Summary This study compared changes in forearm blood flow, forearm vascular resistance, blood pressure, and heart rate elicited by mental stress (mental arithmetic) in 12 adolescents with a hypertensive parent and 13 age-matched adolescents with normotensive parents. The two groups did not differ in resting forearm blood flow, forearm vascular resistance, heart rate, or blood pressure. During mental stress, children with a family history of hypertension had a significantly greater increase in forearm blood flow than did children of normotensive parents (+37.5 ± 8.0 vs +12.8 ± 7.5%; p < 0.05) and a trend toward reduced forearm vascular resistance (p = 0.08). Mental stress significantly increased systolic blood pressure (p < 0.0001), diastolic blood pressure (p < 0.001), and heart rate (p < 0.03) in both groups. The blood pressure and heart rate responses to stress were not significantly different between groups. There was no evidence of a prolonged response or a different pattern of recovery in children with a family history of hypertension. This study indicates that regional blood flow responses underlying similar blood pressure increases during mental stress may be different in adolescents with and without a family history of hypertension.

Key Words • hypertension • stress • forearm blood flow • genetic risk • adolescents

Psychological stress has long been thought to play a role in the development of hypertension. Exposure to such stressors as overcrowding, shock avoidance tasks, and conditioned fear stimuli have been shown to be related to the onset of hypertension in animals. In humans, stressful employment, living conditions, war, and natural disasters have been associated with elevated blood pressure. Laboratory studies have shown that performing difficult mental tasks can elicit transitory elevations in blood pressure and heart rate. These increases are part of an integrated pattern of hemodynamic changes (the defense response) that includes increased blood pressure, heart rate, cardiac output, and blood flow to skeletal muscle and reduced splanchnic blood flow. Folkow has proposed that the effects of repeated, psychologically induced activation of the defense response on baroreceptor function and vascular structure may be important in the pathogenesis of hypertension. Research to date suggests that stress alone is not sufficient to cause hypertension in the absence of a predisposing risk factor. One risk factor is a family history of hypertension, and increasing effort has been made to identify cardiovascular dysfunctions that may be present in children of hypertensive parents. Recent studies have shown enhanced blood pressure and heart rate responses to stress in children and college students with a family history of hypertension. Elevated blood pressure responses to stress have been associated with the development of hypertension. In a 4-year follow-up of children with a family history of hypertension, Falkner et al. found enhanced blood pressure responses to mental stress predicted which children later became hypertensive.

Blood pressure increases during stress are the product of multiple cardiovascular adjustments, including changes in blood flow to different vascular beds. How-
ever, most studies comparing children with and without a family history of hypertension have measured only blood pressure and heart rate. Few studies have examined changes in regional blood flow. The potential value of such study is suggested by Williams et al., who found greater forearm blood flow increases during stress in Type A than in Type B individuals. Further, studies of animals genetically predisposed to become hypertensive indicate there may be differences in regional blood flow responses to stress that are not reflected in blood pressure. Therefore, the goal of this study was to determine whether differences exist in regional (forearm) blood flow, as well as in blood pressure and heart rate, during mental stress in children with and without a family history of hypertension.

Subjects and Methods
Subjects were selected from children whose families participated in the Muscatine Study, a longitudinal study tracking blood pressure and lipid levels of families in Muscatine, Iowa. Thirteen children with a hypertensive parent were compared with 13 age-matched children of normotensive parents. One child with a hypertensive parent missed several testing appointments and was dropped from the study.

A parent was defined as hypertensive after receiving a clinical diagnosis of hypertension if two cardiologists concurred on the diagnosis by chart review. In addition, at least one of the parent's three most recent diastolic blood pressure readings at the Muscatine Health Clinic had to exceed 95 mm Hg (average blood pressure for the 3 visits: systolic, 142.9 ± 10.6 mm Hg; diastolic, 96.0 ± 5.3 mm Hg). A normotensive parent was one with all diastolic blood pressure readings less than 90 mm Hg at the three most recent clinic visits (average blood pressure for the 3 visits: systolic, 122.3 ± 13.1 mm Hg; diastolic, 77.9 ± 6.1 mm Hg). The mean age of normotensive parents was 38.6 years (range, 32-47 years) versus 42.0 years (range, 33-51 years) for hypertensive parents.

