Hemodynamic Characteristics of the Early Phase of Primary Hypertension

The Dutch Hypertension and Offspring Study

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Background. The hemodynamic characteristics of the early phase of primary hypertension are subject to debate. In particular, it remains unclear whether an increased vascular peripheral resistance or a raised cardiac output is involved as the primary hemodynamic alteration in hypertension.

Methods and Results. We studied hemodynamic characteristics and oxygen consumption in relation to 24-hour ambulatory blood pressure measurements in three groups of normotensive children with a different familial predisposition for hypertension. Selection of participants was based on parental blood pressure levels. Mean 24-hour blood pressure was higher in the offspring of two hypertensive parents compared with the offspring of two normotensive parents; there was a difference of 4.7 mm Hg (95% confidence interval [CI], 1.8-7.6) for systolic blood pressure and a difference of 4.8 mm Hg (CI, 2.3-7.3) for diastolic blood pressure. The 24-hour blood pressure pattern was consistently at a higher level for both systolic and diastolic blood pressures in the offspring of two hypertensive parents compared with the offspring of two normotensive parents. The smallest differences in blood pressure were seen at night, and the largest differences in blood pressure between the groups of offspring were seen during periods of physical activity. Echocardiographic examination combined with registration of oxygen consumption did not show a difference in cardiac index and arteriovenous oxygen difference between the study groups. However, differences in cardiac dimensions were apparent, with an increased left ventricular mass index (8.7 g/m²; CI, 2.4-15.0) in the offspring of two hypertensive parents.

Conclusions. These findings do not support the existence of a hyperkinetic circulatory phase but may indicate the presence of an increased left ventricular mass in early primary hypertension. (Circulation 1993;87:1100-1106)

Key Words: blood pressure • hypertension • family history • cardiac function • blood pressure, ambulatory

In the past decades, our understanding of the pathophysiological correlates of primary hypertension has increased greatly. By contrast, however, the mechanisms of initiation and development of high blood pressure and the hemodynamic characteristics of its early phase remain controversial. There are two major hypotheses: one hypothesis suggests that the initial phase of the development of high blood pressure is characterized by an increased peripheral resistance. The other suggests that it is characterized by a raised cardiac output. The first hypothesis assumes that the peripheral resistance increases gradually with age when hypertension develops. The second hypothesis suggests that after a period of a high cardiac output, the so-called hyperkinetic circulatory phase, a secondary increase in peripheral resistance develops. This theory rests on the postulate that disproportionately increased blood flow results in a decreased arteriovenous oxygen difference under normal oxygen consumption. In "early," "mild," "borderline," or "labile" young hypertensives, an increased cardiac output has been reported, at least in a sizable proportion of these groups. However, others could not confirm this or have reported a decrease in cardiac output in young borderline hypertensive subjects compared with normotensive subjects. Although follow-up of borderline hypertensive subjects with an initial high cardiac output showed a decrease in cardiac output and an increase in peripheral resistance over years, blood pressure increased less than in borderline hypertensive subjects initially showing a normal cardiac output and an increased peripheral resistance. Blood pressure in either young hypertensive or young normotensive subjects did not show a relation with cardiac output. However, in children with a wide range of blood pressure, cardiac output was weakly related to blood pressure, but the level
of cardiac output did not predict future blood pressure during follow-up.13

We have studied hemodynamic characteristics including cardiac output, cardiac dimensions, oxygen consumption, and 24-hour ambulatory blood pressure in 155 young normotensive males and females, aged 6–31 years, in three groups; the subjects had two hypertensive parents, one hypertensive and one normotensive parent, or two normotensive parents.

