Effect of Increased Adrenergic Activity on the Relationship Between Electrical and Mechanical Systole

HARISIOS BOUDOULAS, M.D., PARASHOS GELERIS, M.D., RICHARD P. LEWIS, M.D., AND CARL V. LEIER, M.D.

SUMMARY The effect of catecholamines and atrial pacing on the relationship between electrical systole (QT) and mechanical systole (QS₂) was studied in 12 normal subjects and in 32 patients. The studied subjects were divided into three groups. Group 1 included 12 normal subjects in whom serial isoproterenol infusions were performed before and after oral propranolol administration, 160 mg daily for 2 days. During the 24-hour control period, the QT was always shorter than the QS₂ (from 14 ± 3 to 19 ± 4 msec, p < 0.01), while during isoproterenol infusion the QT was always greater than the QS₂ (from 28 ± 5 to 34 ± 5 msec, p < 0.01). Group 2 included 26 patients in whom 24-hour urinary epinephrine (E) and norepinephrine (NE) were measured the same day as systolic time interval measurements. The E + NE was higher in patients in whom the QT was longer than the QS₂ (107 ± 9 vs 61 ± 7 μg/24 hours, p < 0.05). Group 3 included six patients in whom the heart rate was increased with atrial pacing, from 80 to 130 beats/min. The QT was always shorter than the QS₂ (from 13 ± 3 to 24 ± 5 msec, p < 0.01).

Adrenergic stimulation results in a relative prolongation of the QT with the QS₂ shortening and the QT remaining unaffected. The QT is normally shorter than the QS₂, so the duration of QT should always be considered in relationship to the duration of QS₂. Finally, a reversal of the normal QT-QS₂ relationship may provide a simple index of increased adrenergic activity.

OVER the physiologic range of heart rate, a linear relationship exists between electrical systole (QT) and heart rate. The QT is slightly shorter but parallels the duration of mechanical systole (QS₂) obtained from the systolic time intervals. The effect of pharmacologic agents and/or other interventions on the duration of the QS₂ and QT has been studied previously. However, the effect of these interventions on the relationship between QT and QS₂ has not been studied.

The present study was undertaken to define the effect of adrenergic stimulation and atrial pacing on the relationship between QS₂ and QT.

Materials and Methods

Twelve normal volunteers and 32 patients were studied. The studied subjects were divided into three groups.

Group 1 consisted of 12 normal male volunteers, 19–28 years of age, who weighed 60–79 kg. None of the volunteers were taking any medications. Their physical examination, ECGs, routine laboratory studies, chest x-rays, systolic time intervals and echocardiograms were normal. The subjects were admitted to the Clinical Research Center to standardize environmental stimulation throughout the study. Written informed consent was obtained. A control study with serial isoproterenol infusions alone was performed initially. Systolic time intervals were recorded before and during isoproterenol infusion (2 μg/min) lasting 10 minutes and performed at 0, 1, 2, 4, 6, 8, 12, 15 and 24 hours. This dose of isoproterenol was based on a previous study in which 2 μg/min provided a maximal inotropic and near-maximal chronotropic stimulus. By serial measurements it was established that a steady state was reached after 6 minutes of isoproterenol infusion. A constant i.v. infusion line was used throughout the study.

After the isoproterenol infusion control period, propranolol was administered orally at a dose of 40 mg every 6 hours for a total of eight doses. Systolic time intervals were recorded 2 and 24 hours after the last dose of propranolol before and during the isoproterenol infusion period. In six of the subjects, systolic time interval measurements before and during isoproterenol infusion were also performed at 36, 48 and 60 hours after the last dose of propranolol.

Systolic time intervals were measured as previously described. From the systolic time intervals the durations of QT and total electromechanical systole (QS₂) were calculated. A lead that best illustrated the beginning of QRS and the end of the T wave was used. For each subject the same lead was used throughout the study. The QS₂ interval was measured from the onset of ventricular depolarization to the first high-frequency vibration of the aortic component of the second heart sound (fig. 1). The QT interval was measured from the beginning of the Q wave to the end of the T wave. When the end of T wave was not precise (very rarely), the end of the T was taken at the point

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where a line of most rapid descent of the T wave transected the baseline.\textsuperscript{15, 16} At least 10 cardiac cycles were averaged to obtain the QS\textsubscript{2} and the QT intervals.

