Arterial and Retinal Vascular Changes in Hypertensive and Prehypertensive Adolescents

Ilina Murgan,1* Sonja Beyer,1 Konstantin E. Kotliar,1 Lutz Weber,2 Susanne Bechtold-Dalla Pozza,2 Robert Dalla Pozza,2 Aharon Wegner,3 Diana Sitnikova,3 Konrad Stock,1 Uwe Heemann,1 Christoph Schmaderer,1 and Marcus Baumann1

INTRODUCTION
Increasing evidence suggests that arterial hypertension (AHT) may begin in childhood and adolescence, and may result in the premature development of atherosclerosis and occurrence of cardiovascular events. Autopsy studies have demonstrated a high prevalence of aortic and coronary fatty streaks in children and young adults, as well as a strong correlation of atherosclerosis with antemortem cardiovascular risk factors, such as systolic blood pressure (SBP), an elevated level of low-density lipoprotein (LDL) cholesterol, and a high body mass index (BMI).1,2 With the incidence of hypertension in children and adolescents increasing with BMI,3,4 Early hypertension is related to early vascular changes at both the micro- and macrovascular levels.

METHODS
In a cohort of 121 adolescent subjects, we measured peripheral and central blood pressure (pBP and cBP, respectively), pulse pressure (PP), and the augmentation index (AIx), as well as retinal vascular diameters, at baseline and during a cold pressor test (CPT). We measured the central retinal arteriolar equivalent (CRAE) and central retinal venular equivalent (CRVE) and calculated the retinal arteriolar-to-venular ratio (AVR).

RESULTS
Of the adolescent subjects in the study, 54.5% were NT, 25.6% were PHT, and 19.8% were HT. With regard to BMI, central systolic BP (cSBP), aortic pulse pressure (AoPP), and CRAE, the PHT adolescents had values similar to those in the HT group but significantly different than those in the NT group. In the studied population, there was a positive and significant correlation of AIx with cSBP and a negative association of CRAE with both cSBP and peripheral SBP (pSBP). We describe the evolution of these parameters during and after sympathetic stimulation.

CONCLUSION
As compared with the prevalence of hypertension and prehypertension in large studies, involving teenagers and children, an alarming percentage (45.5%) of the adolescents in our study were HT or PHT. Higher pSBP and cSBP were associated with narrower retinal arterioles but not with changes of arterial elasticity. With particular regard to CRAE, the PHT group was more closely related to the HT group than to the NT group. There were no differences among the NT, PHT, and HT groups in the results of the CPT.

Keywords: hypertension; prehypertension; adolescents; retinal arterioles; central retinal arteriolar equivalent; central retinal venular equivalent; retinal arteriolar-to-venular ratio; central blood pressure; pulse pressure; pressure-wave analysis; augmentation index; body mass index; cold pressor test; sympathetic stimulation; blood pressure.

doi:10.1093/ajh/hps091

Increasing evidence suggests that arterial hypertension (AHT) may begin in childhood and adolescence, and may result in the premature development of atherosclerosis and occurrence of cardiovascular events. Autopsy studies have demonstrated a high prevalence of aortic and coronary fatty streaks in children and young adults, as well as a strong correlation of atherosclerosis with antemortem cardiovascular risk factors, such as systolic blood pressure (SBP), an elevated level of low-density lipoprotein (LDL) cholesterol, and a high body mass index (BMI).1,2 With the incidence of hypertension in children and adolescents increasing with BMI,3,4 Early hypertension is related to early vascular changes at both the micro- and macrovascular levels.

