SUMMARY The hemodynamic response to mental stress (mental arithmetic) was studied in adolescents with varying risk factors for essential hypertension (EH). One group (genetic) consisted of normotensive well adolescents who had at least one parent with EH. Another group (labile) consisted of adolescents with labile hypertension each of whom also had at least one parent with EH. The control population consisted of normotensive adolescents with a negative family history of EH. Subjects with labile hypertension demonstrated a sustained increase in systolic and diastolic pressure and heart rate during stress. This response was significantly different than the control population (p < 0.001). The stress response of the nonhypertensive genetic population was qualitatively similar to the group with labile hypertension and significantly different than the controls in diastolic pressure and heart rate (p < 0.001, < 0.02). Post-stress plasma catecholamines were higher in the labile hypertensive and genetic groups than in the control group. These findings demonstrate increased central nervous system mediated adrenergic activity and cardiovascular response in labile hypertension and also in some normotensive subjects with a genetic risk for hypertension.

KEY WORDS • mental stress • adolescents • essential hypertension • labile hypertension • genetic risk

DESPITE varying opinions concerning the etiology of essential hypertension (EH) most investigators agree on the importance of genetic factors. Experimental and epidemiological studies have demonstrated that hypertension is also related to environmental conditions that require continuous behavioral and physiological adjustments. The mechanism through which the interaction of genetic and environmental factors operate, thus directing the development of increased arterial pressure, has yet to be established. However, it is possible that EH results from an altered interaction between various mechanisms involved in normal blood pressure regulation. It is also suggested that these mechanisms are operative in the prehypertensive state. Mental stress can induce a spectrum of physiological changes, and the unfavorable effect of mental stress on established hypertension is generally accepted. Mental stress also has a precipitating effect on the onset of hypertension in young spontaneously hypertensive rats. However, a definite link between stress and a hypertensive mechanism in man has yet to be clearly defined.

It is not known whether young human prehypertensive individuals also manifest a pressor response to mental stress that is greater than or different from normotensive individuals. Additionally, it is not known whether young prehypertensive individuals

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manifest an inherent central hyperreactivity to psychogenic stimuli. These issues were the focus of investigation in this study. Since there is currently no means by which to identify the prehypertensive individual specifically, we have chosen to study a population of adolescents with a high genetic risk for development of EH.

The purpose of this study was to determine if normotensive adolescent offspring of adults with EH (i.e., those with genetic risks) manifest a hemodynamic response to mental stress that is different than the hemodynamic response to stress of adolescents in whom there is no family history of EH.

Methods

The subjects in this study were divided into three groups on the basis of risk for EH. Table 1 presents the subject information on the three study groups. Control subjects were defined as normotensive (diastolic pressure < 90th percentile) well adolescents with no family history of EH for at least three generations. All parents substantiated a negative family history of EH by reporting periodic health examinations at which blood pressure determinations were normal. The study group defined as "genetic" consisted of normotensive well adolescents each of whom had at least one parent with EH. All subjects had blood pressure determinations below the 90th percentile and had no previous history of elevated blood pressure. The study group defined as "labile" consisted of adolescents who had had documented diastolic pressure determinations greater than the 95th percentile interspersed with periods of normotension. Additionally, each subject had at least one parent with EH. All subjects had been evaluated for hypertension with no underlying cause for the hypertension identified in each case. Thus, the labile hypertensive subjects were considered at high risk for EH. In most of them the testing was done following completion of the diagnostic evaluation which required several days of hospitalization. Subjects in control and genetic groups were recruited from Adolescent Ambulatory Health Care Centers where they appeared for periodic health review. Subjects in the labile group were individuals who had been referred to the adolescent hypertension clinic for evaluation of documented elevated blood pressure. The study was explained to each subject and the subject’s parents, and informed consent was obtained before testing.

