Heart Rate as a Predictor of Future Blood Pressure in Schoolchildren

Lifen Zhou, Walter T. Ambrosius, Shirley A. Newman, Mary Anne Wagner, and J. Howard Pratt

Heart rate (HR) has been shown to predict future blood pressures (BP) in studies in adults. We explored the relation of HR to future BP levels in a cohort of 344 black and 456 white schoolchildren ages 5 to 19 years, to examine the hypothesis that HR predicts subsequent BP even very early in life. After making baseline measurements, BP was assessed longitudinally 1 to 24 additional times (mean = 8.25) after the baseline period, at intervals of approximately 6 months. We found that HR was significantly related to future diastolic BP in the black boys (P = .016) after adjusting for baseline diastolic BP, age, and body mass index, but not in the black girls or in the white children. Because HR is reflective of sympathetic nervous system (SNS) activity that in turn can be related to the renin-angiotensin system (RAS), we also explored the relation of HR to the RAS by studying relationships to variants in the angiotensinogen gene and the angiotensin I-converting enzyme (ACE) gene. We found a significantly positive relationship of HR to the presence of the deletion allele of the ACE gene (P = .0015), but, again, only in the black boys. Because blacks in general appear to retain additional sodium when compared with whites, the SNS, as reflected in the HR, may influence BP more when individuals have increased sodium retention. In summary, baseline HR predicted future diastolic BP in the black boys but not in the black girls or in the white children. Am J Hypertens 2000;13:1082–1087 © 2000 American Journal of Hypertension, Ltd.

KEY WORDS: Heart rate, blood pressure, race, angiotensin-converting enzyme gene.
explored the relationship of the HR to the renin-angiotensin system (RAS) by studying the association of RAS genotypes to HR.

**MATERIALS AND METHODS**

**Subjects** Subjects were schoolchildren, ages 5 to 19 years, who participated in a longitudinal study of BP regulation. None had hypertension, renal or cardiac disease, or diabetes mellitus, and none were taking medication that could affect BP. The Institutional Review Board of Indiana University-Purdue University of Indianapolis approved the study. In the case of minors, informed consent was obtained from a parent or a legal guardian, as well as from the subject.

**Measurements** Subjects had visits mostly at their schools for purposes of making measurements of BP and related variables, although about 20% of visits were in the outpatient facility of the General Clinical Research Center. After subjects had been sitting for 5 min, the HR was measured twice 3 min apart. The average of the two readings was used in the analyses. Individuals with a baseline HR exceeding 100 beats/min were excluded from the study, as the assumption was made that such individuals may have had a spuriously high reading because of factors such as emotional or physical stress. BP was measured in the right arm using a random zero sphygmomanometer (Hawksley and Sons, Lansing, Sussex, UK) with the subject seated. The first and fifth Korotkoff sounds were used to designate systolic and diastolic BP, respectively. Three BP readings were obtained, and the average of the last two was used as the final BP. HR, BP, weight, and height were measured approximately every 6 months. The average number of subsequent measurements was 8.25, with a range of 1 to 24.

**Genotyping** DNA was extracted from white blood cells using a standard procedure. Genotyping was performed for the angiotensin I-converting enzyme (ACE) insertion/deletion (I/D) polymorphism, where the D-allele associates with a higher level of ACE activity and the M235T angiotensinogen variant, where the T235 results in a higher level of angiotensinogen. The genomic regions encompassing the polymorphisms were amplified by the polymerase chain reaction. In the case of the ACE polymorphism, the specific alleles were identified after agarose gel electrophoresis. We also genotyped for the M235T angiotensinogen variant, where the T235-allele associates with a higher level of angiotensinogen. The angiotensinogen alleles were identified using the technique of oligonucleotide hybridization.

**Statistical Analysis** Demographic statistics for the continuous variables were calculated. Baseline measurements were compared using analysis of variance. Longitudinal data were modeled using repeated-measures analysis of variance, which allows the correlation between measurements in a given individual to be modeled. We used the compound symmetric covariance structure. Included in the repeated-measures analysis were gender, age, and body mass index (BMI), as well as genotype and baseline BP. Values are reported as the mean ± SD unless noted otherwise. A locally weighted running-line was used to estimate HR and BP as functions of age in the figures.

**RESULTS**

**Characteristics of Subjects** Baseline characteristics are presented for each gender and race subgroup in Table 1. In comparison to the whites, the blacks were about 1 year older ($P < .0001$) and their BMI was 1 to 2 kg/m² higher ($P < .0001$). Heart rate was not significantly different between the black and white children, but was significantly higher in the girls than in the boys ($P = .0054$). Systolic BP was higher in the blacks than the whites ($P < .0001$) and higher in the boys than the girls ($P = .0092$). Diastolic BP was also higher in the blacks ($P = .001$), whereas there was no significant difference in diastolic BP between the boys and the girls.