With regard to the macrovascular aspects of hypertension, great emphasis has been put on arterial stiffness and its effect on systolic blood pressure (SBP) and pulse pressure (PP). Central blood pressure (cBP) and the pressure waveforms produced by left-ventricular contraction have recently come to attention because they represent the workload of the left ventricle and have been shown to have a better prognostic value than peripheral BP (pBP) in terms of the risk of occurrence of cardiovascular events.3–7 Augmentation of cBP by the return, in systole, of the pressure wave reflected in the peripheral circulation can be quantified by the aortic augmentation index (AIx), defined as the ratio of the augmentation of the late peak systolic pressure wave to the PP.8
Vascular Changes in Hypertensive and Prehypertensive Adolescents

The noninvasive measurement of retinal vessel diameters allows insights into microvascular alterations and their relation to cardiovascular risk factors. Of particular relevance are the central retinal arteriolar equivalent (CRAE) and central retinal venular equivalent (CRVE), which respectively represent the average arteriolar and venular diameters in an eye. Studies have suggested that alterations in retinal arterioles predict the risk of hypertension in normotensive persons. However, quantitative data concerning retinal changes in adolescents are lacking.

It is well known that cold exposure induces certain physiologic cardiovascular changes in healthy adults, such as an increase in BP, aortic pulse-wave velocity (PWV), and AIx, most likely due to an increase in adrenergic tone. The cold pressor test (CPT) has been previously used to investigate vascular behavior upon sympathetic stimulation, such as the vascular hyperreactivity that supposedly characterizes prehypertensive (PHT) states.

Because hypertension may begin in childhood and adolescence, it is important to investigate its causes and consequences at both the macrovascular and the microvascular levels to permit the initiation of strategies for preventing it at an early stage. Given that hypertension is associated with vascular changes, we set out to explore whether an increased BP or the vascular alterations that accompany it constitute the initial event in hypertension, to the extent that a cross-sectional study allows this. In this context, we investigated, at the arterial and arteriolar level, the special group of prehypertensive (PHT) individuals consisting of adolescents, and compared them with normotensive (NT) and hypertensive (HT) participants of comparable age. We also analyzed the effects of sympathetic stimulation, i.e., the CPT, on the macro- and microvasculature, and compared the behavior of these parameters among the three participant groups.

**METHODS**

We conducted a cross-sectional study in which we enrolled all students in high school in Munich, Germany, who agreed to participate and who had no prior BP-related medical conditions. Students with current diseases, especially conditions involving the eyes, were excluded.

The study enrolled 121 participants. The parents or legal guardians of the participants gave their informed written consent to the study, and the study protocol was approved by the local ethics committee (Ethikkommission der Fakultät für Medizin der Technischen Universität München). Three trained persons, working simultaneously, completed all measurements on the study participants. The collected data included body weight and height, medical history, personal and familial data, and eating, drinking, and smoking habits.

Body mass index (BMI) was calculated as the individual’s body mass divided by the square of his or her height.

**Blood pressure**

Participants were seated and rested for 5 minutes in a quiet environment, after which their BP was measured sphygmomanometrically 3 times, at 5-minute intervals, with the auscultatory method over the brachial artery. The mean between these measurements was used for further analyses. The study participants were classified into three groups of NT, PHT, or HT according to the definition of childhood and adolescent HT, which takes into account the normative distribution of BP in healthy children, adjusted for height, age, and gender. Both diastolic and systolic BP were considered, and the grouping was done according to the highest value. Participants were considered to be NT if both their SBP and DBP were below the 90th percentile. Prehypertension (PHT) was defined by an SBP, DBP or both that was above the 90th percentile but below the 95th percentile, or if their BP exceeded 120/80 mm Hg even if either BP component was below the 90th percentile. Hypertension was defined as a systolic or a diastolic BP or both that was above the 95th percentile.

**Augmentation index and central blood pressure**

The arterial pressure waveform, which bears information about the properties of the arterial tree, is a composite of the forward pressure wave created by ventricular contraction and a reflected wave. The AIx quantifies the augmentation of pressure at the aortic root that results from reflected, backward-traveling pulse waves. The AIx is defined as the increment in pressure from the first shoulder of the systolic pressure wave to the peak of the systolic pressure wave, expressed as a percentage of the AoPP and has been studied as a useful index of cardiovascular risk. A simple and well-tolerated method of analyzing the three major pulse-wave parameters, consisting of the AoPP, central blood pressure (cBP), and AIx, is radial tonometry. We assessed the central arterial pressure waveform noninvasively by first recording the pulse-wave at the level of the radial artery with a pencil-type probe incorporating a high-fidelity strain-gauge transducer (SPT-301, Millar Instruments, Houston, TX). We then applied a transfer function (Sphygmocor, AtCor, Sydney Australia) to calculate the aortic pressure waveform from the waveform of the radial artery pressure. The AoPP, CBP, and AIx were determined as previously described from the waveform of the AoPP.

