Dipping and Variability of Blood Pressure and Heart Rate at Night Are Heritable Traits

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Background: Blunted nocturnal blood pressure dipping (NBPD) as well as high variability in blood pressure (BPV) and low variability in heart rate (HRV), are associated with increased cardiovascular morbidity and mortality. The aim of this study was to determine whether these traits are heritable.

Methods: We studied 260 healthy siblings without antihypertensive drugs from 118 Swedish families. The BPV and HRV were defined as the standard deviation of BP and heart rate values recorded during 24 h, daytime (6 AM to 10 PM), and night-time (10 PM to 6 AM). The NBPD was defined as the ratio between night-time and daytime BP. Heritability was estimated with a maximal likelihood method implemented in the Solar software package with and without adjustment for significant covariates.

Results: At night, significant heritability was found for systolic (33%, \( P < .05 \)), diastolic (36%, \( P < .05 \)), and mean (42%, \( P < .01 \)) BPV. After covariate adjustment the corresponding heritability values were 23% (\( P = .08 \)), 29% (\( P < .05 \)), and 37% (\( P < .05 \)). Daytime BPV was not heritable. The heritability of NBPD was 38% (\( P < .05 \)) for systolic, 9% (\( P = .29 \)) for diastolic, and 36% (\( P < .05 \)) for mean BP, but after adjustment only systolic NBPD was significant (29%, \( P < .05 \)). Heart rate was highly heritable both during daytime (57%, \( P < .001 \)) and night-time (58%, \( P < .001 \)), but the variability of heart rate, after adjustment, was only significant at night (37%, \( P < .05 \)).

Conclusions: Our data suggest that BPV and HRV are partially under genetic control and that genetic loci of importance for these traits could be mapped by linkage analysis. Am J Hypertens 2005;18:1402–1407 © 2005 American Journal of Hypertension, Ltd.

Key Words: Ambulatory blood pressure, dippers, variability, heritability, genetics of hypertension.
vascular events, underlining the prognostic value of these methods in normotensive subjects as well.\textsuperscript{19}

It is well established that BP and heart rate are heritable traits.\textsuperscript{20,21} In the Malmö family collection for the study of Macrovascular and Hemodynamic Genetics material we recently found that ABP is more heritable than office BP, especially at night.\textsuperscript{22} However, little is known about heritability of BPV and HRV. In the Framingham Heart Study it was demonstrated that HRV, as analyzed by spectral analysis of 2-h continuous electrocardiographic recording, has a heritability of 13% to 23%.\textsuperscript{23} In the same cohort, a genome-wide scan for HRV was performed, pointing out loci linked to this trait on chromosomes 15 and 2.\textsuperscript{24}

Recently another study\textsuperscript{25} analyzing ECG recording during 24 h found significant estimates for genetic contribution to different indices of HRV, ranging from 35% to 48% in different periods of the day. As the heritability of BPV and HRV, measured by ABP monitoring, has not been investigated previously, the aim of this study was to test whether BPV and HRV phenotypes are heritable traits in a family material consisting of siblings free of a history of hypertension and antihypertensive medication.

**Methods**

**Subjects**

All study participants gave written informed consent. The Ethics Committee of the Medical Faculty of Lund University approved the study, and the procedures were conducted in accordance with the institutional guidelines.

Between September 2000 to March 2002, we identified 118 families from Malmö, Sweden, which form the Malmö family collection for the study of Macrovascular and Hemodynamic Genetics.\textsuperscript{22} The probands of the families were ascertained from the population based Malmö Diet and Cancer Study\textsuperscript{26} and the Malmö Preventive Project.\textsuperscript{27} We focused the collection on siblings receiving no antihypertensive medication \((n = 260)\). Siblings with one or two parents with diagnosed and pharmacologically treated primary hypertension were primarily included. Thus 91\% of the included subjects who were without a history of hypertension and free of antihypertensive treatment had at least one first-degree relative with diagnosed primary hypertension. In total we had 104 sibships consisting of two siblings, 16 sibships with three siblings, and one sibship with four siblings. The mean age of the 260 subjects included was 38.3 ± 8.6 years, body mass index (BMI) was 25.2 ± 4.0 kg/m\(^2\), heart rate was 68.6 ± 10 beats/min. Of the subjects, 49\% were male and 22\% were smokers. The ABP and heart rate phenotypes are shown in Table 1. The degree of nocturnal BP dipping (NBPD) analyzed by “long clock-time period” (discussed later here) and expressed as night-to-day ratio was [median (inter quartile range)] 91\% (86\% to 95\%) for systolic, 85\% (79\% to 90\%) for diastolic, and 88\% (83\% to 92\%) for mean BP.