<table>
<thead>
<tr>
<th></th>
<th>Blacks (n = 159)</th>
<th>Whites (n = 230)</th>
<th>Blacks (n = 185)</th>
<th>Whites (n = 226)</th>
<th>Race, $P$ Value</th>
<th>Gender, $P$ Value</th>
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<tbody>
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<td>Age (yr)</td>
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<td>9.6 ± 2.7</td>
<td>10.4 ± 2.9</td>
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<tr>
<td>BMI (kg/m²)</td>
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<td>18.2 ± 4.5</td>
<td>19.7 ± 5.6</td>
<td>17.9 ± 3.7</td>
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<td>.84</td>
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<td>Heart rate (bpm)</td>
<td>80.7 ± 9.6</td>
<td>81.1 ± 9.9</td>
<td>83.1 ± 8.6</td>
<td>82.5 ± 8.9</td>
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<td>.0054</td>
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<td>Systolic BP (mm Hg)</td>
<td>102.6 ± 10.6</td>
<td>99.3 ± 11.3</td>
<td>100.4 ± 10.2</td>
<td>97.2 ± 11.1</td>
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<td>.0092</td>
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<tr>
<td>Diastolic BP (mm Hg)</td>
<td>63.0 ± 10.7</td>
<td>60.3 ± 10.9</td>
<td>62.8 ± 9.5</td>
<td>60.5 ± 10.1</td>
<td>.0010</td>
<td>.87</td>
</tr>
</tbody>
</table>

$BMI = $ body mass index; $BP = $ blood pressure.

Results are presented as mean ± SD. The $P$ value for race is adjusted for gender and vice versa.
Predictors of Longitudinally Measured HR

As shown in Figure 1, HR declined with age, with the boys showing the greatest decline. The differences between the black girls and the black boys ($P < .0001$) and between the white girls and the white boys ($P = .038$) were significant. The black girls showed the smallest decline, although the difference in the level between the black and white girls was only marginally significant ($P = .063$). HR declined from 0.5 beats/min per year in the black girls to 1.28 beats/min per year in the black boys. Baseline HR was strongly associated with the subsequently measured HR for each of the four race-gender groups ($P < .0002$).

In the analysis of longitudinally determined values, HR measured concurrently with the BP was positively associated with systolic BP in all subgroups with $P < .05$, except in black boys, where $P = .15$. On the other hand, the concurrent HR was negatively associated with diastolic BP in the white ($P < .05$) but not in the black children ($P = .28$).

HR and Other Predictors of Longitudinally Measured BP

As can be seen in Figure 2, BP increased with age, as expected.$^{17-19}$ Longitudinal systolic BP were significantly higher in the boys than in the girls ($P < .0001$) for both race groups, whereas longitudinal diastolic BP was not significantly different in the boys and the girls of either race. The black boys, however, had significantly higher longitudinal diastolic BP levels than the white boys ($P = .0136$) and the black girls had significantly higher levels than the white girls ($P = .0031$).

The relationships of baseline HR to future BP are presented in Table 2. All parameter estimates and $P$ values were calculated after adjusting for the other independent variables. Baseline HR was significantly related to the subsequently measured diastolic BP, but only in the black boys ($P = .016$). When no adjustment was made for baseline diastolic BP, a relationship of baseline HR to longitudinal diastolic BP was also significant in the black boys ($P = .0241$). For the black girls, there was a similar trend, with a positive association of baseline HR with longitudinal diastolic BP, but the $P$ value was .18. No relation of baseline HR to longitudinal BP, either systolic or diastolic, was observed for the white subjects. Baseline BP was a significant predictor of future BP for all the race-gender groups ($P < .0003$), and age and BMI were significantly related to the concurrently measured BP, with $P < .0001$ and $P = .0004$, respectively.

Because the activity of the SNS may be related to the RAS,$^{20}$ we also explored the association of HR to the RAS. To do this, we used information gained from genotyping components of the RAS, specifically the M235T variant of the angiotensinogen gene$^{15,21}$ and the I/D polymorphism of the ACE gene.$^{22}$ Although no association of the M235T genotype with HR was observed, a significant association with the D-allele of the ACE gene polymorphism was observed (Table 3). With genotype as the independent variable (1 df) and after adjusting for age and BMI, the presence of the D-allele was significantly related to a higher HR as assessed longitudinally ($P = .0015$) in the black boys. There was no significant relationship of ACE genotype to BP or to BMI when examined within specific race and gender groups.