**Retinal vascular diameters**

Using an FF450 retinal camera (Zeiss, Jena, Germany) integrated in the module of the Dynamic Vessel Analyzer (DVA, Medelsis, Ankara, Turkey), photographs of 30 degrees of retinal area were made for each participant and analyzed with the Visualis High Resolution Imaging and Vessel Map Software system (Imedos Systems, Jena, Germany). The diameters of retinal arterioles and venules were measured as described previously and combined into the summary indices of CRAE and CRVE, which represent the average arteriolar and venular diameters, respectively, of the eye in which the measurements were made. These diameters were additionally expressed as the retinal arteriolar-to-venular ratio (AVR). The AVR compensates for possible differences in magnification among eyes, and an AVR of 1 indicates that the arteriolar diameters in one eye are, on average, the same as the venular diameters in that same eye, whereas a smaller ratio suggests narrower arterioles. This technique has been shown to be highly reproducible.
Cold pressor test

For the CPT, the hand and forearm of each of the study participants were immersed in cold water (4 °C) for 5 minutes. After the hand and forearm were removed from the water, a 5-minute recovery period was allowed. We made all of the measurements mentioned earlier in three phases, consisting of: (i) a 5-minute baseline period; (ii) during cold-water stimulation; and (iii) during the 5-minute recovery period.

Statistical analyses

We used bivariate correlations (Pearson correlation coefficients (r)), analysis of variance (ANOVA), and the Bonferroni post hoc test, t-test, or chi-squared test, where appropriate. We used forward multiple linear regression analysis to determine which parameters influenced the central and peripheral systolic and diastolic BPs (cSBP and pSBP, respectively), and used ANOVA with repeated measures to assess the changes in BP and other parameters during the three stages of the CPT. We set the level of significance for the results of statistical analyses at $P < 0.05$ except for post hoc tests, for which the Bonferroni correction was applied. Parameters such as BP, AIx, AVR, CRAE, and CRVE were analyzed as continuous variables and also as categories divided into quartiles (according to their population distribution).

RESULTS

We surveyed 121 adolescents ranging in age from 13–19 years, of whom 68 (56.2%) were boys and 53 (43.8%) were girls. The results of our examinations of these adolescents are expressed as mean (±SD).

Baseline measurements

The baseline results for various cardiovascular parameters in the study population are given in Tables 1 and 2. The results in Table 1 are classified according to gender and those in Table 2 according to categories of peripheral BP. Of the participants, 54.5% were NT, 25.6% were PHT, and 19.8% were HT. The boys in the study had significantly higher baseline measurements of pSBP than did the girls (124.3 ± 11.3 mm Hg vs. 115.8 ± 9.5 mm Hg, $P < 0.001$). However, BMI alone did not account for the higher SBP toward a greater AIx in girls than in boys (1.35 ± 11.6 vs. −1.12 ± 9.2, respectively), the difference was not statistically significant. As expected, cSBP, cDBP, and AoPP differed significantly in the three BP categories in the study, whereas AIx did not. A further finding was that AIx correlated weakly but significantly negatively with body height ($r = −0.291$, $P = 0.001$), a feature already known in adults but not described in teenagers.

The retinal parameters examined in the study showed no gender-related differences. In post hoc tests, the CRAE was significantly lower ($P = 0.009$) and the AVR was significantly higher ($P = 0.006$) in the PHT group than in the NT group. The values of BMI, cSBP, AoPP, and CRAE in the PHT group were similar to those in the HT group, but significantly different from those in the NT group, and in these measures the PHT group therefore seemed to be more closely related to the HT than to the NT group.