**Phenotyping**

Fasting blood samples were drawn (30 mL) for analysis of metabolic and endocrine parameters as well as for DNA isolation and 24-h urine samples were collected for all subjects. In addition, a standardized questionnaire concerning medical history was completed by all subjects. The BMI was calculated after height and weight were recorded (with subjects wearing light clothing with no shoes). Smoking was defined on the basis of current smoking habit. At the end of the visit an ABPM 90207 device (SpaceLabs Medical Inc., Redmond, WA) was applied on the left arm for ABP measurement. Two different cuff sizes were used depending on arm circumference (24 to 32 cm and 32 to 42 cm, respectively) of the study subjects. Daytime (one recording every 20 min) was defined as 6 AM to 10 PM and night-time (one recording every 60 min) as 10 PM to 6 AM (“long clock-time periods”). As this definition of day and night is not always equivalent to the subjects’ actual awake and sleep times, we also analyzed “short clock-time periods” with 00AM to 6 AM defined as night-time and 10 AM to 8 PM as daytime.\textsuperscript{9,28} in an attempt to avoid the risk that some actual night-time measurements are recorded as daytime measurements and vice versa.

Study subjects were advised to maintain the left arm relaxed along the body during each measurement. None of

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**Table 1.** Blood pressure and heart rate (HR) phenotypes measured by ambulatory blood pressure (ABP) monitoring analyzed by long clock-time period \((n = 260)\)

<table>
<thead>
<tr>
<th>ABP phenotype</th>
<th>24-h</th>
<th>Daytime</th>
<th>Night-time</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP (mm Hg)</td>
<td>123 ± 10</td>
<td>127 ± 10</td>
<td>115 ± 11</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
<td>76 ± 7</td>
<td>80 ± 8</td>
<td>68 ± 8</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>MBP (mm Hg)</td>
<td>92 ± 8</td>
<td>96 ± 8</td>
<td>83 ± 8</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>73.4 ± 9.2</td>
<td>76.8 ± 9.7</td>
<td>65.7 ± 9.2</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>SD of SBP (mm Hg)</td>
<td>11.3 ± 2.7</td>
<td>10.1 ± 2.5</td>
<td>9.8 ± 4.1</td>
<td>NS</td>
</tr>
<tr>
<td>SD of DBP (mm Hg)</td>
<td>10.3 ± 1.9</td>
<td>9.0 ± 2.1</td>
<td>8.6 ± 3.3</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>SD of MBP (mm Hg)</td>
<td>10.5 ± 2.2</td>
<td>9.3 ± 2.1</td>
<td>8.7 ± 3.4</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>SD of HR (beats/min)</td>
<td>11.3 ± 3.4</td>
<td>10.7 ± 3.3</td>
<td>7.4 ± 3.6</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

DBP = diastolic blood pressure; HR = heart rate; MBP = mean blood pressure; SBP = systolic blood pressure; SD = standard deviation.

* Daytime in comparison with night-time.
the subjects were night workers or had a shift of the ordinary day–night cycle for any other reason. None reported having smoked at night. The BPV and HRV were defined as the SD of BP and heart rate recordings during daytime, night-time, and 24-h periods. As an additional measure of BPV and HRV, we used the coefficient of variation (CV) (SD/average BP or heart rate × 100). The NBPD was defined the night-to-day ratio (night-time BP/daytime BP × 100). None of the NBPD phenotypes (systolic, diastolic, and mean BP) were normally distributed, and we therefore used the logarithm of the night-to-day ratio as NBPD phenotype throughout in the heritability calculations.

