Cardiovascular Characteristics in Adolescents Who Develop Essential Hypertension

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SUMMARY The risk parameters for the development of essential hypertension (EH) were evaluated in a group of adolescents with borderline hypertension. A population comprised of 50 adolescents with systolic or diastolic blood pressure between the 90th and 95th percentile was compared to a normotensive (< 90%) family history-negative control population. Evaluative parameters included genetic risk, resting blood pressure, resting heart rate, and cardiovascular response to mental stress. In a follow-up period of up to 41 months, 28 borderline hypertensive adolescents (56%) developed fixed EH. At the time of initial evaluation, these 28 hypertensive adolescents had a strong family history of EH, higher resting heart rate ($p < 0.01$) and blood pressure ($p < 0.01$), and a greater cardiovascular response to mental stress ($p < 0.001$) compared to the normotensive family history-negative control population. Time series analysis of the stress phase also demonstrated a rhythmic cardiovascular response in the normotensive group ($p < 0.05$) that was not present in the hypertensive group. These results indicate that adolescents with borderline hypertension displaying these characteristics have a greater risk for EH than previously reported. (Hypertension 3: 521-527, 1981)

KEY WORDS adolescents · borderline hypertension · cardiovascular response · stress

LITERATURE that currently addresses the issue of pathogenesis of essential hypertension (EH) indicates that dysregulatory mechanisms evolving into the hypertensive state may have their onset in the young. Investigations interested in identifying in the young, with greater precision, predictors of future hypertension have contributed a greater overall understanding of determinants and variations of blood pressure in juveniles. Reports have characterized levels of blood pressure in the young and delineated related parameters such as body weight, height, and maturation. Within the framework of physiologic controls of blood pressure modulated by growth and maturation in the young are the potential contributing effects of genetic factors and environmental conditions.

The literature provides substantial evidence that initial blood pressure levels are the strongest single known predictors of future hypertension. Longitudinal studies have shown that those individuals with blood pressures in the higher normal ranges exhibit a greater rise in blood pressure with age. Therefore, young persons with borderline hypertension should be at greater risk for EH. These levels would correspond with the 90th to 95th percentile by the standards of the Task Force on Blood Pressure Control in Children. However, the risk for development of sustained essential hypertension in adolescents with identified borderline hypertension is not known. Julius and Schork have stated that, while in adults with borderline hypertension the risk of future hypertension is higher than the general population, this risk is not overwhelming and the majority of patients will not develop hypertension. These authors further suggest that it is a potentially identifiable subgroup of adult borderline hypertensives who may be the future hypertensive patients.

We address this issue of identifying adult hypertensives by reporting in this study blood pressure follow-up data in a group of adolescents with borderline hypertension. Further data pertaining to predictive characteristics is presented.
Methods

Subjects were selected from juveniles referred to the pediatric renal and hypertension service for evaluation of elevated blood pressure. Those who had no secondary cause of hypertension and documented blood pressures in the borderline range (90th to 95th percentile) for systolic or diastolic pressure were selected for this study. Blood pressures were determined from an average of three measurements in a seated position on three separate occasions. A total of 50 adolescents met this criteria during the initial period of observation.

In addition to a standard medical evaluation, studies to determine the cardiovascular response to mental stress were performed on all subjects, using a stress test (mental arithmetic) identical to that previously described. First, each subject rested supine for 30 minutes, after which blood pressure and heart rate were recorded at 1-minute intervals for 10 minutes; the mean of the last five recordings was considered the baseline blood pressure and heart rate for each subject. Then each participant was challenged to perform difficult mental arithmetic problems, consisting of sequential subtraction, for 10 minutes. At completion, blood pressure and heart rate measurements were obtained for the first 5 minutes of the recovery phase, using Arteriosonde (Roche).

Subjects in the normotensive control population who participated in the mental stress testing consisted of normotensive well adolescents who were recruited from adolescent health care services where they appeared for routine health assessment. All controls had negative family histories of hypertension and, on the basis of blood pressure and genetic background, were considered to be in a low risk state for future hypertension. They were closely matched for age with the hypertensive group. Informed consent to an institutionally approved protocol was obtained from all participants.