Table 1. Basal values of measured variables in study populationa

<table>
<thead>
<tr>
<th>Variable</th>
<th>Boys</th>
<th>Girls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>16.2 ± 1.5</td>
<td>16.4 ± 1.5</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>22.0 ± 3.7</td>
<td>21.1 ± 2.8</td>
</tr>
<tr>
<td>Peripheral SBP, mm Hg</td>
<td>124.4 ± 11.3</td>
<td>115.8 ± 9.5*</td>
</tr>
<tr>
<td>Peripheral DBP, mm Hg</td>
<td>66.9 ± 6.8</td>
<td>70.33 ± 6.9*</td>
</tr>
<tr>
<td>Peripheral PP</td>
<td>57.3 ± 9.7</td>
<td>45.5 ± 7.2*</td>
</tr>
<tr>
<td>Central SBP, mm Hg</td>
<td>102.7 ± 9.6</td>
<td>99.27 ± 8.7*</td>
</tr>
<tr>
<td>Central DBP, mm Hg</td>
<td>70.3 ± 7.4</td>
<td>72.9 ± 8.0</td>
</tr>
<tr>
<td>AoPP, mm Hg</td>
<td>32.6 ± 7.0</td>
<td>26.4 ± 4.4*</td>
</tr>
<tr>
<td>Aix, %</td>
<td>1.85 ± 0.77</td>
<td>1.98 ± 0.88</td>
</tr>
<tr>
<td>CRAE, µm</td>
<td>192.8 ± 18.2</td>
<td>198.4 ± 21.2</td>
</tr>
<tr>
<td>CRVE, µm</td>
<td>218.1 ± 18.9</td>
<td>223.1 ± 18.0</td>
</tr>
<tr>
<td>AVR</td>
<td>0.89 ± 0.08</td>
<td>0.89 ± 0.08</td>
</tr>
</tbody>
</table>

*aValues are given as mean (±SD).

*The difference between boys and girls is significant at $P < 0.05$.

Abbreviations: Aix, augmentation index; AoPP, aortic pulse pressure; AVR, arteriolar-to-venular ratio; BMI, body mass index; CRAE, central retinal arteriolar index; CRVE, central retinal venular index; DBP, diastolic blood pressure; PP, pulse pressure; SBP, systolic blood pressure.
Vascular Changes in Hypertensive and Prehypertensive Adolescents

Peripheral and central SBP, DBP, and AoPP rose significantly during the CPT. As shown in Table 5, pSBP and cSBP as well as pDBP and cDBP dropped during the recovery phase of the CPT to levels below their baseline values. Thus, for example, pSBP rose from 120.7 ± 11.4 mm Hg to 125.8 ± 13.1 mm Hg and dropped to 115.2 ± 10.2 mm Hg during the recovery phase. Figure 2A shows the changes in pSBP and Figure 2B shows the changes in cSBP during the CPT, with the study participants divided into BP categories. The increase and decrease in SBP and DBP during the CPT were not quantitatively different among participants in different BP categories or for boys vs. girls.

The AIx increased during cold stimulation, from –0.90 ± 10.28% to 1.66 ± 10.41%, and returned to a level of –0.41 ± 9.36%; however, only the decrease from phase 2 to phase 3 of the CPT was significant (P = 0.012); the increase from phase 1 to phase 2 was not significant (P = 0.07). Neither the participants’ retinal vascular diameters nor their AVRs changed significantly during the CPT.

DISCUSSION

Our study, involving a healthy cohort of 121 adolescents, investigated micro- and macrovascular parameters in relation to BP at baseline and after cold stimulation. A high BP in childhood is associated with future hypertension and, via structural and functional alterations of the arterial wall, with cardiovascular mortality and morbidity in adulthood.1,2,21 The baseline measurements in our study showed that as compared with the prevalence of hypertension (3.2%–4.5%) and prehypertension (9%–24%) described in large studies involving school-children and teenagers,22–26 a high proportion of adolescents are PHT (25.6%) or HT (19.8%). The high BP of these latter two groups was strongly correlated with a high BMI, as is widely known for older populations. Interestingly, more boys than girls in our study were classified as being HT or PHT, even though the BMI of the boys was not significantly higher than that of the girls, which suggests that BMI is not the sole factor responsible for this difference in BP. Remarkably, we found retinal micro- and macrovascular alterations in a significant proportion of the healthy adolescents in the study. Because data concerning these issues in teenagers are sparse, we investigated other possible associations of the HT or PHT state, especially with markers of microvascular or macrovascular complications.