Methods

Population

The Dutch Hypertension and Offspring Study is a collaborative study of four Dutch universities and is conducted in Zoetermeer, a suburban residential area near The Hague in The Netherlands. In 1975–1979, residents of two districts of this town were invited to participate in a study of blood pressure and other cardiovascular risk indicators (EPOZ Study).14 Blood pressure was measured in 10,532 of 13,462 (78%) eligible subjects. This group included 1,642 parental couples. A stringent selection procedure was applied to these couples to select groups of offspring with a maximal contrast in familial predisposition for hypertension. The procedures for selection have been described elsewhere.15 In brief, individual parents with both systolic blood pressure (SBP) and diastolic blood pressure (DBP) in the upper (“hypertensive”) or lower (“normotensive”) quartile of the age- and sex-specific blood pressure distribution were selected. Those on antihypertensive medication were included in the hypertensive group. Couples of two hypertensive parents, one hypertensive and one normotensive parent, and two normotensive parents were invited for repeat measurement of blood pressure in 1986. At this occasion, the same criteria for hypertension and normotension were applied as for the initial screening. Of 250 parental couples who were remeasured (80% of those invited), 51 remained in the group with two hypertensive parents, 35 in the group with one hypertensive and one normotensive parent, and 35 in the group with two normotensive parents. Together, these parents had 291 healthy biological children, aged 5–30 years, who were invited to take part in this study. Of these, 155 gave signed informed consent and participated. For the present analysis, only subjects were considered from whom complete data from 24-hour ambulatory blood pressure measurements and echocardiography could be obtained – 40 children of two normotensive parents, 46 children with one hypertensive and one normotensive parent, and 60 children of two hypertensive parents.

The study protocol was approved by the ethical committee of the University Hospital Dijkzigt, and informed consent was obtained from the children and their parents.

Protocol and Measurements

Blood pressure was measured on the left arm with a random-zero sphygmomanometer by a trained paramedical assistant. A series of two readings was made with the subject sitting, and the mean of these readings was used in the analysis. The procedure was repeated with the subject in supine position. Body weight and height were measured with the subject wearing indoor clothes without shoes. Before echocardiography, the subject was positioned supine on the left side and connected to a paramagnetic O2 analyzer and an infrared CO2 analyzer (Oxycon-4, Mijnhardt, Bunnik, The Netherlands) by tube and mouthpiece, with nose clamped, to measure O2 use and CO2 production during echocardiography. At least 5 minutes were allowed while the Oxycon-4 measured and registered mean gas exchange during each 30-second interval. After 5 minutes and with a respiratory quotient at or below 1, a four-chamber echocardiogram was made using two-dimensional echocardiography (Toshiba Sonolayer SSH-60A) and a 3.75-mHz transducer to measure cardiac output. Cardiac dimensions were registered using the parasternal view with M-mode echocardiography. In case the participant was asthmatic, had a severe cold, or was otherwise not willing or able to breathe normally, the tube was disconnected, and the echocardiogram was made without measurement of oxygen consumption. Oxygen measurements could be obtained only in a subset of 60 participants equally distributed across the offspring groups (offspring of two hypertensive parents, 22; of one hypertensive parent, 19; and of two normotensive parents, 19).

The day before visiting the examination center, participants collected one 24-hour urine sample and refrained from smoking and coffee use during that day until after the examination. On a day of their own choice, participants were invited to carry an ambulatory blood pressure measurement device (Spacelabs 90202) during a 24-hour period for measurement of blood pressure and heart rate. The ambulatory blood pressure monitor was applied to the nondominant arm to take measurements at a frequency of one reading per hour between 12:00 midnight and 6:00 AM, three times per hour between 6:00 AM and 6:00 PM, and twice per hour between 6:00 PM and 12:00 midnight. The results of the readings were not disclosed to the participant. During this day, the participant was asked to record physical activities for each hour on a scale of 0 (bedrest, sleeping) to 1 (sitting, reading, watching television, eating), 2 (walking at a normal pace, bicycling quietly), and 3 (sports, running, bicycling fast).