The methodology of testing hemodynamic response to stress was similar to that of Brod et al. However, since this study involved essentially well adolescents, the methodology was simplified and noninvasive techniques were employed. Blood pressure was determined by the Arteriosonde automatic blood pressure monitor (Roche). The heart rate was determined from the auditory signal between systolic and diastolic pressure of each blood pressure determination. Blood pressure and heart rate were measured at 1-minute intervals. All blood pressure measurements presented in this report were performed with the Arteriosonde. Upon arrival at the study center, each subject rested at least 1/2 hour and then voided before the testing. Blood pressure and heart rate were then measured with the subject in the supine position. Talking and activity in the testing room were kept minimal. After at least 10 minutes of monitoring, baseline blood pressure and heart rate were determined from the mean of the last five recordings. Each subject was then challenged to perform difficult mental arithmetic against time. Difficult subtraction problems were given and the subjects were urged to respond with sequential answers as rapidly as possible until a laboratory alarm sounded in 1 minute. When the alarm sounded, the next math problem was immediately given and the subject was again urged to respond. All subjects included in this report actively engaged in the math and, in addition to their hemodynamic response, manifested other evidence of stress such as flushing, staring, grimacing, shaking a foot or arm in struggling to provide responses. Continuous stress was applied in this manner for 10 minutes. At the end of 10 minutes the subject was informed that she/he had performed well and the math testing was completed. Blood pressure and heart rate were recorded for 5 minutes after completion of the mental arithmetic and these measurements were used to determine the mean recovery phase blood pressure and heart rate. After the 5-minute recovery period, a blood specimen was obtained for catecholamine determination. Plasma catecholamines were determined spectrophotometrically with a micro adaptation according to the method of VonEuler and Lishajko. Two persons participated in the testing of each subject. One individual recorded the blood pressure and heart rate. This individual was unaware of the group assignment of the subject being tested. The other individual (one or other of the two authors) applied the
mental stress. The person applying the stress knew the group assignment of the subject but had no knowledge of the pressure and heart rate responses being recorded until completion of the testing. The testor's objective was to apply continuous stress for 10 minutes by urging the subject to perform the difficult arithmetic as quickly as possible. There were no differences in response patterns between the two testers applying the stress.

Results

Baseline blood pressure and heart rate for the three groups are presented in table 1. Under these conditions the baseline pressure was essentially the same in the control and genetic group. When the baseline measurements were compared on the basis of age, race and sex they were also similar. Baseline systolic and diastolic pressures were higher in the labile hypertensives. These differences were more than could be attributed to the slightly higher mean age of the labile group. Therefore, the differences are real but not statistically significant. Although both the genetic and labile subjects manifested a baseline heart rate that was higher than the controls, these differences were also not statistically significant.

The change in systolic pressure in response to stress is presented in figure 1. For each group the mean systolic pressure in mm Hg is plotted against time for 10 minutes and an additional 5-minute recovery phase. The control group manifested a slight rise in systolic pressure during stress that approached the baseline level in the recovery phase. The pattern of systolic response to stress was somewhat higher in the genetic group. The labile group manifested a greater rise in systolic pressure response and during the recovery phase systolic pressure was greater than baseline. The mean of the systolic pressure changes during stress for all labile subjects was higher than in the control group, (controls = $\bar{x} = 5.95$ mm Hg $\pm 5.53$ SD; labile = $12.64$ mm Hg $\pm 5.52$ SD). This difference is statistically different ($p < 0.001$) when analyzed by one-tailed $t$ test.

Major differences among the three groups were demonstrated in the pattern of diastolic response to stress (fig. 2). All subjects in the control group demonstrated a similar pattern of change in diastolic pressures. In each, there was an immediate increase followed by an abrupt drop to baseline or sub-baseline levels. This change occurred in the initial 4 minutes of stress, and was followed by lesser fluctuations. The recovery phase diastolic pressure was less than baseline. The response to stress in the labile group was an abrupt rise in pressure that was significantly higher than the controls. This increase in pressure was sustained throughout the duration of stress and the recovery phase pressure was considerably greater than the baseline. The genetic group

![Figure 1](http://hyper.ahajournals.org/)

**Figure 1.** The change in systolic pressure during stress is plotted against time. Mean pressure $\pm$ SE of each respective group is shown at 1-minute intervals during stress and in the recovery phase. The mean of the pressure changes for all subjects of each group during the entire period of stress is: controls, $\bar{x} = 5.95$ mm Hg; genetic, $\bar{x} = 8.5$ mm Hg; labile, $\bar{x} = 12.64$ mm Hg. The difference between labile and controls is significant ($p < 0.001$). The difference between labile and genetic is also in a significant range ($p < 0.05$).
had a stress-response pattern similar to the labile group with an increase in diastolic pressure that was greater than the controls. Additionally, like the labile group, the increase was sustained throughout the duration of stress and the recovery phase pressure was greater than baseline. The mean of the diastolic pressure changes during stress for all subjects in each group were the following: controls, $\bar{x} = 3.5$ mm Hg; genetic, $\bar{x} = 11.3$ mm Hg; labile, $\bar{x} = 16.2$ mm Hg. A significant difference exists between controls and labiles ($p < 0.001$) and controls and genetics ($p < 0.001$). There is also a difference between genetics and labiles ($p < 0.05$).

The heart rate response to stress is presented in figure 3. The change in heart rate during stress demonstrates a pattern in each group that corresponds to the diastolic pressure response in each group. The controls demonstrated an abrupt increase in heart rate followed by abrupt drop in heart rate approaching baseline in the initial 4 minutes of stress. The labile and genetic groups both manifested an abrupt increase in heart rate that was sustained for the duration of stress. The difference in heart rate change during stress in both labile and genetic groups is significantly different than the control group ($p < 0.001$ in labile and $p < 0.02$ in genetic).