Stress Protocol
After instrumentation for hemodynamic measurements, 5 minutes of supine baseline recordings were taken, followed by 1 minute of task instruction and 9 minutes of mental arithmetic. The stress task followed the methods of Falkner et al. and involved serially subtracting two-digit from four-digit numbers. Subjects were continuously pressured to speed performance. Stress was followed by a 5-minute recovery period.

Subjects were kept actively engaged in the task by altering task difficulty to match a child's ability. All reported the procedure as aversive and showed evidence of stress, such as flushing, shivering, and obvious relief at the end of the stress task. After task completion, subjects were told they had performed a difficult task well.

Two individuals recorded blood pressure and forearm blood flow while a third, unaware of hemodynamic responses, delivered the mental stress. All were unaware of a subject's family history. Subjects were told the study involved measuring cardiovascular responses to intense mental activity and were not told their family history. The study was approved by the Human Experimentation Committee, University of Iowa College of Medicine. Children and parents gave informed, written consent.

Measures
Blood pressure was measured once each minute by an Arteriosonde automatic blood pressure monitor (Model 1216; Roche, Cranbury, NJ, USA), which we have shown to measure accurately systolic and diastolic pressures in children. Heart rate for each minute was read from an electrocardiogram. Forearm blood flow was measured by mercury-in-Silastic strain gauge plethysmography with intermittent venous occlusion timed to allow four measurements per minute. Forearm blood flow (in ml/min/dl forearm volume) was measured during Minutes 1 to 3 of baseline, Minutes 1, 4, 7, and 10 of stress; and Minutes 1, 2, 4, and 5 of recovery. Forearm vascular resistance was calculated by dividing mean arterial pressure (diastolic plus one third pulse pressure in mm Hg) by forearm blood flow.

Data Analysis
Groups were compared by t test on the means of values taken during the 5-minute prestress period. Responses of the two groups during stress were compared by repeated-measures analysis of variance comparing values during the instruction and arithmetic stress periods. The instruction period was included in the stress period because our experience has shown that task instruction elicits considerable anticipatory anxiety. To determine if the pattern of recovery between the groups differed, values during individual minutes of the recovery period were compared by repeated-measures analysis of variance. Stress and recovery period values are expressed as the percent change from baseline. Data are reported as means ± SE. A 0.05 level of significance was used for statistical tests.

Results
Population Characteristics
The 12 children of hypertensive parents (6 boys and 6 girls) had a mean age of 14.8 ± 0.6 years (range, 11-17 years), a mean weight of 54.3 ± 3.8 kg, and a mean height of 159.3 ± 6.2 cm. The 13 children of normotensive parents (8 boys and 5 girls) were of similar age (13.7 ± 0.4 years, range, 11-17 years), weight (49.1 ± 2.8 kg), and height (152.2 ± 7.6 cm). The groups did not differ significantly in age, weight, or height (p > 0.10).

Baseline Measurements
There were no significant group differences during the prestress baseline period in systolic and diastolic blood pressures, forearm blood flow, or forearm vascular resistance (all p > 0.10; Table 1). Baseline heart rate was somewhat lower in the children of hypertensive parents (p = 0.09).
TABLE 1.  Prestress Hemodynamic Values

