Sex-Selective QT Prolongation During Rapid Eye Movement Sleep

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Background—We examined the effects of the various sleep stages on RR and QT intervals in healthy subjects and tested the hypothesis that there is a differential effect of sleep stage on QT interval in women compared with men.

Methods and Results—Eighteen healthy subjects (9 women, age 22 to 45 years) underwent polysomnography and simultaneous recording of ECG, blood pressure, and respiration. RR interval, RR variability, and QT values were measured in stable conditions (no abrupt changes of heart rate or blood pressure, stable breathing pattern) during inactive wakefulness during stages 2 and 3 to 4 of non-REM sleep and during REM sleep. The absolute QT interval was normalized for variations of RR (QTc). In men, RR interval and RR variability increased through all sleep stages. The QTc remained stable from wakefulness through all sleep stages. In women, however, RR interval increased only during non-REM and was virtually identical in wakefulness and in REM. RR variability remained very stable from wakefulness through all stages of sleep. Also, during REM in women, both absolute QT interval and QTc, regardless of the correction maneuver used, increased compared with wakefulness.

Conclusions—The influence of sleep on RR, RR variability, and QTc is sex-dependent. We speculate that these differential sex effects on cardiac rate and repolarization may have important implications for sleep-selected cardiac arrhythmias in women. (Circulation. 2002;106:1488-1492.)

Key Words: sleep ■ sex ■ nervous system

The impact of sleep on arrhythmogenesis has been recognized widely.1,2 The autonomic nervous system seems to play a key role in this complex and poorly defined interaction. Surges in cardiac and muscle sympathetic nerve activity, which are part of the physiology of rapid eye movement (REM) sleep,3,4 have been invoked as possible mechanisms contributing to nocturnal arrhythmias.2,5 Heightened parasympathetic tone, which characterizes non-REM sleep,3,6 and which may also occur in REM,6–8 has also been implicated in both tachyarrhythmias9 and bradyarrhythmias.10

Delayed repolarization of the ventricular myocardium, as evidenced by prolongation of the QT interval, may increase cardiac susceptibility to malignant arrhythmias, such as torsade de pointes.11 Although there is evidence of changes in QT interval during the night,12–14 there are very few data examining the physiological effects of various sleep stages on QT interval.15 No such data exist for healthy humans.

The influence of sex on sleep-related changes in RR and QT intervals is also unknown. There is precedent for a sex-specific interaction with ventricular repolarization. Women have faster resting heart rates and longer QTc than men.16,17 Women are also at increased risk for drug-induced prolongation of ventricular repolarization and consequent cardiac arrhythmias.18,19 Women have a higher incidence of torsade de pointes than men.18 Finally, among patients affected by congenital long-QT syndrome, women are more susceptible to arrhythmias than men.20

We therefore examined the effects of sleep on RR and QT intervals in healthy subjects and tested the hypothesis that there is a differential effect of sleep stage on QT interval in women compared with men.

Methods

Study Population
We studied 18 healthy subjects (9 women), age 22 to 45 years. All subjects were nonsmokers and taking no medications. All women were premenopausal. Subjects were asked to avoid caffeine for 24 hours before the study. The study was approved by the Mayo Foundation Institutional Review Board.

Study Protocol
Subjects presented to the Mayo Clinic GCRC Sleep Laboratory at 7 PM, and after a brief assessment, including personal and family medical history, physical examination, and 12-lead ECG, they...
underwent a sleep study using full polysomnography with simultaneous continuous recording of ECG, blood pressure, and respiration.

**Measurements**

Monitored polysomnography was performed according to a standard clinical protocol, with recording of EEG (C3-A2, Fz-Cz, Cz-Oz), submental and anterior tibialis electromyography, electrooculography, electrocardiography, and oronasal airflow (thermocouples). The thoracic and abdominal respiratory activity was monitored by inductive plethysmography (Respiracé; Ambulatory Monitoring) and upper airway sounds by a microphone. The oxyhemoglobin saturation was measured by a finger-probe oxymeter (Nellcor pulse oximeter). Data were recorded by a multichannel recording system (Network concepts, Inc).

Simultaneous 2-lead ECG (lead II by Colin Medical Instrument Corp; lead III by Gould Instrument System, Inc), continuous noninvasive tonometric arterial blood pressure (Colin Medical Instrument Corp), and respiration (Respiracé) were recorded, digitized, and stored for subsequent analysis.