**Statistical Analysis**

Descriptive measurements are presented as means ± SD unless otherwise specified. For normally distributed continuous variables the t test was used to compare group means; otherwise, the Mann-Whitney test was used. The χ²-test was used for comparisons of group frequencies. Comparisons of different BP phenotypes within the same subject were performed by paired t test. Before calculating the heritability of BPV, NBPD, and HRV, we screened for significant covariates in multiple linear regression analyses. Potential covariates for BPV included in the regression analyses were age, sex, BMI, NBPD (only for 24-h BPV), smoking, and at the corresponding measurement period the mean BP (systolic, diastolic, or mean depending on the BPV phenotype), pulse pressure, and HRV. Potential covariates for NBPD were age, sex, BMI, 24-h BP and pulse pressure, HRV, and smoking; and for HRV age, sex, BMI, smoking and at the corresponding measurement period pulse pressure and heart rate. Each heritability analysis for BPV, NBPD, and HRV was performed with and without adjustment for significant covariates. Variables for which a normal distribution of the residuals in the regression model was not achieved were transformed in logarithmic scale. All of these analyses were performed using NCSS statistical software, version 6.0.21 (Statistical Solutions Limited, Cork, Ireland).

Heritability estimates of each phenotype were performed using standard quantitative genetic variance component analysis using the SOLAR software package (South-West Foundation for Biomedical Research, San Antonio, TX).  

**Results**

In accordance with a previous population-based study we found that age, sex, BMI, HRV, and either the corresponding (measurement period and type of BP) BP or pulse pressure were significant covariates for most of the BPV and NBPD phenotypes in the multiple regression analyses (data available on request); and we also confirmed that NBPD was an independent determinant of 24-h BPV. For most of the HRV phenotypes the significant covariates were heart rate, age, sex, and smoking (data available on request), which is also in line with previous reports. None of the models accounted for more than 49% of total phenotype variance (range 4% to 49%).

When analyzed by long clock-time periods the heritability of NBPD was significant for systolic and mean BP; however, after full adjustment the heritability was significant only for systolic NBPD (Table 2). Raw and adjusted heritability estimates for BPV are shown in Table 2, and these estimates for heart rate and HRV are shown in Table 3. The heritability of unadjusted night-time BPV and that after partial adjustment (that is, for the classical BP covariates age, sex, and BMI) was significant for systolic, diastolic, and mean BP (Table 2). After full adjustment, including BP indices, BPV heritability decreased somewhat but remained significant for diastolic and for mean BP (Table 2). No heritability was found for daytime BPV (Table 2). Heart rate was heritable during both day and night, but after full adjustment significant HRV was found only at night (Table 3).

In the supplementary analyses of heritability (Table 4) using short clock-time period (in contrast to the long
clock-time periods; Tables 2 and 3), the indices of heritability of daytime BPV were higher (although not significant), whereas some indices of heritability of night-time BPV were lower. All indices of heritability of NBPD were found to be higher, and systolic and mean BPV heritabilities were significant. The heritability indices of HRV both during daytime and night-time increased somewhat, but only night-time HRV was significant.

Discussion

The key finding of this study is that night-time diastolic and mean BPV, as well as HRV, are significantly heritable after adjustment for all significant covariates, whereas BPV and HRV during the day are not.