It was expected that subjects in the genetic group would consist of a heterogenous population. On the basis of the pattern of stress response, two subgroups were clearly identified (fig. 4). One subgroup consisted of low responders who had a diastolic pressure response similar to the controls. The other subgroup consisted of high responders who had diastolic pressure responses that were both qualitatively and quantitatively similar to the labile group. A summary of the statistical analysis is presented in table 2. Since the primary interest in this study was to detect significant increases between a priori chosen groups, it was not considered meaningful to consider decreases as statistically significant. Therefore, a one-tailed rather than a two-tailed $t$ test was chosen as the more appropriate statistical test. Application of the one-tailed $t$ test to the data from these two subgroups demonstrates a clear separation. Particularly with respect to diastolic pressure, the high-response subgroup was clearly different than control. Additionally, systolic pressure and heart rate results were statistically different. Analysis of the variances between the three groups indicates no significant differences between the variances. Therefore, the differences in the means is an indication that the entire frequency distribution of the differences is shifted in the same direction as the mean. Furthermore, the genetic group is divided into two subgroups on the basis of the distribution of the differences.

**Figure 2.** The change in diastolic pressure during stress is plotted against time. Mean pressure ± se of each group is presented at 1-minute intervals during stress and in the recovery phase. The mean of the pressure changes for all subjects of each group during the entire period of stress is: controls, $\bar{x} = 3.5$ mm Hg; genetic, $\bar{x} = 11.3$ mm Hg; labile, $\bar{x} = 16.2$ mm Hg. A significant difference exists between controls and labiles ($p < 0.001$) and controls and genetics ($p < 0.001$). There is also a difference between genetics and labiles ($p < 0.05$).
A significant finding appeared to be the change in diastolic pressure in the recovery phase. These data are presented in figure 5. Most control subjects had a mean diastolic pressure in the recovery phase that was near the baseline (mean 70 mm Hg ± 2.0). All subjects in the labile group demonstrated a significantly higher recovery phase diastolic pressure (mean 84 mm Hg ± 2.1). The genetic group demonstrated a mean recovery phase diastolic pressure of 76 mm Hg ± 2.0, which was higher than the controls. However, the genetic group consisted of a mixture of low and high responders.

The results of the post-stress plasma catecholamine determinations demonstrate that both the labile and genetic groups had higher plasma levels than the controls (table 3). Although there was considerable variation, this difference is reflected in the mean values as well as the number of individuals who had elevated plasma levels greater than 1.0 μg/l. Since plasma catecholamine values are not statistically distributed in a Gaussian (normal) distribution, the proportion of individuals with elevated values is a more reliable index of difference between groups. Four of 20 control subjects (20%) had plasma values exceeding 1.0 μg/l at the completion of the test when the blood sample was taken. By contrast, 57% of the individuals in the labile group and 41% of those in the genetic group had values in excess of 1.0 μg/l. The largest values observed were 3.12 μg/l for an individual in the labile group and 5.45 μg/l for a high responder among the genetic group. Within the two subgroups of genetic subjects, two of nine low responders (22%) had plasma catecholamine levels exceeding 1.0 μg/l versus nine of 18 (50%) high responders.

Discussion

Mental stress has been defined as “a set of events in the social milieu which modify steady state conditions so as to activate adaptive mechanisms.” Various clinical and experimental studies have demonstrated an association between stress and elevated blood pressure. A relevant question is to what degree does a given type of stress simulate common environmental events. In human subjects, stressors that evoke active coping behavior are apt to involve beta-adrenergic mechanisms and produce a shift in baseline heart rate and systolic blood pressure. All subjects in this study actively engaged in the arithmetic activity and although the task was difficult to perform they were able, to some degree, to succeed. Mental arithmetic demands an active coping
The results of the diastolic pressure response in the two subgroups of the genetic subjects are shown. The low-response group demonstrated a stress-response pattern similar to the controls (low response, $\bar{x} = 3.90$ mm Hg) and the stress-response pattern in the high-response group is similar to the labile group (high response, $\bar{x} = 15.53$ mm Hg). The difference between controls and the high-response subgroup is significant ($p < 0.001$). There is no statistically significant difference between controls and the low-response subgroup.

behavior$^{17}$ and therefore would appear to be an effective and consistent type of stressor in the study of neurohemodynamic function in school-age children.