Cardiac output was calculated as the mean from six four-chamber echocardiograms by the area-length method.16 Cardiac index was estimated from cardiac output and body surface area according to Dubois and Dubois.17 Left ventricular mass was estimated from left ventricular end-diastolic diameter, intraventricular septum, and left ventricular posterior wall and indexed for body surface area.16 Mean arterial pressure was calculated from SBP and DBP measured in the supine position and was used to calculate total peripheral vascular resistance by dividing mean arterial pressure by cardiac index. From 10 consecutive Oxycon registrations during 5 minutes in the middle of the echocardiography, oxygen consumption per minute was calculated. The arteriovenous oxygen difference was estimated by dividing oxygen consumption by cardiac output.18

To obtain mean 24-hour ambulatory SBP, DBP, and heart rate, the parameters were calculated per period of the day (midnight to 6:00 AM, 6:00 AM to 6:00 PM, and 6:00 PM to midnight) if at least 75% of the measurements per period were successful. Of the 155 partici-
TABLE 1. Casual Blood Pressure and Other Characteristics in Offspring of Two Normotensive Parents, of One Hypertensive and One Normotensive Parent, and of Two Hypertensive Parents

<table>
<thead>
<tr>
<th></th>
<th>Offspring of two normotensive parents</th>
<th>Offspring of one hypertensive parent</th>
<th>Offspring of two hypertensive parents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males/females (n)</td>
<td>24/16</td>
<td>25/21</td>
<td>37/23</td>
</tr>
<tr>
<td>Age (years)</td>
<td>19.5±7.6</td>
<td>21.8±6.1</td>
<td>22.8±6.5</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>166.9±21.3</td>
<td>172.7±14.0</td>
<td>173.5±13.9</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>59.0±21.1</td>
<td>63.3±13.9</td>
<td>66.5±15.2</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>20.3±3.9</td>
<td>21.0±2.9</td>
<td>21.8±3.1</td>
</tr>
<tr>
<td>Body surface area (m²)</td>
<td>1.65±0.40</td>
<td>1.75±0.26</td>
<td>1.79±0.27</td>
</tr>
<tr>
<td>SBP sitting (mm Hg)</td>
<td>116.4±12.9</td>
<td>125.7±13.4</td>
<td>126.9±11.6</td>
</tr>
<tr>
<td>DBP sitting (mm Hg)</td>
<td>71.0±9.2</td>
<td>76.2±9.4</td>
<td>78.7±7.9</td>
</tr>
<tr>
<td>MAP supine (mm Hg)</td>
<td>78.5±8.3</td>
<td>83.6±8.4</td>
<td>86.7±8.4</td>
</tr>
<tr>
<td>SBP sitting (mm Hg)*</td>
<td>119.0±9.4</td>
<td>125.5±9.4</td>
<td>125.4±9.4</td>
</tr>
<tr>
<td>DBP sitting (mm Hg)*</td>
<td>71.9±8.4</td>
<td>76.0±8.4</td>
<td>78.3±8.4</td>
</tr>
<tr>
<td>MAP supine (mm Hg)*</td>
<td>79.9±7.3</td>
<td>83.7±7.2</td>
<td>85.7±7.2</td>
</tr>
</tbody>
</table>

SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial blood pressure. Values are mean±SD.

*Adjusted for differences between the groups in age, height, body weight, and proportion of males.

pants, 146 (95%) (60 offspring of two hypertensive parents, 46 offspring of one hypertensive and one normotensive parent, and 40 offspring of two normotensive parents) had sufficient blood pressure data to be analyzed. Most of the offspring had normal blood pressures, although there was a large distribution of blood pressure levels (SBP: P10, 106 mm Hg; P90, 140 mm Hg) that can in part be explained by variation in age. Mean 24-hour ambulatory SBP, DBP, and heart rate were averaged from the three periods and weighted for number of hours per period. As a measure of 24-hour variability, mean 24-hour SBP, DBP, and heart rate were divided by their standard deviation. Categories of mean activity scores per hour were used to calculate blood pressure by activity level.

Data Analysis

Descriptive data for the three groups are presented as mean values and standard deviations. For comparisons among groups, mean values and standard errors are given with the difference and 95% confidence intervals (CI) of the difference among groups. Adjustments for differences in age, height, weight, and proportion of males among the three groups were made by entering these variables simultaneously with indicator variables for each group in a model for multiple linear regression. Associations between study variables were studied among the groups adjusted for group characteristics (using indicator variables) and age, height, weight, and sex by multiple linear regression analysis. To further assess the differences among groups, data were analyzed by two blood pressure groups and two age groups, based on median cutoff points.