The QT interval is approximately equal to the duration of the intracellular action potential. The QS\textsubscript{2} interval consists of the duration of the electromechanical delay (Q wave to the onset of the left ventricular pressure), isovolumic contraction time and left ventricular ejection time and ends with the first high-frequency vibration of the aortic component of the second heart sound. The exact time at which the mechanical systole ends has never been defined. The end of ejection is an arbitrary point that defines the end of systole. Theoretically, total systolic time should also include the relaxation time, which ends after the second heart sound when the mitral valve opens (D point of the echocardiograph, figure 1). However, both biochemical systole and muscular contraction end before the second heart sound. In the absence of knowing the true end point of systole, we have selected the QS\textsubscript{2} interval because of its ease of measurement and the large body of preexisting data, where the QS\textsubscript{2} has been used to define the duration of systole.

The blood pressure was measured by sphygmomanometry, with each systolic time interval determination. Blood samples for plasma propranolol levels were obtained at 2 and 24 hours after the last dose of propranolol. Propranolol was measured with a gas chromatographic procedure.\textsuperscript{18}

Group 2 consisted of 26 patients, 15 males and 11 females, ages 17–61 years. All patients had a form of chronic stable heart disease — 10 coronary artery disease, eight mitral valve prolapse, five valvular heart disease and three primary myocardial disease. The patients had no metabolic or electrolytic abnormalities and were not on medications during the study. All patients had normal resting ECGs. Systolic time intervals and 24-hour urinary epinephrine and norepinephrine were measured the same day.\textsuperscript{14} The QT and QS\textsubscript{2} were measured from the systolic time intervals.

To test the hypothesis that changes in the relationship between QT and QS\textsubscript{2} are caused by adrenergic stimulation and not only by changes in heart rate, the durations of QT and QS\textsubscript{2} were measured at rest and during right atrial pacing at rates of 80–130 beats/min in six patients (ages 45–50 years) who were undergoing diagnostic electrophysiologic studies (group 3).

Statistical evaluation was performed using the \(t\) test and two-way analysis of variance using a Hewlett-Packard 9300 B computer calculator.

**Results**

**Group 1**

The duration of the QT and QS\textsubscript{2} intervals before and during isoproterenol infusions throughout the 24-hour control period for group 1 are shown in table 1 and figure 2. During the entire control period, the QT

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**Table 1. Total Mechanical Systole and Electrical Systole Before and During Isoproterenol Infusion**

<table>
<thead>
<tr>
<th>Time (hours)</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>4</th>
<th>6</th>
<th>8</th>
<th>12</th>
<th>15</th>
<th>24</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Before isoproterenol</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>QS\textsubscript{2} (msec)</td>
<td>405 + 8</td>
<td>407 + 7</td>
<td>407 + 8</td>
<td>402 + 6</td>
<td>402 + 5</td>
<td>400 + 6</td>
<td>408 + 6</td>
<td>411 + 6</td>
<td>415 + 7</td>
</tr>
<tr>
<td>QT (msec)</td>
<td>386 + 10</td>
<td>393 + 9</td>
<td>390 + 9</td>
<td>388 + 8</td>
<td>386 + 7</td>
<td>382 + 8</td>
<td>390 + 9</td>
<td>394 + 8</td>
<td>397 + 9</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>64 + 5</td>
<td>65 + 5</td>
<td>63 + 4</td>
<td>65 + 4</td>
<td>66 + 6</td>
<td>65 + 5</td>
<td>65 + 3</td>
<td>63 + 4</td>
<td>63 + 4</td>
</tr>
</tbody>
</table>

| **Isoproterenol (2 \(\mu\)g/min for 10 min)** |    |    |    |    |    |    |    |    |    |
| QS\textsubscript{2} (msec) | 323 + 10 | 324 + 9 | 324 + 10 | 323 + 8 | 329 + 9 | 319 + 9 | 321 + 8 | 322 + 9 | 323 + 10 |
| QT (msec)    | 355 + 12 | 354 + 11 | 352 + 11 | 354 + 11 | 352 + 13 | 353 + 14 | 352 + 12 | 352 + 11 | 354 + 13 |
| Heart rate (beats/min) | 88 + 6 | 87 + 5 | 85 + 5 | 86 + 5 | 87 + 6 | 87 + 6 | 88 + 5 | 85 + 6 | 87 + 4 |

