomic modulation.

We used spectral analysis of heart rate as a surrogate to quantify the effect of trimethaphan on cardiac autonomic tone. It should be noted, however, that this technique only reflects autonomic tone to the sinus node and not to ventricular tissue. Previous studies have shown that MSA patients have greater residual sympathetic tone to the vasculature\(^{13}\) and to the ventricles\(^{22}\) compared with PAF patients. Our results also suggest that MSA patients have greater parasympathetic than sympathetic impairment to the sinus node, because high frequency heart rate variability was already very low at baseline and changed little with trimethaphan. In support of this interpretation, resting heart rate, which depends mostly on parasympathetic tone, did not increase significantly during trimethaphan in MSA patients. In contrast, low frequency variation of heart rate was not as impaired in MSA as in PAF patients, and it decreased significantly with trimethaphan. This implies that low frequency heart rate variability does reflect autonomic function to the sinus node and that sympathetic tone contributes to this index more than to high frequency heart rate variability.

We conclude that in healthy subjects, interruption of sympathetic and parasympathetic nerve traffic by the ganglionic blocker trimethaphan causes prolongation of the QT interval to a similar duration as previously observed in PAF patients. Furthermore, blockade of residual autonomic tone in PAF patients is associated with a further increase in QT
interval length. Patients with MSA have greater residual autonomic tone and greater prolongation of the QT interval during ganglionic blockade than PAF patients.

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References
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