<table>
<thead>
<tr>
<th>Variable</th>
<th>Children of hypertensive parents (n = 12)</th>
<th>Children of normotensive parents (n = 13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (beats/min)</td>
<td>74.5 ± 2.9</td>
<td>80.9 ± 2.3*</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>113.6 ± 2.0</td>
<td>114.7 ± 3.3</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>71.1 ± 1.6</td>
<td>74.4 ± 2.7</td>
</tr>
<tr>
<td>FBF (ml/min/dl)</td>
<td>4.6 ± 0.5</td>
<td>3.9 ± 0.4</td>
</tr>
<tr>
<td>Forearm vascular resistance (MAP/FBF)</td>
<td>21.1 ± 2.0</td>
<td>25.4 ± 2.9</td>
</tr>
</tbody>
</table>

Values are means ± SE. BP = blood pressure; FBF = forearm blood flow; MAP = mean arterial pressure. *p = 0.09, compared with values for children of hypertensive parents.

Stress Period

Mental stress significantly increased heart rate (p < 0.03), systolic blood pressure (p < 0.001), and diastolic blood pressure (p < 0.001) in both groups. In no case was the difference between the children of hypertensive and normotensive parents significant. Heart rate increased by approximately 15% during the first minute of stress and remained elevated throughout the mental stress period (Figure 1). Systolic blood pressure increased during the first 4 minutes and remained approximately 8% above baseline (Figure 2). Diastolic blood pressure increased gradually, peaking at approximately 18% above baseline during Minutes 5 to 7 of the stress period (Figure 3). In contrast to blood pressure and heart rate, there was a significant difference between groups in forearm blood flow increases during stress (p < 0.05; Figure 4). The peak increase in forearm blood flow for the children of hypertensive parents was 37.5 ± 8.0%. This increase was almost three times greater than the peak increase of 12.8 ± 7.5% for the children of normotensive parents. Further, children of hypertensive parents had a reduction in forearm vascular resistance to −15.8 ± 5.3%, while children of normotensive parents had an increase in resistance to a peak of +10.8 ± 1.5%; (Figure 5). The difference in forearm vascular resistance responses between groups approached significance (p = 0.08).

To assess sex differences in response to stress, sex by parental classification analyses were performed. The difference between male and female subjects was not significant for any variable. To assess the relation of age and weight to stress responses, they were entered as covariates in the analyses. Neither was a significant covariate.
FOREARM BLOOD FLOW DURING MENTAL STRESS/Anderson et al.

Recovery Period

There was no significant difference between groups in the pattern of recovery over time on any measure. In both groups, heart rate quickly returned to prestress levels (see Figure 1) and did not change significantly during the recovery period \((p = 0.86)\). Similarly, forearm blood flow quickly returned to prestress levels, with no significant change during the recovery period \((p = 0.93; \text{see Figure 4})\). Forearm vascular resistance did not change significantly over the recovery period \((p = 0.16)\), although resistance increased markedly in both groups during the first minute of recovery (see Figure 5). Only systolic and diastolic blood pressures changed significantly during recovery \((p < 0.001)\). Blood pressure in both groups gradually returned to prestress levels (see Figures 2 and 3).

Discussion

Mental stress causes increased heart rate, blood pressure, and skeletal muscle blood flow as well as reduced blood flow to skin, renal, and splanchnic vascular beds. Recent studies indicate that blood pressure and heart rate responses to stress may be greater in children with a family history of hypertension than in those with no such family history. Falkner et al. reported that exaggerated blood pressure responses to stress may predict which children will later become hypertensive. However, Falkner et al. noted that, at the time of original testing, the adolescents who later became hypertensive weighed significantly more than those who did not. Although the foregoing results are intriguing, other studies have failed to find differences in hemodynamic responses in genetically susceptible persons, and it is unclear whether differences in weight may have been a contributing factor when response differences were observed. However, measuring blood pressure and heart rate alone cannot reveal differences in regional blood flow that may underlie similar blood pressure responses. For example, exaggerated regional vasoconstrictor and vasodilator responses may offset each other, resulting in similar blood pressure responses. This study examined the possibility that stress-induced cardiovascular responses may include a genetically based difference in reactivity of a specific vascular bed. The current study is, to our knowledge, the first to compare a regional (forearm) circulation during stress in children with and without a family history of hypertension. The principal finding was that the increase in forearm blood flow during stress was almost three times greater in children with a family history of hypertension than in those without a family history of hypertension. In addition, children with a family history of hypertension had a reduction in forearm vascular resistance, whereas resistance increased in children of normotensive parents. There was no difference in blood pressure or heart rate responses to stress.