We found that AIx was correlated with central SBP and DBP, but we found no significant correlation between AIx and peripheral SBP or DBP, and no difference in AIx among the three BP categories in our study, presumably because of the shorter cumulative exposure to higher BP in adolescents as compared with adults. Because changes in the elasticity of the arterial walls and in pulse-wave reflection patterns caused by long-standing hypertension can play a role in the pathogenesis of cardiovascular disease, pulse-wave analysis has become clinically useful.6,13,27 Furthermore, a very recent, large study showed that brachial–ankle pulse-wave velocity (PWV), a marker of arterial stiffness, is an independent predictor of longitudinal increases in BP and new-onset HT.28
Figure 1. Panels A and B depict the relationship between AIx and peripheral SBP ($r = 0.062, P = 0.501$) and central SBP ($r = 0.301, P = 0.001$), respectively. Panels C and D show the relationship between CRAE and peripheral SBP ($r = -0.201, P = 0.043$) and central SBP ($r = -0.205, P = 0.041$), respectively. Panel E represents the relationship between CRAE and AIx ($r = -0.159, P = 0.114$).
Central SBP, central AoPP, and Alx are determined by arterial stiffness, the amplitude of reflected pulse waves, the point of pulse-wave reflection, and the duration and pattern of ventricular ejection. Accordingly, Alx is more than a marker of arterial stiffness, reflecting rather the overall interaction between the arterial tree and the left ventricle. In both NT and HT adults, a higher Alx is associated with increased left-ventricular mass. In a large cohort of healthy, NT individuals, the Alx of participants under 20 years of age was –2 ± 8% in men and 5 ± 10% in women. AIx values were higher overall in women than in men and for each decade of life. We did not find any significant gender difference in Alx in our adolescent study population.

Regarding the retinal circulation, we found that CRAE correlated negatively with both pSBP and cSBP. The retinal circulation undergoes pathophysiological changes in response to hypertension. Initially, these consist of vasoconstriction, seen clinically as a generalized narrowing of the retinal arterioles, followed by exudative and sclerotic stages. Considering that such changes were noted in our study in participants without a history of hypertension, it is noteworthy, but not wholly unexpected, that retinal arteriolar changes were evident in the adolescents in our study. It is still unclear whether these changes are mere markers of prehypertension, or play a pathophysiological role in the development of future hypertension, or both. These findings are significant because generalized arteriolar narrowing bears a modest association with the risk of stroke, coronary heart disease, and death.

It has been suggested that generalized and focal narrowing of the retinal arterioles may be markers of a PHT state because they predict the risk of hypertension in NT persons. Numerous studies in adults > 40 years of age have shown that generalized retinal arteriolar narrowing is strongly associated with past and current hypertension. In the Beaver Dam Eye Study (BDES), after adjustment for age, gender, diabetes, smoking, and other vascular risk factors, each 10 mm Hg increase in mean arterial BP was associated with a 6 µm (or 3%) decrease in retinal arteriolar diameter. In two populations of children aged 6–8 years, higher BP was significantly associated with retinal arteriolar narrowing. Daniels et al., using a qualitative ophthalmoscopic method, reported a 41% prevalence of retinal arteriolar narrowing in children and adolescents with essential hypertension. We are not aware of such data involving a quantitative technique in adolescents.