We have defined sustained hypertension as diastolic or systolic pressures repeatedly above the 95th percentile for age (Task Force) for more than 3 months (table 1). At least three measurements above the 95th percentile taken in intervals of 4 weeks or more were necessary to meet the criteria for EH. Data obtained at the time of initial evaluation from adolescents with borderline hypertension were further evaluated for distinguishing characteristics. Those adolescents who later progressed to sustained hypertension were termed "hypertensive." Those with follow-up blood observations in the borderline and normotensive range were evaluated as a separate group termed "borderline."

Differences between hypertensives vs normotensive controls and borderline vs normotensive controls in group mean values of blood pressure and heart rate were analyzed for significance utilizing a Student's one-tailed t test. The cardiovascular responses to mental stress testing was further analyzed for qualitative differences between the two groups. A harmonic analysis (Fourier) was applied to the time series data of the stress phase. The complete methodology is detailed in a preceding report. Briefly, the harmonic analysis is applied to the data of an 8-minute interval of the stress phase from the 2-minute to the 10-minute reading inclusive. The first minute determination of the stress phase represented a portion of the large increase in cardiac response due to the initial shock of the stress. By the second minute determination, the adaptability or rhythmic pattern, if it exists, would have begun. The Fourier coefficients and the Fourier series approximation of the cardiac response over the stress interval were calculated by a rectangular approximation for each cardiac response (systolic pressure, diastolic pressure, and heart rate) of each subject. The mean of the Fourier coefficients, or Fourier series, for each group and each cardiac response was obtained, and from the fitted curves the amplitude and periods of the significant Fourier terms were determined. For each cardiac response and each group, an analysis of variance was used to test the fitted average Fourier series about the observed time series data.

Results

In the follow-up period of 5-41 months (median, 17 months), 28 of the total group of 50 adolescents developed sustained hypertension. Twelve adolescents still maintained a blood pressure pattern in the borderline range (90th to 95th percentile), and six had blood pressure values in the normotensive range (< 90th-95th percentile. Follow-up data were unavailable in four males.

Family History

Of the 28 adolescents who developed sustained hypertension, the family history for EH was consistently positive: 16 had at least one parent with EH; nine had either both parents with EH or one parent...
and more than three cases in paternal and maternal relatives; one male had a negative family history; and two subjects lived in foster homes, with no family medical history available. The family history of EH in the borderline group consisted of 10 adolescents in whom the history of EH was positive, seven with a strongly positive history, and one with a negative family history of EH. Baseline data (obtained at the time of initial evaluation) for those adolescents who progressed to sustained hypertension (hypertensives) compared to the normotensive family history-negative control group are presented in table 2 together with the baseline data of the borderline group.

### Body Weight

The hypertensives were considerably heavier than control. The controls did not have uniformly normal weights, some being overweight. However, the prevalence of overweight subjects was greater in both male and female hypertensives. Eleven of 18 hypertensive males were of normal weight and seven were overweight. Borderline males were similar to hypertensives in age and weight. The hypertensive females were uniformly overweight. Borderline females were younger than hypertensive and control females, and weighed considerably less than the hypertensives, with a mean weight matching the control females.

### Cardiovascular Data

Baseline blood pressure and heart rate data (table 2) were obtained in all subjects following 30 minutes of quiet rest and prior to the mental stress studies, by the Arteriosonde (Roche) indirect blood pressure monitor with the subject in a supine position.

### Blood Pressure

The baseline blood pressures in the hypertensives obtained under these conditions were not elevated, but the mean values were greater than those obtained in the normotensive control group under the same conditions, and the difference is statistically significant. In the borderline group, only the baseline systolic pressure of the females was significantly greater than in controls.

Although the differences in mean systolic and diastolic blood pressure at baseline were significant, considerable overlap existed in individual values between control and hypertensives. However, during stress, these blood pressure and heart rate differences between the two groups increased. Stress systolic pressure, diastolic pressure, and heart rate were determined for each subject from the mean of each measurement at 1-minute intervals during the 10-minute stress phase. The systolic pressure, diastolic pressure, and heart rate of each subject (normotensive-control and hypertensive) at baseline and during stress are presented in figure 1. There was very little shift in the group mean systolic pressure or the range of pressure for the normotensive controls from the baseline state to the stress state. The hypertensives demonstrated an increase in group mean pressure during stress, with more subjects manifesting a mean stress pressure beyond the range of the controls. A similar pattern is depicted for diastolic pressure, with more hypertensive subjects emerging from the control range during stress.