Abbreviations: QS\textsubscript{2} = mechanical systole; QT = electrical systole.
was always significantly shorter than the QS2 (p < 0.01). The differences between QT and QS2 before and during isoproterenol infusion were constant. The relationships between the QS2 and heart rate and the QT and heart rate before and during isoproterenol infusion are shown in figure 3. As the heart rate increases, both the QS2 and the QT were shortened, but for any given heart rate during isoproterenol infusion the QS2 was shortened more than expected from changes in heart rate alone, while the shortening of the QT was the same as expected from changes in heart rate. The 95% confidence level for the QS2 was calculated using the formula of Weissler et al. and the equation for the QT was obtained from 200 normal resting subjects and for males it is 521–2.0 HR. An example of the relationship between QT and QS2 before and during isoproterenol infusion is shown in figure 4. The durations of the QT before and during isoproterenol infusion were 390 and 349 msec, respectively, while the durations of QS2 before and during isoproterenol infusion were 405 and 323 msec, respectively.

The duration of the QT and the QS2 before and during isoproterenol infusion, before propranolol administration and up to 60 hours after the last dose of propranolol are shown in table 2 and figure 5. The QT was greater than the QS2 before propranolol administration (p < 0.01); this difference was abolished 2 hours after the last dose of propranolol but became exaggerated 24–60 hours after the last dose of propranolol (p < 0.01). Two hours after the last dose, propranolol was 33.8 ± 5 μg/ml and it was undetectable 24 hours after the last dose.
TABLE 2. Total Mechanical Systole and Electrical Systole Before and During Isoproterenol Infusion Up to 60 Hours After the Last Dose of Propranolol (n = 6)

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>2</th>
<th>24</th>
<th>36</th>
<th>48</th>
<th>60</th>
</tr>
</thead>
<tbody>
<tr>
<td>QS&lt;sub&gt;2&lt;/sub&gt; (msec)</td>
<td>405 ± 5</td>
<td>437 ± 4</td>
<td>431 ± 5</td>
<td>396 ± 10</td>
<td>414 ± 9</td>
<td>404 ± 7</td>
</tr>
<tr>
<td>QT (msec)</td>
<td>386 ± 4</td>
<td>420 ± 6</td>
<td>411 ± 10</td>
<td>378 ± 12</td>
<td>395 ± 13</td>
<td>386 ± 11</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>68 ± 5</td>
<td>53 ± 9</td>
<td>59 ± 3</td>
<td>71 ± 4</td>
<td>64 ± 4</td>
<td>65 ± 3</td>
</tr>
</tbody>
</table>

Abbreviations: QS<sub>2</sub> = mechanical systole; QT = electrical systole.

FIGURE 5. During isoproterenol infusion, electrical systole (QT) is shorter than the mechanical systole (QS<sub>2</sub>) before propranolol administration (p < 0.01). This difference is diminished 2 hours after the last dose of propranolol (p < 0.01), but becomes exaggerated 24–60 hours after the last dose (p < 0.01).

Group 2

In 12 patients the QT was greater than the QS<sub>2</sub>, while in the remaining 14 the QT was equal to or shorter than the QS<sub>2</sub>. The 24-hour urinary epinephrine and norepinephrine excretion was significantly greater (p < 0.05) in patients in whom the QT was greater than the QS<sub>2</sub> compared with patients in whom the QT was equal or shorter than the QS<sub>2</sub> (fig. 6). The changes in QT-QS<sub>2</sub> relationship were due to a shortening of the QS<sub>2</sub>. The QT was longer than the QS<sub>2</sub> by 13.5 ± 4 msec. The correlation between QT-QS<sub>2</sub> and the 24-hour urinary epinephrine and norepinephrine excretion was r = 0.61 (p < 0.01).

Group 3

The duration of the QT and the QS<sub>2</sub> at different heart rates is shown in table 3. During atrial pacing and at rates up to 130 beats/min, the QT was always shorter than the QS<sub>2</sub>, although as the heart rate increased the difference between QS<sub>2</sub> and QT became shorter. An example of the relationship between QT and QS<sub>2</sub> at heart rates of 60, 100 and 120 beats/min is

TABLE 3. Total Mechanical Systole and Electrical Systole Before and During Atrial Pacing (n = 6)