It is not possible from this study to determine the neural or humoral mechanism(s) involved in the increased forearm blood flow. Possible mechanisms include reduced sympathetic vasoconstrictor outflow to forearm skeletal muscle, activation of a sympathetic neurogenic vasodilator pathway, increased \(\beta\)-adrenergic receptor sensitivity or density, increased adrenomedullary epinephrine secretion, or decreased neurotransmitter metabolism.

Falkner et al. reported that total plasma catecholamine levels were higher after stress in children with hypertensive parents. Williams et al. reported that the augmented forearm blood flow responses of Type A versus Type B subjects during mental arithmetic were associated with greater increases in plasma epinephrine and norepinephrine levels. These results suggest an enhanced sympathoadrenomedullary response.

The findings of this study are consistent with Folkow’s hypothesis of an exaggerated defense response...
in genetically susceptible persons. However, the importance of the blood flow responses in later hypertension in these children cannot be determined from this study. Although the sample size was sufficient to detect differences in forearm blood flow, only a small percentage of children with hypertensive parents become hypertensive.\(^{15}\) Longitudinal studies are required to determine if forearm blood flow responses predict later blood pressure levels. However, current evidence suggests that hypertension results from an interaction of genetic, environmental, and dietary factors, such as sodium intake.\(^{14}\) Exaggerated forearm blood flow responses may reflect a genetically determined risk factor that interacts with environmental factors, dietary factors, or both factors to cause hypertension.

The finding that the increased flow did not reduce blood pressure responses to stress suggests that it was offset by increased stroke volume or exaggerated vasoconstriction in other vascular beds. The latter possibility is supported by studies of young spontaneously hypertensive (SHR) and Wistar-Kyoto rats (WKY).\(^{18,19}\) Callahan et al.\(^{18,19}\) reported that presenting rats with a conditioned fear stimulus was associated with immediate mesenteric vasoconstriction and subsequent hindlimb vasodilation (primarily skeletal muscle). Both SHR and WKY had similar blood pressure and heart rate responses to stress.\(^{19}\) However, there were significant differences in regional blood flow responses between SHR and WKY (A.K. Johnson, personal communication, 1987). Specifically, both the initial mesenteric vasoconstriction and subsequent hindlimb vasodilation were greater in SHR. They speculated that augmented hindlimb blood flow buffered exaggerated mesenteric vasoconstriction.

Stress can differentially augment sympathetic outflow to the kidney in genetically susceptible animals. Koepke and DiBona\(^ {15}\) reported that stress (air jet to head) increased sympathetic outflow to the kidney in SHR but not in WKY. Koepke et al.\(^ {26}\) reported that stress causes greater increases in renal sympathetic nerve activity in rats with deoxycorticosterone acetate-salt hypertension than in their controls. Increased renal nerve activity and decreased urinary sodium excretion and flow rate were observed despite similar effects on arterial pressure.

These studies, as well as the current study, indicate that changes in regional blood flow underlying similar blood pressure responses to stress may differ in those genetically predisposed to become hypertensive. This study indicates the importance of measuring regional blood flow when assessing cardiovascular responses to stress in children with and without a family history of hypertension.

In summary, this study demonstrates greater forearm blood flow during mental stress in children with a family history of hypertension. These increases occurred in the absence of greater blood pressure and heart rate responses. The mechanism(s) of this response and its relationship to the development of hypertension are not known. However, the increased skeletal muscle blood flow may be associated with increased stroke volume or exaggerated vasoconstriction in other vascular beds. This study suggests that children with a genetic risk for hypertension have altered regional blood flow responses to stress.

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