**DISCUSSION**

Heart rate and BP are known to be positively related.$^{23,24}$ In fact, the development of hypertension, especially in young individuals, is often characterized by what appears to be an increased hemodynamic...
response that can be reflected in a faster HR.\textsuperscript{25–27} In the CARDIA study of young adults, HR was found to be a predictor of diastolic BP up to 10 years later in whites and in black men, even after adjusting for baseline BP,\textsuperscript{10} the strongest predictor of future BP. We performed a similar analysis but in an even younger group, individuals 5 to 19 years of age at baseline. The BP was measured in follow-up every 6 months for up to 12.9 years. We found that baseline HR predicted future diastolic BP only in the black boys, although in the black girls there was a trend for a similar relationship. No relationship of baseline HR to future BP was observed in the whites. Our study may have lacked sufficient power to detect a significant relationship of baseline HR to future BP in the black girls and in the white subjects.

Berenson et al\textsuperscript{23} found that although HR was positively associated with stratum of BP in white schoolchildren, it did not, in contrast with our results, associate with BP in black schoolchildren. The present study was longitudinal whereas theirs was cross-sectional, and in ours there were many more subjects participating. We did find in both the whites and the blacks that concurrently measured HR and systolic BP were significantly and positively related, although relationships to diastolic BP were less consistent. On the other hand, the main observation of our study was the relationship of HR to the BP level in the future, and here this was significant only in black males.

To the extent that HR is reflective of SNS activity, the SNS would appear to have influenced BP more in the black children. Although it is unclear why this might occur, we suggest that it may result from an interaction of the SNS with greater sodium retention. Blacks appear to reabsorb more sodium than whites, based on the evidence of plasma renin activity (PRA) being lower\textsuperscript{23,28} and sensitivity of BP to salt intake being more common in blacks than in whites.\textsuperscript{29} With greater retention of sodium, the SNS may convey a greater influence on vascular tone. Indeed, in primary

<table>
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<tr>
<th>Response</th>
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<td>Systolic BP (mm Hg)</td>
<td>Baseline systolic BP (mm Hg)</td>
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<td>0.24</td>
<td>.0001</td>
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<td>52.0</td>
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<td>Diastolic BP (mm Hg)</td>
<td>Baseline diastolic BP (mm Hg)</td>
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<td>0.16</td>
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<td>.0001</td>
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<td>−0.003</td>
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<td>.18</td>
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<td>89.3</td>
<td>91.7</td>
<td>85.4</td>
<td>90.9</td>
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</tbody>
</table>

Abbreviations as in Table 1.

TABLE 3. RELATIONSHIP OF THE D-ALLELE OF THE ACE GENE POLYMORPHISM WITH HEART RATE

<table>
<thead>
<tr>
<th>Predictors</th>
<th>Blacks</th>
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<td>−0.37</td>
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<tr>
<td>BMI (kg/m\textsuperscript{2})</td>
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<td>.65</td>
<td>0.08</td>
<td>.37</td>
<td>0.02</td>
<td>.87</td>
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<tr>
<td>ACE genotype</td>
<td>3.37</td>
<td>.0015</td>
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<td>.69</td>
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<tr>
<td>Intercept</td>
<td>89.3</td>
<td>91.7</td>
<td>85.4</td>
<td>90.9</td>
<td>89.3</td>
<td>91.7</td>
</tr>
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</table>

ACE = angiotensin-converting enzyme; other abbreviation as in Table 1.
aldosteronism, where the hypertension results principally from retention of excess sodium, there appears to be an additionally important SNS component to the hypertension in that cardiac index, left ventricular ejection, and HR are all increased.\textsuperscript{30} We found in a previous study that the average norepinephrine excretion rate, which partially estimates SNS activity, was slightly but significantly lower in the blacks than in the whites.\textsuperscript{31} Thus, it would appear that SNS activity per se may not have been higher in black boys (HR was also not higher), but rather there may be an important interaction with other pressor systems, such as volume expansion from increased sodium retention.

Heart rate and the D-allele of the ACE gene polymorphism were significantly related, but again only in the black boys. This may be consistent with the known interactions of the SNS with the RAS.\textsuperscript{20} Although we were unable previously to show a relationship between the D-allele and a higher ACE level in blacks,\textsuperscript{22} the D-allele could have been associated with a higher tissue level of angiotensin II. We showed previously in studies of the same young cohort that the serum ACE level (although not the ACE genotype) was significantly related to BP,\textsuperscript{22} as did two other groups, one that also studied children\textsuperscript{32} and another where normotensive adults were studied.\textsuperscript{33} A higher level of ACE may also interact with other systems, such as the SNS and sodium balance, to augment BP.

In summary, baseline HR predicted future diastolic BP independently of baseline diastolic BP in the black boys, a group at increased risk for developing hypertension. HR did not, however, predict future BP in the black girls or in the whites.

REFERENCES


