Morning Blood Pressure Peak, QT Intervals, and Sympathetic Activity in Hypertensive Patients

Raffaele Marfella, Pasquale Gualdiero, Mario Siniscalchi, Caterina Carusone, Mario Verza, Salvatore Marzano, Katherine Esposito, Dario Giugliano

Abstract—We investigated the relation between morning blood pressure (BP) variations, sympathetic activity, and QT intervals in 156 never-treated subjects with essential hypertension and different patterns of morning BP increase. The morning BP peak (MP) was defined as a rise in systolic BP ≥50 mm Hg and/or diastolic BP ≥22 mm Hg during early morning (6:00 to 10:00 AM) compared with mean BP during the night. Clinical characteristics of patients with morning BP peak (MP+, n= 69, morning systolic BP=+54±4, diastolic BP=+32±5 mm Hg) did not differ from patients without BP peak (MP−, n= 87, morning systolic BP=+24±5, diastolic BP=+19±3 mm Hg). The daytime (10:00 AM to 10:00 PM) and the nighttime (10:00 PM to 6:00 AM) BP profile did not differ between the two groups. During daytime and nighttime ECG monitoring, the corrected QT (QTc) interval, and QTc dispersion did not differ significantly between the two groups, whereas during the morning period the QT values were significantly broader in the MP+ group compared with the MP− group (P<0.001). Morning LF/HF ratio was significantly higher in MP+ patients than in MP− patients (P=0.02). Both systolic and diastolic morning BP, in combination with ratio LF/HF power, were significant predictors of QTc dispersion (adjusted R²=0.59, P=0.01) and QTc interval (adjusted R²=0.41, P=0.01), whereas inclusion of physical activity and echocardiographic parameters did not add explanatory information. The prolongation of cardiac repolarization times and morning sympathetic overactivity coexist in hypertensive patients with morning BP peaks, and they might contribute to raised cardiovascular risk in these patients. (Hypertension. 2003;41: 237-243.)

Key Words: hypertension, essential blood pressure sympathetic nervous system

Many studies in the past decade have demonstrated diurnal variation in the onset of acute cardiovascular disorders in hypertensive patients, such as myocardial ischemia, acute myocardial infarction, cardiac arrhythmias, and sudden cardiac death. The results consistently have showed an increased incidence of acute cardiac events in the morning hours (between 6 AM and noon) and a low incidence at night. Blood pressure (BP) falls markedly during the night because of the reduction of sympathetic activity (and the increase in vagal drive) that is brought about by sleep and then increases steeply when in the morning the subject awakes and resumes his or her daily activities. This increase occurs together with a peak incidence of myocardial infarction, sudden death, and cardiac arrhythmias in the morning hours. However, the mechanisms underlying this association are not clear. According to many studies, ventricular arrhythmias are more frequent in hypertensive individuals compared with normotensive individuals, and this frequency is particularly high in those with morning BP peak. Furthermore, several other phenomena potentially dangerous for the heart, such as heart rate, fibrinolytic activity, platelet aggregability, and circulating catecholamines, also show peak adverse modifications in the morning that may make the morning BP rise at most a pathophysiological cofactor in the determination of the increased morning rate of cardiovascular morbidity and fatality events. The increase in plasma catecholamines and in cardiac afterload might explain the occurrence of arrhythmia in hypertensive patients with morning BP peak. It is widely accepted that catecholamines and cardiac afterload may influence ventricular electrical activity by modifying ventricular repolarization time. A prolonged heart rate–adjusted QT (corrected QT interval, QTc) is considered a marker of ventricular instability, is usually associated with an increased sympathetic drive, and is a risk factor for ventricular arrhythmias and sudden death in patients with myocardial infarction as well as in hypertension. In light of such evidence, we investigated the relations between morning BP variations, autonomic nervous system activity, and cardiac repolarization times in never-treated subjects with essential hypertension and with different patterns of morning BP increase.