**Data Analysis**

Sleep studies were scored according to standard methods. Poly- somnographic data acquired included sleep efficiency (total sleep time divided by the total time in bed), the percentage of each stage of sleep, the arousal index (number of arousals per hour of sleep), periodic leg movements index (number of periodic limb movements per hour of sleep), apnea hypopnea index (number of apneas and hypopneas per hour of sleep), and mean oxygen saturation (mean Sao2) (Table 1).

ECG data (PowerLab System for MAC OS) were used for the computation of RR interval, QT interval, and blood pressure. One-minute segments of recording of cardiovascular and respiratory signals were selected for inactive wakefulness (eyes closed and light out, at the beginning of the study) and each stage of sleep according to the following criteria.

First, segments were selected, when possible, between 11 PM and 2 AM, to reduce any possible bias attributable to time of inactivity on RR and QT intervals. Second, segments were selected 1 minute after the beginning of each stage and at least 1 minute away from arousals, to minimize any effects of possible transient abrupt changes in autonomic tone associated with cortical and subcortical activation.

Third, only segments with a stable breathing pattern were selected, to avoid any QT changes associated with changes of the breathing pattern. None of the subjects had sleep-disordered breathing.

Fourth, only segments with stable BP and RR interval were selected, to limit any effect of hemodynamic changes on QT.

Fifth, stage 1, which is a transition stage often lasting less than a minute, was excluded from the analysis.

According to these criteria, the longest duration consistently available for all stages in all subjects was ≈1 minute. Data were analyzed blind to sex and date of study. Data selected were processed by ScopeWin QT software, which allows the automatic detection of R wave peak, QRS onset, and end of T wave. All of the recordings were automatically analyzed, manually edited and corrected, and then recomputed to obtain QT values. The average absolute QT was normalized for variations of RR by applying several common and widely used correction models, as follows: (1) nonlinear, with Bazett’s formula: QTc = QT/RR0.3514; (2) nonlinear, with Fredricia’s formula: QTc = QT/RR0.3532; (3) nonlinear, with Malik’s formula: QTc = QT/RR0.37124; (4) linear, with Sagie’s formula: QTc = QT + 0.154×1−ln(RR); and (5) logarithmic formula: QTc = QT−0.1378×ln(RR).

**Statistical Analysis**

Comparison between men and women was performed using an unpaired t test. P<0.05 was considered statistically significant. In each group, the trend of individual parameters was examined with respect to sleep stages (wake, stage 2, stages 3 and 4, REM) using one-way ANOVA with repeated measures. For statistically significant trends, multiple comparison tests were performed using an overall P value of 0.05.

**Results**

Demographic characteristics and sleep measurements according to sex are reported in Table 1. Both males and females were similar for age and body mass index. Sleep efficiency and the relative percentage of non-REM and REM sleep were also similar for both sexes. Although women had a higher average incidence of arousals than men, this was primarily attributable to a high incidence of arousal in 2 women. Arousal index in the remaining 7 women was similar to the levels in men (15±5 versus 19±6, NS).

In men, the RR interval increased significantly during sleep, as did RR variability (all values shown in Table 2). Parallel to the increased RR interval, the absolute QT interval also increased. Hence, the corrected QT, regardless of the correction formula used, remained remarkably stable from wakefulness through all sleep stages in men. Respiratory frequency tended to decrease from wakefulness to sleep (Table 2).

In women, the RR interval increased only during non-REM and was virtually identical in wakefulness and in REM (Table 3). In contrast to men, RR variability in women was also very stable from wakefulness through all sleep stages. The absolute QT increased during non-REM. During REM sleep, there was a paradoxical QT response. The absolute QT interval increased, whereas the RR interval decreased slightly. Thus, the QTc during REM in women, regardless of the correction maneuver used, increased compared with wakefulness (Table 3 and Figure). The respiratory frequency tended to increase during REM (Table 3). Changes in breathing frequency from wakefulness to REM were significantly different in women compared with men (Figure).

**Discussion**

In this study, we describe the effects of sleep and sleep stages on cardiac rate and repolarization characteristics in healthy humans. The novel findings include that modulation of RR, RR variability, QT, QTc, and breathing frequency during REM sleep is different between men and women. There is therefore an important influence of sex, first, on the interac-
tion between sleep and autonomic control of the sinus node, second, on the physiology of the QT/RR relationship, and, third, on the control of breathing during REM. In men, the RR interval and RR variability profiles suggest a parasympathetic dominance of sinus node control in non-REM as well as in REM sleep. The prolongation of absolute QT with a stable QTc suggests that the QT adapts appropriately to the changes in RR in men. By contrast, in women, RR variability did not change throughout sleep, and the RR interval shortened during REM compared with non-REM sleep, suggesting a sympathetic dominance of sinus node control during REM. The capability of the QT to adapt to RR variation is preserved during non-REM sleep, but there seems to be a paradoxical response during REM, resulting in a significant increased QTc.