Results

General Characteristics

Table 1 gives a general description of the three groups. At a mean age of 21.6 years, a difference in sitting SBP and DBP and supine mean arterial pressure between the offspring of two hypertensive parents and the offspring of two normotensive parents was already present. The blood pressure difference remained after adjustments for differences in age, height, weight, and proportion of males among the groups; the difference between the offspring of two hypertensive parents and the offspring of two normotensive parents was 6.4 mm Hg (95% CI, 2.6–10.2) for SBP, 6.3 mm Hg (CI, 2.9–9.7) for DBP, and 5.8 mm Hg (CI, 2.8–8.8) for mean arterial pressure (Table 1).

The number of hours spent at different levels of physical activity during the 24-hour ambulatory blood pressure measurement did not differ among the groups and showed a good range of different activities throughout the day.

Ambulatory Blood Pressure Measurements

In Figure 1, SBP and DBP for each hour of a 24-hour period are given for each of the three groups. At each

![Figure 1. Twenty-four-hour ambulatory blood pressure pattern for systolic and diastolic blood pressure in offspring of two normotensive parents, of one hypertensive and one normotensive parent, and of two hypertensive parents. Hourly values were calculated as the mean of three measurements per hour between 6:00 AM and 6:00 PM, of two measurements per hour between 6:00 PM and 12:00 midnight, and of one measurement between 12:00 midnight and 6:00 AM. All values were adjusted for differences in age, height, body weight, and sex among the groups.](http://circ.ahajournals.org/.../April1993)

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time of the day, DBP of offspring of two hypertensive parents was higher than that of the offspring of two normotensive parents, with the offspring of one hypertensive parent between the two levels. For SBP, a similar pattern of differences was seen during the 24-hour period, except at 12:00 midnight and 3:00 AM, when SBP was the same in the offspring of two hypertensive parents as in the offspring of two normotensive parents. The three groups of offspring showed a similar circadian pattern for 24-hour SBP and DBP with a low level during 1:00 AM and 6:00 AM, a rise between 7:00 AM and 11:00 AM, a continuously high level between 11:00 AM and 5:00 PM, and a period of decline starting between 5:00 PM and 8:00 PM and ending at 1:00 AM.

The offspring of two hypertensive parents had a slightly lower heart rate throughout the 24-hour period compared with the offspring of two normotensive parents (Table 2). Moreover, the offspring of one hypertensive and one normotensive parent showed the highest heart rates during the 24-hour period. The pattern of the 24-hour heart rate was similar for the three groups: biphasic with a similar pattern of rise and decline as for 24-hour SBP and DBP.

Calculated mean 24-hour ambulatory SBP and DBP were higher in the offspring of two hypertensive parents than in the offspring of two normotensive parents (Table 2). No difference in mean 24-hour heart rate was seen among the groups. Although the differences in SBP and DBP among the three groups changed in magnitude during the 24-hour period (Figure 1), SBP and DBP did not show a difference in variability (Table 2).

When the groups were compared for blood pressure and heart rate at an increasing physical activity level, at each level of activity the offspring of two hypertensive parents showed higher SBP compared with the offspring of two normotensive parents. However, the difference was smallest and statistically nonsignificant at activity level 0 (difference, 2.7 mm Hg; 95% CI, −0.8 to 6.2) (Figure 2). At activity score 0, the difference in DBP between the offspring of two hypertensive and two normotensive parents was slightly higher (3.9 mm Hg; CI, 1.0–6.8). Heart rate did not differ among the groups at any level of activity score.

Cardiovascular Characteristics

The offspring of two hypertensive parents had a lower resting heart rate than the offspring of two normotensive parents, which, however, just failed to reach statistical significance (Table 3). Mean stroke volume, measured by the area-length method, was not significantly different in the offspring of hypertensive parents. Cardiac output and cardiac index were the same in the three groups. No differences in absolute oxygen consumption or in arteriovenous oxygen difference were present among the groups. However, cardiac dimensions showed differences among the offspring groups; the thickness of both the left ventricular posterior wall and the intraventricular septum was increased, although not reaching statistical significance, and the left ventricular end-diastolic diameter was significantly increased in the offspring of two hypertensive parents. The estimated left ventricular mass and mass index, calculated from these parameters, were 12.3 g and 8.7 g/m², respectively, greater in the offspring of two hypertensive parents compared with offspring of two normotensive parents. To further assess whether the differences in left ventricular mass index were dependent on blood pressure, data were analyzed separately in children with a relatively low blood pressure (below or median). Low blood pressure offspring of two hypertensive parents had an index of 109.9 g/m² (SEM, 3.2), and low blood pressure offspring of two normotensive parents had an index of 101.2 g/m² (SEM, 2.6); the difference is 8.7 g/m², and the 95% CI is 0.5–17.0. If additional adjustments were made for small and nonsignificant differences in blood pressure between the groups in each stratum (SBP in lowest stratum was 114.9±1.7 mm Hg