### Heart Rate

With heart rate there was a significant difference between the two groups both at baseline and a greater difference during stress. In the boys very little difference in heart rate was present between the two groups at baseline. One striking finding was the high resting heart rate in the females with borderline hypertension who later developed sustained hypertension. Also, the females in the borderline group had baseline heart rates that were significantly greater than the normotensive control. No significant difference was present in the mean baseline heart rate among the three groups of boys. However, during stress, several hypertensive males developed heart rates well beyond the

### Table 2. Baseline Data During Initial Evaluation

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Males</th>
<th></th>
<th>Females</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normotens control</td>
<td>Hypertens</td>
<td>Borderline</td>
<td>Normotens control</td>
</tr>
<tr>
<td>Number</td>
<td>14</td>
<td>18</td>
<td>9</td>
<td>14</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>14.7 ± 0.5</td>
<td>15.5 ± 0.4</td>
<td>14.8 ± 0.6</td>
<td>15.1 ± 0.6</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>63.6 ± 5.3</td>
<td>83.6 ± 4.1**</td>
<td>80.4 ± 10.1</td>
<td>57.5 ± 5.0</td>
</tr>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic pressure (mm Hg)</td>
<td>110 ± 4.7</td>
<td>128 ± 2.9**</td>
<td>116 ± 4.4†</td>
<td>100 ± 4.1</td>
</tr>
<tr>
<td>Diastolic pressure (mm Hg)</td>
<td>71 ± 2.3</td>
<td>79 ± 2.3*</td>
<td>76 ± 3.3</td>
<td>67 ± 3.0</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>78 ± 3.4</td>
<td>83 ± 2.1</td>
<td>81 ± 3.9</td>
<td>78 ± 2.0</td>
</tr>
</tbody>
</table>

Values presented are mean ± standard error. Baseline blood pressure was determined by Arteriosonde in rested supine position. Significance values for hypertensive vs normotensive control and borderline vs normotensive control are determined by one-tailed t test. * = p < 0.05; ** = p < 0.01; *** = p < 0.001. Significance for hypertensive vs borderline are noted † = p < 0.05; †† = p < 0.01.
control range ($p < 0.01$). The females demonstrated a different pattern in that, at baseline, the hypertensives had heart rates greater than the control ($p < 0.001$); the difference increased further during stress. As figure 1 shows, all but one of the hypertensive females had heart rates during stress beyond the range of the normotensive control females.

Therefore, the hypertensives were as a group distinguishably different from the normotensive controls in blood pressure and heart rate in a resting state, and this difference became quantitatively greater during stress testing. Those subjects in the borderline group who had baseline values that were not strikingly different from the normotensive control, with the exception of the female heart rate, manifested increased blood pressure and heart rate during mental stress that were also greater than the normotensive control, and significantly different (systolic pressure during stress, $p < 0.01$; diastolic pressure, $p < 0.001$; heart rate, $p < 0.001$).

Statistical Analysis

The data were further analyzed by time series analysis for qualitative differences in the cardiovascular response to stress among the three groups. Figure 2 provides the mean values for systolic pressure, heart rate, and diastolic pressure during the stress phase for the hypertensives and normotensive controls. These curves depict the minute-to-minute variation in cardiovascular response parameters and demonstrate the patterns identified by the time series analysis. Time series analysis of the stress phase data indicates a rhythmic cardiovascular response for the normotensive groups with a period of approximately 4.5 minutes. During the mid-8 minutes of the stress phase, a statistically significant ($p < 0.05$) periodic regression was found for heart rate and systolic blood pressure. For diastolic blood pressure, the statistical significance of the periodic regression approached the 0.05 level ($p = 0.052$).
By contrast, in the hypertensive group the cardiovascular response was near constant for the same time period. None of the coefficients of the periodic regression was statistically significant. In the hypertensives, the average slopes computed from a linear regression analysis for each of the cardiovascular response parameters were not statistically different from zero. Therefore, the periodic regression in cardiovascular response during stress that was demonstrated in the normotensive controls was absent in those adolescents with borderline hypertension who progressed to sustained hypertension. The borderline group also had no significant periodic regression in any of the cardiac parameters.

Of 50 adolescents who met the criteria of borderline hypertension, 28 (56%) progressed to a state of sustained hypertension within 4 years. Previous studies that investigated the eventual outcome in populations with borderline hypertension have demonstrated an incidence of EH greater than in the general population, but none has described a high incidence in a relatively short follow-up period, such as that reported here.