### Table 3. Results for dependent variables in analysis of regression against peripheral systolic blood pressure

<table>
<thead>
<tr>
<th>Variable</th>
<th>Beta</th>
<th>Standard deviation</th>
<th>t</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI</td>
<td>1.335</td>
<td>0.279</td>
<td>4.784</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Alx, %</td>
<td>–</td>
<td>0.097</td>
<td>–0.788</td>
<td>0.433</td>
</tr>
<tr>
<td>CRAE, µm</td>
<td>–0.096</td>
<td>0.042</td>
<td>–2.306</td>
<td>0.023</td>
</tr>
</tbody>
</table>

Abbreviations: Alx, augmentation index; BMI, body mass index; CRAE, central retinal arteriolar index.

### Table 4. Results for dependent variables in analysis of regression against central systolic blood pressure

<table>
<thead>
<tr>
<th>Variable</th>
<th>Beta</th>
<th>Standard deviation</th>
<th>t</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI</td>
<td>0.930</td>
<td>0.222</td>
<td>4.185</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Alx, %</td>
<td>0.183</td>
<td>0.077</td>
<td>2.369</td>
<td>0.020</td>
</tr>
<tr>
<td>CRAE, µm</td>
<td>–0.096</td>
<td>0.042</td>
<td>–2.306</td>
<td>0.023</td>
</tr>
</tbody>
</table>

Abbreviations: Alx, augmentation index; BMI, body mass index; CRAE, central retinal arteriolar equivalent.

### Table 5. Changes in measured variables during cold pressor test

<table>
<thead>
<tr>
<th>Phase</th>
<th>HR, bpm</th>
<th>Peripheral SBP, mm Hg</th>
<th>Peripheral DBP (mm Hg)</th>
<th>Peripheral PP, mm Hg</th>
<th>Central SBP, mm Hg</th>
<th>Central DBP, mm Hg</th>
<th>AoPP, mm Hg</th>
<th>Alx, %</th>
<th>CRAE, µm</th>
<th>CRVE, µm</th>
<th>AVR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase 1</td>
<td>76.1 ± 12.7*</td>
<td>120.7 ± 11.4**</td>
<td>68.4 ± 7.1**</td>
<td>52.2 ± 10.5†</td>
<td>101.2 ± 9.4†</td>
<td>85.9 ± 8.1**</td>
<td>28.9 ± 6.3*</td>
<td>–0.90 ± 10.28</td>
<td>194.9 ± 19.5</td>
<td>220.0 ± 19.8</td>
<td>0.89 ± 0.09</td>
</tr>
<tr>
<td>Phase 2</td>
<td>78.4 ± 11.6*</td>
<td>125.8 ± 13.1**</td>
<td>72.9 ± 9.5**</td>
<td>52.8 ± 10.6†</td>
<td>105.5 ± 11.1**</td>
<td>74.2 ± 9**</td>
<td>31.3 ± 7.2**</td>
<td>1.66 ± 10.41</td>
<td>192.6 ± 20.1</td>
<td>218.7 ± 20.4</td>
<td>0.89 ± 0.09</td>
</tr>
<tr>
<td>Phase 3</td>
<td>77.3 ± 10.7</td>
<td>115.2 ± 10.2†</td>
<td>65.5 ± 7.5**</td>
<td>49.6 ± 9.4†</td>
<td>97.66 ± 11.6**</td>
<td>68.1 ± 8.2**</td>
<td>29.3 ± 0.4†</td>
<td>–0.41 ± 9.36†</td>
<td>193.7 ± 20.5</td>
<td>219.8 ± 19.8</td>
<td>0.89 ± 0.09</td>
</tr>
</tbody>
</table>

*Values are given as mean ± SD.
†The difference between phase 2 and 3 is significant at P < 0.05.
‡The difference between phase 1 and 2 is significant at P < 0.05.
In our study, the retinal parameters AVR and CRVE were not correlated with BP. This was consistent with the findings in studies of adults and of small children, in which high BP had no influence on retinal venular diameter.\textsuperscript{19,37,39} We also found no correlation of the retinal vascular parameters that we examined and the macrovascular parameter AIx, in contrast to the findings of the Atherosclerosis Risk in Communities Study (ARIC) study, in which carotid arterial stiffness was strongly correlated with generalized retinal arteriolar narrowing.\textsuperscript{41} The explanation for our not finding a correlation of retinal vascular parameters with AIx in our study population could be the short cumulative exposure of children and adolescents to high BP, as mentioned earlier. Presumably, the changes in vascular elasticity and pulse wave reflection that occur in hypertension occur at a later stage than does retinal arteriolar narrowing.