Although the interaction between sleep and cardiovascular disease is increasingly being recognized, there are very limited data regarding the effects of sleep stage on cardiovascular function, particularly in healthy humans. Direct measurements of muscle sympathetic nerve activity have provided clear evidence of REM-related increases in sympathetic traffic to blood vessels. The magnitude and consequences of sympathetic and parasympathetic drive to the sinus node during sleep, particularly in REM, are less clear. The RR interval has been consistently reported to increase in non-REM. During REM, RR decreases to values either similar to or above waking levels. Studies on spectral analysis of heart rate variability showed that the vagally mediated high-frequency components increase during non-REM and decrease during REM. Muscle sympathetic nerve activity decreases during non-REM and markedly increases during REM. However, the regulation of RR and its variability is clearly more complex than a simple increase in parasympathetic dominance in non-REM and an increase in sympathetic dominance in REM. Clinical observations and

**TABLE 2. Cardiovascular Parameters During Wakefulness and the Different Sleep Stages in Men (One-Way ANOVA With Repeated Measures and Multiple Comparison)**

<table>
<thead>
<tr>
<th></th>
<th>Wakefulness</th>
<th>Stage 2</th>
<th>Stages 3–4</th>
<th>REM (ANOVA)</th>
<th>P</th>
<th>Multiple Comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean RR, ms</td>
<td>1056</td>
<td>1126</td>
<td>1130</td>
<td>1106</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>RR variability, ms</td>
<td>40</td>
<td>76</td>
<td>68</td>
<td>83</td>
<td>0.06</td>
<td></td>
</tr>
<tr>
<td>QT, ms</td>
<td>412</td>
<td>427</td>
<td>427</td>
<td>425</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>SdQT, ms</td>
<td>7</td>
<td>8</td>
<td>7</td>
<td>8</td>
<td>0.88</td>
<td></td>
</tr>
<tr>
<td>QTcBazett, ms</td>
<td>403</td>
<td>404</td>
<td>405</td>
<td>407</td>
<td>0.73</td>
<td></td>
</tr>
<tr>
<td>QTcFramingham, ms</td>
<td>403</td>
<td>407</td>
<td>407</td>
<td>409</td>
<td>0.63</td>
<td></td>
</tr>
<tr>
<td>QTcFredrica's, ms</td>
<td>405</td>
<td>409</td>
<td>409</td>
<td>411</td>
<td>0.53</td>
<td></td>
</tr>
<tr>
<td>QTcMalik, ms</td>
<td>404</td>
<td>408</td>
<td>409</td>
<td>410</td>
<td>0.51</td>
<td></td>
</tr>
<tr>
<td>QTcShapiro, ms</td>
<td>405</td>
<td>411</td>
<td>411</td>
<td>412</td>
<td>0.43</td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>112</td>
<td>96</td>
<td>103</td>
<td>100</td>
<td>0.12</td>
<td></td>
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<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>64</td>
<td>53</td>
<td>56</td>
<td>54</td>
<td>0.07</td>
<td></td>
</tr>
<tr>
<td>Breathing frequency, n/min</td>
<td>18</td>
<td>16</td>
<td>16</td>
<td>16</td>
<td>0.08</td>
<td></td>
</tr>
</tbody>
</table>

*Difference between wakefulness and St2; †difference between wakefulness and St3; and ‡difference between wakefulness and REM.

**TABLE 3. Cardiovascular Parameters During Wakefulness and the Different Sleep Stages in Women (One-Way ANOVA With Repeated Measures and Multiple Comparison)**