The data in this study revealed a striking contrast between the control and labile groups in the hemodynamic response to a central nervous system stressor. In all control subjects there was an immediate stress response of an abrupt rise in heart rate and pressure followed by a decrease in diastolic pressure and heart rate in face of continued stress. In contrast, the subjects within the labile group demonstrated a higher baseline heart rate and a stress-response pattern of a sustained increase in heart rate and diastolic pressure. Experimental evidence to explain mechanisms directing the hemodynamic response to mental stress in children is quite limited. Studies in animals$^8$ and in human adults$^{21}$ utilizing pharmacologic blockade with beta-adrenergic blockers and atropine have demonstrated the significance of sympathetic and parasympathetic activity in hemodynamic response to stress.

Clinical investigation of labile hypertension in adults has documented that the hemodynamic pattern includes an increased cardiac output with a calculated total peripheral resistance that is not significantly different than controls.$^{22}$. Possible mechanisms to account for this hyperkinetic circulatory state include emotional hyperreactivity,$^{24}$ attenuated baroreceptor sensitivity$^{25}$ and increased adrenergic input to the heart.$^{26}$ Our findings of a sustained increase of diastolic pressure and heart rate during stress in the labile subjects and in many of the genetic subjects, with an absence of the early drop of pressure and heart rate as seen in the controls may be due to sympathetic overactivity or possibly due to sympathetic excitation combined with vagal suppression.

Experimental studies have investigated the activity of the autonomic nervous system in the young of spontaneously hypertensive animals. It has been demonstrated that very young (1–2 months) spontaneously hypertensive rats display an increased cardiac turnover of epinephrine as compared with normotensive control rats.$^{37}$ On the other hand, studies that have compared cardiac epinephrine turnover times of older hypertensive rats to normotensive control rats suggest a lower rate of epinephrine turnover in the hypertensive animals.$^{28}$ Further indirect evidence, which implicates an increased cardiac sympathetic activity in young spontaneously hypertensive rats, is the effectiveness of early beta-adrenergic blockade treatment in reducing an increase in blood pressure with advancing age.$^{29},^{30}$ However, when the young spontaneously hypertensive animals were treated with a beta-adrenergic blocker that did not enter the brain, the characteristic progressive increase in arterial pressure occurred, although the heart rate
and cardiac output remained low. Further support of the hypothesis that genetic hypertension is mediated through central adrenergic hyperreactivity has been provided in studies where application of mental stress to young normotensive Okamoto rats resulted in a dramatic elevation in arterial pressure and in earlier onset of hypertension. The findings in the above reports indicate that in spontaneously hypertensive rats, there is an increase in neurogenic influence on the heart and vascular system at a young age before the development of hypertension.

The findings in the above reports indicate that in spontaneously hypertensive rats, there is an increase in neurogenic influence on the heart and vascular system at a young age before the development of hypertension. The results in the genetic group of children in our study provide data that correspond to the findings in the animal model for hypertension. Our subjects were all well adolescents and were all normotensive. Their only vascular risk factor was that of a significant family history of hypertension. Within this group were a number of subjects who demonstrated a sustained diastolic pressure response to the mental stress which was similar to the labile group consisting of subjects with a significant family history of EH plus labile hypertension. Although it is not certain that either the labile subjects or the normotensive adolescents in the genetic group will eventually become hypertensive, the similarity of the stress-response pattern is striking in face of a strong genetic potential for EH.

Clinical investigations performed to determine the role of catecholamines in essential hypertension have produced equivocal results. Ziegler and associates have demonstrated an increase in noradrenaline with age. It has also been reported that there is no difference in plasma norepinephrine levels when the results are adjusted for age. On the other hand, Sever et al. have recently demonstrated differences in levels of plasma norepinephrine in hypertensive versus control subjects in response to postural change. In their study, the differences between control and hypertensive groups were more apparent in younger subjects. Therefore, it was suggested that, in some patients,
autonomic overactivity may be important in early stages of hypertension with other factors subsequently becoming involved in maintaining the pressure elevation. That hypertension in some patients may be neurogenic and possibly originate from the central nervous system has also been proposed from results of clinical study by others. The results of post-stress catecholamines in our study support these experimental and clinical findings.

Our observations on plasma catecholamines show distinct differences in the control group as compared to the labile and genetic groups. However, the design of the study does not permit an evaluation of whether the elevated plasma catecholamine values observed reflected an exaggerated and/or maintained adrenergic response versus an elevated basal level of plasma catecholamines in these individuals.

In conclusion, this study has demonstrated that adolescents with early labile hypertension manifest a sustained increase in heart rate and diastolic pressure response to mental stress, with a higher recovery phase pressure. This pattern is quite different than the control population. These findings are consistent with the explanation that the hyperkinetic circulatory state is associated with increased sympathetic activity or possibly a combination of reduced parasympathetic and increased adrenergic cardiac influences. Additionally, these changes are mediated through the central nervous system. Our findings also show that some normotensive adolescents with a genetic risk for essential hypertension manifest a similar hemodynamic response to mental stress and have corresponding elevated plasma catecholamines.

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