Methods

We studied 156 subjects with essential hypertension never treated with antihypertensive drugs. All subjects were recruited from the Department of Geriatric and Metabolic Diseases, Second University of Naples, Naples, Italy.
outpatient department of the teaching hospital at the Second University of Naples, Italy. All subjects had a clinic systolic BP ≥ 140 mm Hg and/or diastolic BP ≥ 90 mm Hg on at least 3 visits at 1-week intervals and fulfilled all of the following inclusion criteria: no clinical or laboratory evidence of heart failure, coronary heart disease, previous stroke, valvular defects, obesity, or secondary causes of hypertension; high-quality echocardiographic tracings; and at least 1 valid BP measurement per hour over 24 hours during ambulatory BP monitoring (ABPM). To exclude coronary heart disease, exercise testing, thallium scintigraphy, or both were performed when clinically indicated. Subjects engaged in regular physical training were excluded from the study. A physician measured clinic BP with a mercury sphygmomanometer in the hospital clinic before the beginning of ABPM, with the subject sitting for at least 10 minutes. The average of 3 measurements was considered for analysis. The arm with higher BP values at office evaluations was chosen for the ABPM, which was performed with Dyna Pulse 5000A (Pulse Metric, Inc). The cuff size for the ABPM was chosen individually according to the JNV VI guidelines. To reduce errors during the measurements caused by the position of the upper arm during the day, we asked all subjects to ensure that the arm was always parallel to the trunk when the cuff was inflated. Readings were obtained automatically at 15-minute intervals from 6:00 AM to 10:00 PM and 30-minute intervals from 10:00 PM to 06:00 AM by an oscillometric technique. All patients kept a diary in which they documented all the relevant events during the day as well as the time of waking and returning to bed. Daytime and sleep periods were derived from diary entries. Normal daily activities were allowed and encouraged, and subjects were told to keep their nondominant arm still and relaxed at their side during measurements. To abide by the actual wakefulness-sleep rhythm reported in subjects’ diaries, we defined daytime as between 10:00 AM and 10:00 PM and nighttime as between 1:00 AM and 6:00 AM. The morning BP peak was defined as a rise in systolic BP ≥ 50 mm Hg (90% percentile of normotensive patients) and/or diastolic BP ≥ 22 mm Hg during the early morning (6:00 to 10:00 AM), arbitrarily defined as the morning period, compared with the mean BP during the night. Subjects without a morning BP peak were defined as the MP− group and the others as the MP+ group. The normal values (mean ± SD) of morning BP peak obtained from 18 normotensive patients 45 ± 6 years of age were as follows: systolic, 21 ± 5 mm Hg; diastolic, 12 ± 4 mm Hg. Subjects with a nocturnal reduction of systolic and/or diastolic BP ≥ 10% were defined as dippers and the others as nondippers. Nighttime workers, subjects going to bed later than 1:00 AM, and patient with sleep disorders were excluded from the present study; therefore, all study workers were in bed during the entire nighttime period and were awake and active during the morning and daytime interval.

On the same day, all subjects underwent 24-hour ambulatory ECG recording (H-SCRIBE, Mortara Instruments). A 2-channel bipolar recorder was used. The system was fully automatic and computerized; tracings were analyzed by two investigators who were unaware of the results of other investigations. The QT interval was measured from the earliest onset of the QRS complex to the terminal portion of the T wave, where it met the baseline. The R-R interval from the preceding cardiac cycle was measured from the peaks of the R waves to correct the QT interval for heart rate (QTc). QT intervals were corrected with Bazett’s formula (QTc = QT/R-R). QTc dispersion was calculated as interlead variability of the QTc interval (QTc dispersion = QTcmax – QTcmin). A clinician who was blinded from other information did the QT interval analysis with the aid of calipers and magnifying lens for 7 consecutive beats in lead II. Heart rate variability was analyzed in accordance with international guidelines. Three ECG leads (modified leads V5, V6, and aVF) and a time signal to correct for tape speed irregularities were recorded. The 24-hour recordings were divided into 288 segments of 5 minutes. Twelve 5-minute segments were averaged to obtain hourly mean values of the heart rate variability parameters. All ectopic beats were classified, and only segments with <15% ectopy were used. Each nonnormal R-R interval was substituted by the subsequent R-R interval. Low-frequency (LF) (0.05 to 0.15 Hz, mediated by inter-
TABLE 1. Clinical and Echocardiographic Characteristics of Patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>MP− (n=87)</th>
<th>MP+ (n=69)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>47±6</td>
<td>49±7</td>
<td>0.42</td>
</tr>
<tr>
<td>Males, %</td>
<td>69</td>
<td>61</td>
<td>0.58</td>
</tr>
<tr>
<td>Currently smokers, %</td>
<td>34</td>
<td>45</td>
<td>0.25</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>23±2</td>
<td>24±2</td>
<td>0.11</td>
</tr>
<tr>
<td>Waist-hip ratio</td>
<td>0.73±0.04</td>
<td>0.74±0.05</td>
<td>0.21</td>
</tr>
<tr>
<td>Glucose, mmol/L</td>
<td>5.0±0.5</td>
<td>5.1±0.6</td>
<td>0.19</td>
</tr>
<tr>
<td>HDL-cholesterol, mmol/L</td>
<td>1.0±0.3</td>
<td>1.1±0.3</td>
<td>0.09</td>
</tr>
<tr>
<td>Serum sodium, mmol/L</td>
<td>78.5±2.7</td>
<td>80.2±2.9</td>
<td>0.18</td>
</tr>
<tr>
<td>Plasma norepinephrine, pg/mL</td>
<td>47.7±6.5</td>
<td>56.5±8.6</td>
<td>0.08</td>
</tr>
<tr>
<td>Plasma epinephrine, pg/mL</td>
<td>249.9±25</td>
<td>252.6±24</td>
<td>0.21</td>
</tr>
<tr>
<td>Clinic SBP, mm Hg</td>
<td>159±16</td>
<td>162±16</td>
<td>0.15</td>
</tr>
<tr>
<td>Clinic DBP, mm Hg</td>
<td>99±9</td>
<td>101±9</td>
<td>0.11</td>
</tr>
<tr>
<td>Clinic heart rate, bpm</td>
<td>74±9</td>
<td>75±11</td>
<td>0.55</td>
</tr>
<tr>
<td>Standard ECG QTc, ms</td>
<td>413±19</td>
<td>422±21</td>
<td>0.10</td>
</tr>
<tr>
<td>Standard ECG QTc dispersion, ms</td>
<td>51±8</td>
<td>59±9</td>
<td>0.09</td>
</tr>
<tr>
<td>LVMI, g/m²</td>
<td>116±18</td>
<td>137±20</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>FS, %</td>
<td>35±5</td>
<td>35±6</td>
<td>0.69</td>
</tr>
<tr>
<td>IVS-LVPW ratio</td>
<td>1.13±0.15</td>
<td>1.05±0.11</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Data are presented as mean±SD. BMI indicates body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; LVMI, left ventricular mass index; FS, fractional shortening; LVIDD, left ventricular internal diastolic diameter; IVS, interventricular septum; and LVPW, left ventricular posterior wall.