![FIGURE 2](image-url) Mean systolic blood pressure at increasing levels of activity in the three groups adjusted for differences in age, height, body weight, and sex. Activity score 0 is bedrest; 1 is sitting, eating, reading, and watching television; 2 is walking at normal pace and bicycling leisurely; and 3 is sports activities, running, and bicycling fast. *p<0.05 for the difference with the offspring of two normotensive parents.
TABLE 3. Cardiovascular Parameters in the Offspring of Two Normotensive Parents, of One Hypertensive and One Normotensive Parent, and of Two Hypertensive Parents

<table>
<thead>
<tr>
<th></th>
<th>Offspring of two normotensive parents (A)</th>
<th>Offspring of one hypertensive parent (B)</th>
<th>Offspring of two hypertensive parents (C)</th>
<th>Difference between B and A</th>
<th>Difference between C and A</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (bpm)</td>
<td>72.5 (1.8)</td>
<td>71.3 (1.6)</td>
<td>68.5 (1.4)</td>
<td>-1.2 [-5.9, 3.5]</td>
<td>-4.0 [-8.4, 0.4]</td>
</tr>
<tr>
<td>Stroke volume (mL)</td>
<td>44.6 (2.0)</td>
<td>43.8 (1.9)</td>
<td>45.1 (1.8)</td>
<td>-0.8 [-6.2, 4.6]</td>
<td>0.5 [-4.7, 5.7]</td>
</tr>
<tr>
<td>Cardiac output (L/min)</td>
<td>3.09 (0.12)</td>
<td>3.01 (0.12)</td>
<td>3.05 (0.11)</td>
<td>-0.08 [-0.43, 0.27]</td>
<td>-0.04 [-0.38, 0.30]</td>
</tr>
<tr>
<td>Cardiac index (L/min/m²)</td>
<td>1.82 (0.07)</td>
<td>1.77 (0.07)</td>
<td>1.80 (0.06)</td>
<td>-0.05 [-0.24, 0.14]</td>
<td>-0.02 [-0.20, 0.16]</td>
</tr>
<tr>
<td>Oxygen consumption (mL/min)</td>
<td>253 (6)</td>
<td>261 (4)</td>
<td>257 (5)</td>
<td>8 [-6, 22]</td>
<td>4 [-11, 19]</td>
</tr>
<tr>
<td>AVO₂ difference (mL/L)</td>
<td>79 (5)</td>
<td>87 (5)</td>
<td>83 (4)</td>
<td>8 [-5, 21]</td>
<td>4 [-8, 16]</td>
</tr>
<tr>
<td>AVO₂ difference (mL/L/m²)</td>
<td>46 (3)</td>
<td>48 (3)</td>
<td>50 (3)</td>
<td>2 [-4, 8]</td>
<td>4 [-2, 10]</td>
</tr>
<tr>
<td>LVPW (mm)</td>
<td>8.8 (0.1)</td>
<td>8.8 (0.1)</td>
<td>9.0 (0.1)</td>
<td>0.0 [-0.3, 0.3]</td>
<td>0.2 [-0.1, 0.5]</td>
</tr>
<tr>
<td>IVS (mm)</td>
<td>9.0 (0.1)</td>
<td>9.1 (0.1)</td>
<td>9.2 (0.1)</td>
<td>0.1 [-0.3, 0.5]</td>
<td>0.2 [-0.1, 0.5]</td>
</tr>
<tr>
<td>LVED (mm)</td>
<td>48.0 (0.4)</td>
<td>48.8 (0.4)</td>
<td>49.3 (0.4)</td>
<td>0.8 [-0.4, 2.0]</td>
<td>1.3 [0.2, 2.4]</td>
</tr>
<tr>
<td>LVM (g)</td>
<td>189.7 (4.3)</td>
<td>193.9 (4.0)</td>
<td>202.0 (3.5)</td>
<td>4.2 [-7.5, 15.9]</td>
<td>12.3 [1.3, 23.3]</td>
</tr>
<tr>
<td>LVM1 (g/m²)</td>
<td>106.1 (2.5)</td>
<td>110.4 (2.3)</td>
<td>114.8 (2.0)</td>
<td>4.4 [-2.4, 11.0]</td>
<td>8.7 [2.4, 15.0]</td>
</tr>
<tr>
<td>TPR (mm Hg/L/min/m²)</td>
<td>45.1 (1.9)</td>
<td>49.4 (2.1)</td>
<td>48.2 (1.7)</td>
<td>4.3 [-1.3, 9.9]</td>
<td>3.1 [-2.0, 8.1]</td>
</tr>
</tbody>
</table>