A likely explanation for the day–night discrepancy could be that one proportion of variance in BPV and HRV (which is related to varying degree of emotional stress and physical activity) is not genetically mediated, whereas another proportion of BPV and HRV variance, which is determined by autonomous physiologic systems, is partially under control of genetic factors. Supporting this hypothesis, at least for HRV, Kupper et al.25 found higher heritability for HRV during night-time ECG recordings than during daytime recordings when considering specific genetic components. Obviously the environmental influence of physical activity and emotional stress, as well as the influence of other lifestyle factors (such as caffeine and alcohol intake) that are difficult to quantify and therefore to adjust for appropriately, is greater during the day than at night, thereby diluting the genetic component of daytime BPV and HRV. Thus although BPV and HRV seems to be clearly more heritable with regard to night-time values than those during the day, it cannot be ruled out that a larger study sample than the present one may be able to detect a significant heritability also of daytime BPV and HRV. Furthermore, we defined the night-time period arbitrarily so as to be able to pre-program the device with fewer measurements at night in an attempt not to disturb nocturnal sleep. However, it could well be that we have underestimated both daytime and night-time BPV and HRV heritability by defining the night-time arbitrarily rather than as the subjects’ actual sleeping times.33 In an attempt to exclude the influence on BPV and HRV of subjects whose sleeping times deviated from the ones defined by the long clock-time periods, we also analyzed heritability of BPV and HRV measured during short clock-time periods. The higher heritabilities for daytime BPV and NBPD may be consequences of less influence on daytime variability of subjects getting up late or going to bed early. On the other hand, some of the heritability indices of night-time BPV decreased somewhat. As BP recordings were less frequent at night than during the day, in order not to disturb night sleep, the night-time phenotypes may be more vulnerable than daytime phenotypes to reducing the number of measurement points. One potential explanation for the reduction in some of the night-time heritability indices during the short clock-time period could thus be lower accuracy of the measured phenotypes when compared with those measured at night during the long clock-time period.

We recently found significant heritability for ABP BP phenotypes, especially for systolic, diastolic and mean BP at night and for pulse pressure regardless of measurement period.22 Because the heritability estimates for night-time BPV in the present study decreased somewhat after BPV adjustment for significant covariates including BP and pulse pressure (Table 2), it is likely that part of the

Table 3. Heritability (%) of heart rate (HR) and heart rate variability (HRV) measured by ambulatory blood pressure (ABP) monitoring (n = 260) and analyzed by long clock-time periods

<table>
<thead>
<tr>
<th>Phenotype (%)</th>
<th>SBP</th>
<th>DBP</th>
<th>MBP</th>
<th>HRV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daytime SD</td>
<td>20</td>
<td>12</td>
<td>11</td>
<td>5</td>
</tr>
<tr>
<td>Night-time SD</td>
<td>19</td>
<td>31</td>
<td>23</td>
<td>48†</td>
</tr>
<tr>
<td>Daytime VC</td>
<td>22</td>
<td>22</td>
<td>11</td>
<td>6</td>
</tr>
<tr>
<td>Night-time VC</td>
<td>15</td>
<td>27</td>
<td>22</td>
<td>48†</td>
</tr>
<tr>
<td>NBPD</td>
<td>35*</td>
<td>20</td>
<td>39*</td>
<td>NA</td>
</tr>
</tbody>
</table>

NA = not applicable; other abbreviations as in Tables 1 and 2. Heritability was calculated after “full adjustment” (see Methods and Tables 2 and 3).

* p < .05; † p < .01.

Table 4. Heritability (%) of blood pressure variability, heart rate variability (HRV), and nocturnal blood pressure dipping (NBPD) measured by ambulatory blood pressure monitoring and analyzed by short clock-time period (n = 260)

<table>
<thead>
<tr>
<th>Phenotype (%)</th>
<th>Unadjusted</th>
<th>Partially adjusted</th>
<th>Fully adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SD</td>
<td>VC</td>
<td>SD</td>
</tr>
<tr>
<td>Time period</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24-h</td>
<td>58†</td>
<td>35§</td>
<td>61†</td>
</tr>
<tr>
<td>Daytime</td>
<td>57†</td>
<td>24</td>
<td>57†</td>
</tr>
<tr>
<td>Night-time</td>
<td>58†</td>
<td>27</td>
<td>58†</td>
</tr>
</tbody>
</table>

† HR was adjusted for age, sex, and body mass index. * Adjusted for age, sex, body mass index and smoking, whereas HRV was adjusted for age, sex, and, body mass index, HR, corresponding pulse pressure, and smoking whenever significant; † P < .001; § P < .01.
heritability of night-time BPV reflects co-heritability with BP and pulse pressure. This hypothesis is supported by similar heritability estimates for the unadjusted night-time BPV phenotype of CV, which by definition is normalized for BP, as for the night-time BPV expressed as SD after full adjustment (Table 2). However, diastolic and mean night-time BPV remained significant supporting existence of genetic factors controlling these BPV phenotypes, which are separate from those controlling BP.