131±10 to 155±14 mm Hg, P<0.001; diastolic: from 85±7 to 102±10 mm Hg, P<0.001) and quickly decreased during the subsequent hours, reaching steady-state levels around 145/90 mm Hg at 9 AM (Figure 2). Moreover, the MP+ group had a significant increase in both systolic and diastolic BP compared with the MP− group (P<0.01) during the whole morning period, whereas the daytime and the nighttime profile did not significantly differ between the two groups (Figure 1, Table 2); there were 16 nondippers in the MP+ group (18%) and 13 in the MP− group (19%, P=NS).

Morning BP increases were significantly correlated with left ventricular posterior wall thickness (r=0.15, P=0.05 and r=0.16, P=0.02, respectively) and left ventricular internal diastolic diameter (r=0.19, P=0.01 and r=0.15, P=0.05, respectively). During daytime and nighttime ECG monitoring the QTc interval, QTc dispersion, QRS duration, and the average R-R interval did not differ significantly between the two study groups, whereas during morning time period the QT values were significantly broader and R-R intervals significantly shortened in the MP+ patients compared with MP− patients (Table 2). In MP+ patients, the parameters of QT interval showed a biphasic profile: the QTc interval and QTc dispersion moderately increased to their peak levels in the morning hours (between 6 to 9 AM) (QTc: from 414±22 to 481±27 ms, P<0.001; QTc dispersion: from 54±10 to 75±14 ms, P<0.001) and constantly decreased during the subsequent hours, finally reaching steady-state levels around 418 ms and 54 ms, respectively, at 1 PM (Figure 2). In MP− patients, the biphasic profile of the QTc interval and QTc dispersion was not observed, and the hourly values were significantly lower during the morning period compared with the MP+ patients (Figure 2).

The QTc interval (r=0.24, P=0.02) and QTc dispersion (r=0.28, P<0.01) had a positive correlation with morning diastolic BP increases, less significant positive correlation with morning systolic BP increases (r=0.16, P=0.04; r=0.18, P=0.05, respectively), and were significantly positively correlated with left ventricular posterior wall thickness (r=0.16, P=0.04 and r=0.18, P=0.01, respectively) and left ventricular internal diastolic diameter (r=0.18, P=0.02 and r=0.16, P=0.04, respectively). To rule out a possible confounding effect of the heart rate correction, we also analyzed the data by using QT dispersion and QT without correction for heart rate; the results and associations were similar (QT dispersion versus morning diastolic BP: r=0.21, P<0.03; QT versus morning diastolic BP: r=0.16, P<0.04).
LF/HF ratio was significantly higher in the MP group during day and nighttime period. The morning LF/HF ratio (adjusted \( R^2=0.49, P<0.005 \)) and QTc interval (adjusted \( R^2=0.35, P<0.005 \)) as well as in combination with ratio LF/HF power were significant predictors of QTc dispersion (adjusted \( R^2=0.59, P<0.001 \)) and QTc interval (adjusted \( R^2=0.41, P<0.001 \)), whereas inclusion of age, physical activity, echocardiographic parameters, and metabolic parameters did not add explanatory information. Nevertheless, urinary catecholamine (epinephrine and norepinephrine) levels were significantly associated with the increase of QTc dispersion (\( P<0.01, P<0.05 \), respectively) and the QTc interval (\( P<0.01, P<0.05 \), respectively).

