Blood Pressure and Retinal Arteriolar Narrowing in Children

Paul Mitchell, Ning Cheung, Kristin de Haseth, Bronwen Taylor, Elena Rochtchina, F.M. Amirul Islam, Jie Jin Wang, Seang Mei Saw, Tien Y. Wong

Abstract—Retinal arteriolar narrowing is a known response of hypertension and independently predicts cardiovascular mortality in adults. Whether elevated blood pressure leads to retinal arteriolar narrowing in young children is unknown. We examined the relationship of retinal vascular caliber and blood pressure levels in 2 population-based cohorts among children aged 6 to 8 years in Sydney, Australia (1572 children) and Singapore (380 children). Participants had digital retinal photographs and measurement of retinal arteriolar (or small artery) and venular (or small vein) caliber. Children with higher quartiles of blood pressure had significantly narrower retinal arterioles than those with lower blood pressure (retinal arteriolar caliber 162.8, 161.0, 157.8, and 157.1 μm (P for trend<0.001), comparing increasing quartiles of systolic blood pressure in Sydney, and 164.9, 164.0, 159.1, and 159.4 μm (P for trend=0.0024 in Singapore). After controlling for age, sex, race, body mass index, refraction, and birth parameters, each 10-mm Hg increase in systolic blood pressure was associated with narrowing of the retinal arterioles by 2.08 μm (95% confidence interval: 1.38 to 2.79; P<0.0001) in Sydney children and 1.43 μm (95% confidence interval: 0.27 to 2.59; P=0.016) in Singapore children. These associations were consistent across age, sex, body mass index, and birth parameters. Retinal venules were not affected by blood pressure. We conclude that higher childhood blood pressure is associated with retinal arteriolar narrowing. Our data provide evidence that the effects of elevated blood pressure may manifest early in life. 

(Hypertension. 2007;49:1156-1162.)

Key Words: retinal arteriolar narrowing ■ blood pressure ■ children ■ microcirculation ■ hypertension

Hypertension is the leading risk factor for cardiovascular disease and mortality in middle-aged and older people.¹ There is now a body of evidence that a person’s risk of hypertension and cardiovascular disease may have etiologic origins to blood pressure levels in early life.²⁻⁴ Prospective studies show that childhood blood pressure is associated with future hypertension,⁵ carotid atherosclerosis,⁶⁻⁹ and cardiovascular mortality¹⁰ in adulthood.

However, the exact pathophysiological mechanisms underlying these associations remain uncertain. It has been hypothesized that elevated blood pressure may cause structural damage to the vasculature in children, which predisposes them to the subsequent development of clinical cardiovascular disease.² Available studies have focused on the relationship of blood pressure in adolescents and young adults and atherosclerosis later in life.⁶⁻⁹ Whether elevated blood pressure in younger children leads to target organ damage and structural vascular changes is unclear.

Retinal arteriolar narrowing is a recognized consequence of chronic hypertension and independently predicts cardiovascular morbidity and mortality.¹¹ Recent studies in adult populations have shown that retinal arteriolar narrowing is strongly associated with past, current, and future blood pressure levels¹²⁻¹⁷ and independently predicts incident stroke,¹⁸ coronary heart disease,¹⁹ and cardiovascular mortality.²⁰ There are no data on the relationship of blood pressure to retinal arteriolar caliber in children. The aim of the current study was to determine the effect of blood pressure on retinal arteriolar caliber in healthy children.

Methods

Study Population

We conducted 2 parallel, population-based studies in 2 countries, Australia and Singapore, of children aged 6 to 8 years. These have been described in detail previously.²¹⁻²⁴ The Sydney Childhood Eye Study examined grade 1 school children in 34 primary schools across the Sydney metropolitan region selected during 2003–2004 using random cluster sampling.²²,²³ After parental consent of 238 eligible children, 1740 were examined, of whom 1572 (90.3%) had blood pressure measurements and gradable retinal photographs.