The reason why systolic night-time BPV heritability decreased more after adjustment than did diastolic and mean night-time BPV heritability suggests relatively stronger co-heritability between systolic night-time BPV and night-time pulse pressure. Night-time pulse pressure was a strong determinant of all night-time BPV values, and the correlation between night-time pulse pressure and systolic night-time BPV was stronger than those between night-time pulse pressure and diastolic and mean night-time BPV, respectively (data available on request). In addition, the heritability value of systolic BPV, as compared with diastolic and mean night-time BPV, was slightly lower both before and after adjustment (Table 2). Because emotional stress increases systolic BP more than diastolic and mean BP, this may be a consequence of relatively higher environmental heritability dilution of night-time systolic BPV caused by factors such as intermittent emotional stress during sleep.

In accordance with previous work in the general population, we found that HRV and pulse pressure were strong determinants of BPV, indicating that baroreceptor function and arterial stiffness are important determinants of raw BPV. Recent studies have found high heritability for baroreflex function and pulse pressure; but the fact that night-time diastolic and mean BPV heritability remained significant after adjustment for HRV and pulse pressure suggests that there are also genetic factors that affect these BPV phenotypes via pathways unrelated to baroreceptor function and arterial stiffness.

In contrast to the situation with night-time BPV heritability, systolic NBPD heritability was significant after adjustment for significant covariates, whereas diastolic and mean NBPD were not. Importantly, NBPD, which reflects the degree of day-to-night BP reduction, is a very different variability measure than BPV, which reflects constantly ongoing phasic changes in BP. In general, increased NBPD and BPV, respectively, have opposite relationships with future cardiovascular risk, further underlining the distinct nature of these two phenotypes. The finding of significant systolic NBPD heritability, indicating a genetic effect, may be clinically meaningful, as systolic NBPD has been most strongly related to future cardiovascular risk.

Our finding of significant heritability of night-time HRV, measured by ABP monitoring, is in accordance with previous studies performed with ECG recordings demonstrating that some measures of HRV, such as frequency and time domain variables, are heritable.3,25 Similar to our findings on BPV, daytime HRV was not significant. In part, this discrepancy may have an explanation similar to the lack of heritability of daytime BPV, that is, the dilution of heritability by environmental influences. However, the studies based on ECG recordings reported significant HRV heritability also during daytime periods, and it is important to remember that ABP monitoring is not as accurate as ECG recording for measuring HRV. In any case, it seems clear that night-time HRV has a significant heritability independent of known HRV determinants, suggesting the existence of genetic factors that determine HRV via pathways that are yet to be discovered.

Both BPV and HRV measured with ABP, like the more exact beat-to-beat measures of BPV and HRV recorded intra-arterially and by continuous ECG, have been shown to predict cardiovascular events, but the molecular mechanisms that determine these traits are unknown. Our finding of significant heritability of systolic NBPD and night-time measures of BPV and HRV, independently of known covariates, suggests that it may be possible to map genes of importance for these cardiovascular risk phenotypes by linkage analysis and thereby elucidate pathophysiological mechanisms for cardiovascular disease.

To date, there are no clear guidelines of how to use the information on NBPD, BPV, and HRV in clinical practice and, in particular, when and how it is worth treating them. Recently a study in spontaneously hypertensive rats showed that nitrendipine compared with hydralazine could significantly decrease BPV, thereby inducing organ protection, despite the same BP reduction suggesting that additional cardiovascular risk reduction may be achieved by monitoring and specifically treating BPV.

In conclusion, the present study shows that systolic NBPD and night-time BPV and HRV are heritable independent of known covariates, suggesting that genetic factors controlling these cardiovascular risk factors may be mapped by linkage analyses. Discovery of genetic factors for NBPD, BPV, and HRV could be helpful in identifying novel pathophysiological pathways for cardiovascular disease and in developing new, more specific drugs for cardiovascular prevention.

References