### Discussion

To the best of our knowledge, this is the first study to investigate the relation between morning BP, nervous autonomic function, and cardiac repolarization times in never-treated hypertensive patients with different patterns of morning BP increase. The main findings of our study describe an association between QT intervals, morning BP, and sympa-
thetic activity in never-treated hypertensive patients: Notably, morning increases of QTc dispersion and the QTc interval are associated with a morning BP peak and morning sympathetic overactivity. This association is present independent of potential confounding factors (age, smoking, metabolic parameters, and physical activity). Moreover, obese and patients with sleep disorder breathing were excluded from the study to avoid any confounding influence of these conditions on the morning BP.

Some available studies report that the QT times are increased in association with an increased left ventricular mass index in hypertensive individuals. Our data confirm the association of delayed cardiac repolarization and left ventricular hypertrophy since MP+ patients had significantly longer QTc dispersion and QTc interval (only in the morning hours), longer left ventricular internal diastolic diameter, and thicker interventricular septum and left ventricular posterior wall compared with MP− patients. We also found a significant linear association between left ventricular posterior wall thickness and left ventricular internal diastolic diameter and morning BP increases. These findings support those by Gosse et al., who found that the systolic BP on arising was significantly better correlated than office BP with left ventricular mass index and wall thickness. Moreover, Kuwajima et al. also reported a significant association between the changes in systolic BP after arising from bed and left ventricular mass index. As for the background for this association, the present study provides the first evidence of an association between left ventricular hypertrophy, morning BP peak, morning increases of LF/HF ratio (considered as a marker of sympathetic overactivity), and morning prolongation of cardiac repolarization times in never-treated subjects with essential hypertension. Although the probable cause of delayed cardiac repolarization times in hypertensive patients with morning BP peak may be left ventricular hypertrophy, Perkiomaki et al. showed that left ventricular hypertrophy was correlated only with QT apex dispersion times but not with the dispersion of the whole QRS complex duration or the QTc interval, demonstrating that left ventricular hypertrophy results in a more marked inhomogeneity of the plateau phase of repolarization than in the downslope phase of repolarization or in the depolarization phase. Moreover, we observed in a multiple regression analysis that both systolic and diastolic morning BP in combination with ratio LF/HF power were significant predictors of QTc dispersion and the QTc interval, whereas inclusion of echocardiographic parameters did not add explanatory information. Thus, left ventricular hypertrophy could be a cofactor in the association between morning BP peak and prolongation of QT times.

The length of the QT interval, which is easily obtained from standard resting ECG, represents the time interval between the start of activation of the ventricle and completion of its repolarization. QT interval is influenced by the autonomic tone and represents an index of myocardial refractoriness and electrical stability; this is a critical determinant of ventricular fibrillation and sudden death. Dispersion of repolarization is a consequence of predominance of sympathetic nerve activity and might be responsible for a high risk of ventricular fibrillation. Sympathetic stimulation unopposed by vagal activity might induce ventricular electrical instability, resulting in a risk of arrhythmia and sudden death. An association between a prolonged QT interval and sudden cardiac death has been found in coronary artery disease, congestive heart failure, and in obese and hypertensive patients. Although a direct link between morning BP peak and sudden cardiac death has not yet been established, it might be hypothesized that the surge in BP may be a factor predisposing to ventricular arrhythmias by a QT lengthening. Consistent with this, sudden cardiac death in hypertensive patients presents a circadian variation with a peak at 6 to 9 AM, the same time when a physiological increase in BP occurs. There are several theoretical possibilities through which a morning-raised BP may influence cardiac repolarization time. First, an increase in afterload predisposes to electrophysiological changes and QTc lengthening. In experimental models, an increase in cardiac afterload has been shown to alter action potential durations through mechanoelectrical feedback. This may result in an altered dispersion of action potential repolarization in the ventricle. Direct effects of increased load on repolarization are probably caused by activation of stretch-activated, nonselective cation channels and changes in calcium handling. Second, the link between morning BP peak and increase of QTc dispersion may be represented by local myocardial ischemia inducing an electrical instability that might induce arrhythmias. In fact, local myocardial ischemia may determine marked electrophysiological heterogeneity between epicardium and endocardium. Last, the left ventricular hypertrophy, evidenced in patients with morning BP peak, might affect QTc and QTc dispersion: Myocardial hypertrophy may alter the ion channels that are operative during the early repolarization phase. Abnormalities in the potassium channels in hypertrophied myocytes have been shown to contribute to the prolongation of action potential duration. Moreover, it is tempting to speculate that a sudden rise in BP causes an acute hemodynamic burden, which might predispose the hypertrophied ventricular myocardium to initiate an arrhythmic event in response to trigger factors, such as sympathetic overactivity.