bpm: Beats per minute; AVO₂: difference, arteriovenous oxygen difference; LVPW, left ventricular posterior wall thickness; IVS, intraventricular septum thickness; LVED, left ventricular end-diastolic diameter; LVM, left ventricular mass; LVM1, left ventricular mass index; TPR, total peripheral vascular resistance.

Values are mean with SEM in parentheses and differences between means with 95% confidence intervals in brackets; adjusted for differences in age, height, body weight, and sex.

*Parameters indexed for square meter of body surface area are adjusted for differences in age and sex only.

For offspring of hypertensive parents and 110.7 ± 1.5 mm Hg for offspring of two normotensive parents), the left ventricular mass index between the groups remained 110.0 ± 3.2 g/m² for low blood pressure offspring of two hypertensive parents and 101.1 ± 2.6 g/m² for low blood pressure offspring of two normotensive parents (difference, 8.9 g/m²; 95% CI, 0.7–17.1). In the high blood pressure offspring separately, no significant difference in left ventricular mass was present between the offspring groups. This analysis indicates that the overall findings cannot be explained by elevated blood pressure in a subgroup of children because the difference in left ventricular mass index is most pronounced for the low blood pressure group. Similarly, data were analyzed according to two age groups based on median age, indicating that findings are most pronounced in the youngest group; left ventricular mass index adjusted for differences in proportion of males, SBP, and age was 112.2 g/m² (SEM, 2.9) in the younger offspring of two hypertensive parents and 100.5 g/m² (SEM, 3.0) in the younger offspring of two normotensive parents (difference, 11.7 g/m²; 95% CI, 3.4–20.0).

As both casual (Table 1) and 24-hour ambulatory blood pressures (Figure 1 and Table 2) were increased in the offspring of hypertensive parents, this might be related to the differences in left ventricular mass index. If the differences in left ventricular mass index were adjusted for differences in mean 24-hour SBP, the difference became only slightly smaller (offspring of two normotensive parents, 106.8 ± 2.5 g/m²; offspring of two hypertensive parents, 114.5 ± 2.0 g/m²; difference, 7.7 g/m²; 95% CI, 1.3–14.1). The calculated total peripheral vascular resistance was slightly but not statistically significantly higher in the offspring of hypertensive parents.

No relations between cardiac index or left ventricular mass index and mean ambulatory blood pressure, blood pressure variability, or blood pressure at different activity levels were seen.

**Discussion**

The findings of this study do not support the presence of a difference in cardiac index between the offspring of hypertensive parents and the offspring of normotensive parents. Moreover, no signs of a decreased arteriovenous oxygen difference in the offspring of hypertensive parents was present. Although not confirmative of the existence of a hyperkinetic phase in prehypertensive subjects, the findings may be compatible with the presence of structural cardiac changes in the early phase of primary hypertension; dimensions of the left ventricular cardiac muscle and left ventricular mass index were higher in the offspring of hypertensive parents. From the 24-hour blood pressure measurements, it appeared that the offspring of hypertensive parents had a higher SBP and DBP throughout the day compared with the offspring of two normotensive parents, with the differences most pronounced at a high activity level and lowest during rest. No differences in heart rate at rest or during 24-hour measurements were seen.