The 28 adolescents progressing to EH manifested a number of characteristics at the time of their initial evaluation that clearly distinguished them from the normotensive-family history negative control population. They are also not typical of the borderline hypertensive populations of previous surveys and may well represent the “subgroup” to which Julius and Schork alluded.

Nearly all of the hypertensive adolescents had a strong family history of EH. In general, they were heavier. While the females were uniformly heavier, the males who progressed to EH included a mixture of normal weight and overweight boys. A consistent finding in those adolescent females who progressed to sustained hypertension was the presence of a high resting heart rate. A similar observation was made in some but not all adolescent males who progressed to sustained hypertension. Additionally, all of our adolescent patients who progressed to EH manifested a high blood pressure and/or heart rate in response to mental stress. With a characteristic pattern quite different from the low-risk normotensive control population. The 22 adolescents who did not develop fixed EH, whom we have identified for this report as borderline, continue to be followed. As a group they were younger at the time of study than those who have already become hypertensive, and had lower baseline blood pressures. However, as a group they also demonstrated a high cardiovascular response to mental stress. Since the follow-up period is relatively short, we cannot predict with any certainty whether they will develop fixed EH.

Many of the characteristics described in the 28 adolescents who progressed to fixed EH are not unique to this study. Excess body weight is a recognized risk factor for EH, and has some predictive strength for EH. However, as previously noted, many of the males in this report who progressed to EH were in a normal range of body weight. An elevated heart rate has been associated with borderline hypertension. The strength of transient tachycardia as an independent predictive factor in adults appears to be weak. No longitudinal data are available pertaining to the power of an elevated heart rate identified in childhood or adolescence as an independent predictor of future hypertension. However, the combination of transient tachycardia with systolic pressure elevation was found to be related to the highest subsequent prevalence of EH in a survey of young adults by Levy et al.
Essential hypertension occurs more frequently in individuals with a positive family history. Furthermore, the progression from borderline hypertension to EH is at a higher prevalence ratio when the family history is positive. In this report, the family history of EH was uniformly strong in those adolescents who progressed to EH. An elevated blood pressure response to mental stress in borderline hypertension has been previously described. Despite previous observations, the predictive value of this exaggerated response has not been proven. However, a major characteristic elicited in this population of adolescents with the combination of borderline hypertension plus strong family history of EH was the pronounced blood pressure and heart rate response to mental stress. Not only were their baseline values higher but the absolute increase during stress was greater than in control. Additionally, there was a characteristic pattern of response noted in the hypertensive adolescents. The normal dampening effect in the responses of heart rate and blood pressure observed in the controls with continued stress was not present in the hypertensives. These observations would suggest limitation or withdrawal of normal feedback or adaptive mechanisms.

The hyperkinetic cardiovascular state of borderline hypertension has been well described. Changes provoked by mental stress should be mediated through the central nervous system. Previous studies have demonstrated a state of impaired neurogenic activity in borderline hypertension. The hyperkinetic state described in borderline hypertension may be associated with increased sympathetic activity or a combination of reduced parasympathetic and increased adrenergic activity. In this group of hypertensive adolescents, not only was the cardiovascular stress response quantitatively greater than control but the qualitative pattern of blood pressure and heart rate response was quite different. The normotensive controls demonstrated an initial increase of heart rate and blood pressure at the onset of stress. As indicated through Fourier analysis, the normotensive controls demonstrated a rhythmic progressive reduction in heart rate and systolic pressure despite continued stress. In the hypertensives, not only was the periodicity of the cardiac response blunted but the initial increases of blood pressure and heart rate were sustained throughout the stress; these subjects did not manifest a pattern of cardiovascular adaptation to continued stress as seen in the controls. These observations may imply a reduced feedback or compensatory mechanism and are suggestive of an impaired neurogenic component of blood pressure control. Whether this pattern represents a unique type of hypertension or is one portion of a composite requiring other factors such as disturbances of blood volume, distribution, or flow is as yet an unresolved issue, and we did not attempt to evaluate these areas in this group of adolescents.

The results of this study indicate that some adolescents with borderline hypertension have a greater risk for progression to sustained EH than previously reported. Characteristics of those who develop EH include a uniformly strong family history of EH, higher body weight and resting heart rate (particularly in females), and a cardiovascular response to mental stress greater and qualitatively quite different than normotensive-family history negative controls. These findings are consistent with the concept of a dysregulatory neurogenic component in essential hypertension.

References

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