We investigated NT, PHT, and HT adolescents during cold stimulation, and could not find any difference in the degree of change in the BPs of these three groups during the stages of the CPT. Nor were there any gender-related differences in the degree of this change. The CPT produces sympathetic release of norepinephrine and epinephrine and an increase in BP and heart rate (HR). In a study of 24 healthy adults, the aortic PWV and AIx increased significantly during the CPT.\textsuperscript{11} We are not aware of such data for children or adolescents. In our study, even though the peripheral and central SBP and DBP, as well as the AoPP, increased during cold stimulation, we could not detect any significant change in AIx.

In our study, the retinal diameters and AVR of the participants did not change significantly during the CPT. A study involving 16 healthy volunteers found that the retinal vascular diameters measured by laser Doppler velocimetry decreased after a mean of 2.9 ± 0.3 minutes of the CPT. This change occurred with a certain latency as compared with the increase in the subjects’ BPs, and it was presumed to reflect the autoregulation of blood flow.\textsuperscript{42} However, the question arises of why these changes did not occur in our group. Narrowing the retinal arterioles in adolescents with higher BPs during the CPT could reflect the normal autoregulatory response to cold, as in the study just described. That the arteriolar diameters of the participants in our study did not change further upon sympathetic stimulation and exposure to an increasing BP during the CPT may suggest that these vascular changes are not functional but are already structural.

We also directed attention to the vascular and hemodynamic behavior in the PHT group in comparison with the other two BP groups in our study. In many measures, such as BMI, cSBP, AoPP, and CRAE, the PHT group did not differ significantly from the NT group, but did differ significantly as compared with the HT group. Much like the HT participants, the PHT group had narrower retinal arterioles than the NT group. This suggests that at the microvascular level, narrowing of the retinal vessels may predate the development of hypertension. With respect to the macrovascular parameter AIx, there were no significant differences among the three BP groups. In the CPT, neither the PHT nor the HT participants, in contrast to the NT group, exhibited any significant differences from one another in the increments in SBP, DBP, or HR. In conclusion, we could not detect any vascular hyperreactivity in the PHT or HT group. However, it should be noted that during sympathetic stimulation with the CPT, the hemodynamic variables in the PHT group reached HT values.

A limitation of our study may be that our subjects were classified into BP categories after three measurements made on a single occasion. Measurements made three times on separate occasions would have been more reliable because they could have accounted for incidentally higher BP values caused by possibly concurrent stressful situations. However, repeating all of the BP measurements in the large number of healthy volunteers in the study was impracticable because of school schedules, among other reasons, and we deemed it
unethical to do this with our young subjects. Furthermore, classifying individuals into distinct groups based on specific BP cutoff values, such as for, normotension, prehypertension, and hypertension, may be faulty, since the relationship between BP and cardiovascular risk is continuous. Another possible drawback of our study may be that the CPT has not been validated for sympathetic stimulation.

In conclusion, the noteworthy findings in our study of vascular and hemodynamic effects of differing BPs in adolescents included early retinal arteriolar narrowing in association with higher BPs. We also found that the PHT group in the study had values of the CREA equivalent to those of the HT group and significantly lower than those of the NT group in the study, which may suggest that arteriolar narrowing precedes the development of HT. AIx as a marker of arterial stiffness correlated with central but not with peripheral measures of BP, indicating that the changes in arterial elasticity in hypertension may occur later than retinal arteriolar narrowing. The adolescent subjects in the study showed no significant changes in AIx or retinal vascular parameters during the CPT.

DISCLOSURE

The authors have no conflicts of interest to declare.

REFERENCES