<table>
<thead>
<tr>
<th></th>
<th>Wakefulness</th>
<th>Stage 2</th>
<th>Stages 3–4</th>
<th>REM (ANOVA)</th>
<th>P</th>
<th>Multiple Comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean RR, ms</td>
<td>843</td>
<td>933</td>
<td>934</td>
<td>839</td>
<td>0.001</td>
<td></td>
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<tr>
<td>RR variability, ms</td>
<td>43</td>
<td>48</td>
<td>46</td>
<td>49</td>
<td>0.651</td>
<td></td>
</tr>
<tr>
<td>QT, ms</td>
<td>405</td>
<td>426</td>
<td>427</td>
<td>418</td>
<td>0.000</td>
<td></td>
</tr>
<tr>
<td>SdQT, ms</td>
<td>9</td>
<td>10</td>
<td>9</td>
<td>10</td>
<td>0.433</td>
<td></td>
</tr>
<tr>
<td>QTcBazett, ms</td>
<td>443</td>
<td>444</td>
<td>445</td>
<td>456</td>
<td>0.003</td>
<td></td>
</tr>
<tr>
<td>QTcFramingham, ms</td>
<td>429</td>
<td>437</td>
<td>437</td>
<td>443</td>
<td>0.000</td>
<td></td>
</tr>
<tr>
<td>QTcFredrica's, ms</td>
<td>432</td>
<td>438</td>
<td>439</td>
<td>445</td>
<td>0.000</td>
<td></td>
</tr>
<tr>
<td>QTcMalik, ms</td>
<td>433</td>
<td>439</td>
<td>439</td>
<td>447</td>
<td>0.000</td>
<td></td>
</tr>
<tr>
<td>QTcShapiro, ms</td>
<td>430</td>
<td>437</td>
<td>438</td>
<td>443</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>110</td>
<td>107</td>
<td>96</td>
<td>104</td>
<td>0.056</td>
<td></td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>67</td>
<td>63</td>
<td>57</td>
<td>64</td>
<td>0.015</td>
<td></td>
</tr>
<tr>
<td>Breathing frequency, n/min</td>
<td>15</td>
<td>14</td>
<td>14</td>
<td>16</td>
<td>0.08</td>
<td></td>
</tr>
</tbody>
</table>

*Between wakefulness and St2; †between wakefulness and St3; ‡between wakefulness and REM; §between St2 and REM; and ††between St3 and REM.
data in animals provide clear evidence for central and reflex parasympathetic influences on sinus node function during REM, which is often defined as a state of autonomic instability. This present evidence of different patterns of RR and RR variability in men and women during REM suggests that sex is an additional important element contributing to this complexity.

Previous studies of QT control during sleep in healthy humans are also limited and have not addressed sex-specific differences. Browne et al. first reported a prolongation of the QT during the night. Other studies have reported a circadian variation of QT and RR interval (both increased at night) but a blunted or absent variation of QTc. These evaluations were made from Holter recordings, where sleep was assumed and changes in sleep stages were not taken into consideration. Heterogeneous effects of sleep stage on RR and QT, any effects of sex on the sleep-related changes in RR control, as well as the potential effects of cortical and subcortical arousals could all potentially affect both heart rate and QT during sleep, making the existing data difficult to interpret. Other confounding factors, such as the presence of undiagnosed sleep-disordered breathing, speak to the importance of detailed polysomnographic monitoring of sleep, sleep stage, and breathing in any evaluation of sleep-related changes on RR and QT interval.

Gillis et al. studied 9 nonapneic patients with ventricular arrhythmias and heart disease and noted a prolongation of QT and QTc in non-REM as well as REM sleep compared with active wakefulness. By contrast, no significant differences were observed between sleep and prolonged resting wakefulness, nor between REM and non-REM. Subjects were 6 men and 3 women, ranging in age from 28 to 73 years. Thus, factors such as age, unequal sex distribution, small sample size, and coexisting disease limit the application of these data to understanding cardiac control during sleep in healthy men and women.

There is consistent evidence of differences in neural circulatory control mechanisms in men and women. Previous studies of QT control during sleep in healthy men and women. 28–30 There is also precedent for a sex-specific interaction with ventricular repolarization. 16–20 Our data provide the first evidence that sleep, and REM in particular, differentially affects the heart rate and repolarization in women and men. This sex-dependent differential effect on QTc may have important relevance for sex-specific interactions between sleep and arrhythmia.

Shorter RR interval, decreased RR variability, and longer QTc in REM may be consistent with lower parasympathetic activity, QTc, and breathing frequency. The RR interval increases in women, leading a statistically significant difference between the 2 groups.

Conclusions

Our study shows that there are clear sex-dependent influences on the effects of sleep stage on the RR interval, RR variability, QTc, and breathing frequency. The RR interval increases in all sleep stages in men. In women, RR in REM is the same as during wakefulness. RR variability increases through all
sleep stages in men but remains very stable from wakefulness through sleep in women, even in REM. There is a significant prolongation of QTc in women during REM, whereas in men the QTc remains very stable from wakefulness through all sleep stages. During REM, the breathing frequency increased in women whereas it decreased in men, possibly contributing to the differences in RR, RR variability, and QTc.

We speculate that these differential sex-related effects on RR, RR variability, and QTc during REM may have important implications for understanding the predisposition of women to drug-induced QT prolongation, torsade de pointes, and sudden death events in the setting of the long-QT syndromes.

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References
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