Many other investigators have studied the importance of changes in cardiac output in relation to blood pressure development. Studies in young borderline hypertensive subjects were not conclusive; findings in favor or against a hyperkinetic circulatory phase have been reported. The prerequisite of a true hyperkinetic circulation, the existence of a similar or decreased oxygen consumption together with an increased cardiac output and thus a decreased arteriovenous oxygen difference, has not been described in borderline hypertension. There appears to be no “luxury” perfusion that
by whole body autoregulation could secondarily increase peripheral resistance and decrease cardiac output. In young subjects with a wide range of blood pressure, no clear relation between cardiac index and blood pressure level\textsuperscript{11,12} or blood pressure increase\textsuperscript{13} has been reported.

In our study, selection of participants was not based on individual blood pressure level but rather on parental blood pressure. The strategy was to select offspring at different risks for hypertension irrespective of actual blood pressure level. Hemodynamic factors reported to be predictive of future blood pressure rise in young normotensive subjects include an initially increased blood pressure reactivity to mental stress,\textsuperscript{19} an increased SBP response during physical exercise,\textsuperscript{13} an initially high SBP,\textsuperscript{13,19} an initially large left ventricular mass,\textsuperscript{13} and a family history of hypertension.\textsuperscript{19} In our study, the hemodynamic profile of the offspring of two hypertensive parents compared with the offspring of two normotensive parents (i.e., higher usual and mean ambulatory blood pressure, greater increase in SBP for each activity level, and an increased left ventricular mass index but a similar cardiac index) resembles the hemodynamic profile observed in other studies\textsuperscript{13,19} of children exhibiting the largest pressure rise in these studies. Both individual and familial risks for primary hypertension appear to be characterized by high initial blood pressure levels, high blood pressure responses during stress, and increased left ventricular mass index but not by a high cardiac output. This is supported by others comparing offspring of hypertensive and normotensive parents, who showed an increased left ventricular mass in males with hypertensive parents,\textsuperscript{20-22} although in one small study among young sons and daughters of hypertensive parents, no clear increase of left ventricular mass was seen.\textsuperscript{23} A study comparing male offspring groups at a mean age of 34 years did not show the increased hemodynamic response in offspring of hypertensive parents during mental or physical stress, but at rest the differences between the offspring groups in cardiac index, blood pressure, and total peripheral resistance showed a similar pattern compared with our study at a mean age of 22 years.\textsuperscript{24}

Our finding of an increased left ventricular mass index in offspring of hypertensive parents, which remained after adjustment for the differences in 24-hour ambulatory blood pressure, could indicate the presence of structural changes of the heart in the early phase of primary hypertension. This could suggest that cardiac hypertrophy occurs due to stimuli other than increased afterload only. In a recent randomized trial, a similar reduction of blood pressure with either verapamil or atenolol was accompanied by a reduction of left ventricular mass in verapamil-treated patients only, suggesting that reduction of left ventricular mass was not solely dependent on blood pressure decrease.\textsuperscript{25} It has been suggested that an increase of intrinsic growth factors due to a genetic predisposition or due to an increased adrenergic stimulation or sensitivity might cause cardiac hypertrophy.\textsuperscript{26,27} These different stimuli as well as an increased afterload would increase intracellular calcium, which triggers the induction of proto-oncogenes, thereby stimulating protein synthesis.\textsuperscript{28} These factors may be similar to the factors that give rise to vascular hypertrophy.

In conclusion, the absence of a difference in cardiac output and oxygen consumption at rest between offspring of hypertensive parents and offspring of normotensive parents does not support the existence of a hyperkinetic circulation in the early phase of primary hypertension. The difference in left ventricular mass appears to be independent of differences in blood pressure between the groups, suggesting that the finding is not the consequence of an increase in afterload only. Whether the rise in left ventricular mass is the result of functional or structural vascular and cardiac changes, or a combination of both, remains to be established.

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