In addition to BP, there are also morning variations of heart rate variability. Our study showed a significant relation between QTc dispersion, the QTc interval, morning BP peak, and altered sympathovagal balance, suggesting that sympathetic overactivity may be a common mechanism unifying all these alterations observed in hypertensive patients with morning BP peak. Morning increase in LF/HF ratio, considered as a marker of sympathetic overactivity and morning increase of urinary catecholamine levels observed in MP+ patients, might be responsible for both the morning rise in BP and cardiac time prolongation in hypertensive patients. Moreover, the variation of BP was positively correlated with that of LF/HF ratio during the morning period, whereas this association was not obtained during the day and nighttime period. Thus, BP variation might be related to variation of sympathetic nervous system activity in the morning period only. The variations observed during day and nighttime periods also support this line of reasoning. In fact, reductions in LF/HF ratio were associated with significant and parallel
changes in QTc dispersion, the QTc interval, and morning BP. Moreover, QT intervals, morning BP, and LF/HF ratio showed a trend to normalize during day and nighttime periods, suggesting that the abnormalities found during morning period are functional in origin and not due to structural damage within the baroreflex pathway. In keeping with this conclusion, therapeutic approaches with β-blockers increased morning BP peak and improved baroreflex sensitivity in hypertensive patients. Finally, the multivariate analysis of our data showed that changes in morning BP and LF/HF ratio were associated with change in QTc-d and the QTc interval. Thus, the shortening of QTc dispersion and the QTc interval during day and nighttime periods was strictly associated with a decrease in morning BP and LF/HF ratio.

In conclusion, the prolongation of cardiac repolarization times and morning sympathetic overactivity coexist in hypertensive patients with morning BP peak and might contribute to their raised cardiovascular risk. A likely mechanism for this association is through sympathetic overactivity, which correlates with both morning BP and cardiac repolarization times. It will be important to address in future studies evaluating whether morning BP peak, combined with increased QT times and impaired heart rate variability, may specifically identify hypertensive patients with left ventricular hypertrophy who are at high risk for life-threatening arrhythmias and sudden death.

Perspectives

The prolongation of cardiac repolarization times and morning sympathetic overactivity coexist in hypertensive patients with morning blood pressure peak and might contribute to their raised cardiovascular risk. A likely mechanism for this association is through sympathetic overactivity, which correlates with both morning blood pressure and cardiac repolarization times. Thus, this study may explain the reason why in the early hours of the morning there have been observed the higher number of fatal and nonfatal cardiovascular events. Similarly, this study also gives important information to guide in the choice of right treatment in hypertensive patients with morning blood pressure peak.

However, it will be important address in future studies evaluating whether morning blood pressure peak, combined with increased QT times and impaired heart rate variability, may specifically identify hypertensive patients with left ventricular hypertrophy who are at high risk for life-threatening arrhythmias and sudden death.

References


18. Leary AC, Struthers AD, Donnan PT, MacDonald TM, Murphy MB. The morning surge in blood pressure and heart rate is dependent on levels of physical activity after waking. J Hypertens. 2002;20:865–870.


34. Weber MA. The 24-hour blood pressure pattern: does it have implications for morbidity and mortality? Am J Cardiol. 2002;89:27A–33A.


Morning Blood Pressure Peak, QT Intervals, and Sympathetic Activity in Hypertensive Patients
Raffaele Marfella, Pasquale Gualdiero, Mario Siniscalchi, Caterina Carusone, Mario Verza, Salvatore Marzano, Katherine Esposito and Dario Giugliano

Hypertension. 2003;41:237-243; originally published online December 30, 2002;
doi: 10.1161/01.HYP.0000050651.96345.0E

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://hyper.ahajournals.org/content/41/2/237

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Hypertension can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Hypertension is online at:
http://hyper.ahajournals.org/subscriptions/