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Pace 80 beats/min</th>
<th>Pace 90 beats/min</th>
<th>Pace 100 beats/min</th>
<th>Pace 110 beats/min</th>
<th>Pace 120 beats/min</th>
<th>Pace 130 beats/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>QS&lt;sub&gt;2&lt;/sub&gt; (msec)</td>
<td>390 ± 8</td>
<td>387 ± 6</td>
<td>367 ± 5</td>
<td>350 ± 4</td>
<td>334 ± 4</td>
<td>318 ± 3</td>
<td>297 ± 4</td>
</tr>
<tr>
<td>QT (msec)</td>
<td>367 ± 11</td>
<td>363 ± 5</td>
<td>340 ± 6</td>
<td>325 ± 4</td>
<td>309 ± 5</td>
<td>303 ± 5</td>
<td>284 ± 4</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>74 ± 5</td>
<td>80</td>
<td>90</td>
<td>100</td>
<td>110</td>
<td>120</td>
<td>130</td>
</tr>
</tbody>
</table>

Abbreviations: QS<sub>2</sub> = mechanical systole; QT = electrical systole.
shown in figure 7. At a heart rate of 60 beats/min, the QS2 was 418 msec and the QT was 395 msec, at rate of 100 the QS2 was 348 msec and the QT 329 msec and at rate of 120 the QS2 was 315 msec and the QT 304 msec.

**Discussion**

The results of the present study show that adrenergic stimulation produces a relative prolongation of QT in relation to QS2. The reversal of the QT-QS2 normal relationship is abolished by propranolol, but becomes exaggerated for 2 days after propranolol withdrawal. The normal QT-QS2 relationship was unchanged when the heart rate increased with atrial pacing.

Adrenergic stimulation results in a shortening of the duration of mechanical systole and therefore a shortening of the QS2. Adrenergic stimulation, however, does not always produce a shortening of the action potential and the duration of QT. In fact, it may produce an increase in the duration of QT.

Studies in the papillary muscle have shown that the effect of catecholamines on the duration of the action potential and duration of QS2 are related to both catecholamines and calcium. Most often, catecholamines produce an increase of the duration of the plateau of the action potential, an increase in the force of contraction and a shortening of the duration of contraction. Even when the action potential duration shortens, the shortening of QS2 is greater than the shortening of QT. The effect of catecholamines on the action potential is secondary to an increase of calcium inward flow during the plateau phase of repolarization and increase of the potassium outward flow throughout the action potential. The augmentation of myocardial contractility is secondary to an increase of calcium availability mediated in part by increase in cyclic AMP.

Studies have shown that administration of catecholamines after β-blockade abolished both the effect on action potential and myocardial contractility.

The reversal of the QT-QS2 normal relationship produced by catecholamines in this study most likely is due to same mechanisms noted in experimental animal preparations. Thus, electromechanical systole at any given heart rate was consistently shortened during isoproterenol infusion, while the QT at any given heart rate was either unchanged or occasionally was slightly prolonged. The reversal of the QT-QS2 normal relationship produced by isoproterenol infusion was diminished with propranolol, became exaggerated after propranolol withdrawal and was present in patients with high endogenous catecholamines. Thus, relative prolongation of the QT (QT longer than the QS2) in the absence of metabolic-electrolyte abnormalities or drugs may provide a simple index of increased adrenergic activity. Furthermore, a QT longer than the QS2 must be considered abnormal even if the absolute QT value is normal.

The hypersensitivity to isoproterenol after propranolol withdrawal is probably related to an increase of the number of active adrenergic receptors during β blockade when receptors are not stimulated or a change in the affinity of the adrenergic receptor for isoproterenol, or a change in the rate of metabolism. Previously, hypersensitivity to isoproterenol after propranolol withdrawal was demonstrated 24-48 hours after the last dose of propranolol using the QS2 only. In the present study, using both QS2 and QT, the hypersensitivity to isoproterenol was found to be present at least up to 60 hours after the last dose of propranolol.

The reversal of the QT-QS2 normal relationship produced by catecholamines was not the result of the
effect upon the heart rate alone. Indeed, QT-QS relationship remained normal when the heart rate increased with atrial pacing.

The QT normally is shorter than the QS, so the duration of QT must always be considered in relation to the duration of QS. To define abnormalities in the duration of QT due to interventions or pharmacologic agents, measurements of both intervals are necessary.

A long QT is well known to be associated with rhythm disturbances and sudden death. Whether relative prolongation of QT (QT longer than the QS) predisposes to dysrhythmias or sudden death has yet to be defined.

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