© 2007 American Heart Association, Inc.
The Singapore Cohort Study of Risk Factors for Myopia examined 1979 children aged 7 to 9 years in 3 Singapore schools, selected from the eastern, northern, and western parts of Singapore in 1999–2001. Children with chronic medical conditions, such as heart disease or cancer, and chronic eye conditions, such as cataract, were excluded. Of the cohort, 400 were randomly sampled for retinal photography and blood pressure measurement in 2001. Of these, 380 had gradable retinal photographs and are included in the current study.

The Sydney study was approved by the University of Sydney Human Research Ethics Committee and the Department of Education and Training, both in Sydney. The Singapore study was approved by the institutional review board of the Singapore Eye Research Institute, Singapore. Both studies followed the tenets of the Declaration of Helsinki, and written informed consent was obtained from all of the parents.

Retinal Photography and Measurement of Retinal Vascular Caliber

In each study, children were examined on the school premises by a team of ophthalmologists, optometrists, and research staff using similar procedures. After pupil dilation with cyclopentolate 1%, digital retinal photographs centered on the optic disc were taken of both eyes using standardized settings. Retinal photography at the 2 sites used Canon digital retinal cameras (Model 60-UVi for Sydney and Model CR6-NM45 for Singapore; Canon Inc).

Methods used to measure and summarize retinal vascular caliber from the digitized retinal photographs followed an identical protocol, as described in previous reports in adult populations. Briefly, a computer imaging program was used to measure the caliber of all of the retinal arterioles, small arteries and venules, or small veins located a half- to 1-diameter from the optic disc margin in the retinal photograph. These measurements were summarized as central retinal arteriolar and venular equivalents, representing the average arteriolar and venular caliber of that eye, respectively.

For each study, a single grader, masked to blood pressure measurements and participant characteristics, performed all of the retinal measurements. We used data from the right eye unless images from this eye were unavailable, in which case left eye data were used. Quality control procedures of remeasurement of photographs by the same grader showed high reproducibility. In Singapore, we remeasured 50 retinal images 2 weeks apart by the same grader with intra-grader correlation coefficients consistently >0.85 for arteriolar caliber and >0.97 for venular caliber. A previous adult study in Sydney (Blue Mountains Eye Study) using the same semi-automated retinal grading system has demonstrated similarly high reproducibility for the retinal vessel measurements, although a specific reproducibility test was not performed in the Sydney Childhood Eye Study.

Blood Pressure Measurement

Blood pressure was measured on the school premises according to a standard protocol. After 5 minutes of rest, blood pressure was measured in a seated position using an automated sphygmomanometer (HEM 907 in Sydney and HEM 705LP in Singapore; Omron Healthcare Inc) with appropriate cuff size. We followed general recommendations on selecting cuff size to ensure that the bladder length was ~80% and width was ~40% of the arm circumference, covering the upper arm without obscuring the antecubital fossa. A single blood pressure measurement was taken in Sydney, whereas 3 separate measurements were taken in Singapore, with the later averaged for analysis. Mean arterial blood pressure was calculated as one third of the systolic plus two thirds of the diastolic blood pressure.

Other Measurements

Height was measured with children standing, without shoes. Weight in kilograms was measured using a standard portable weighing machine calibrated before the beginning of the study. Body mass index (BMI) was calculated as weight divided by the height squared (kilograms per meter squared). The refractive status of the eye was measured using an autorefractor (RK-F1 in Sydney and RK-5 in Singapore; Canon Inc) and converted to spherical equivalent. Axial length of the eye was obtained using a laser interferometer in Sydney (IOMaster, Carl Zeiss) and an ultrasound biometry unit in Singapore (Echocan US-800, Nidek).

Parents of the participants were asked to complete a number of questionnaires, written in English or Chinese. Questions covered topics such as indicators of socioeconomic status and medical and ocular history. Childhood record books were used to obtain information on birth parameters, such as birth weight, head circumference, and gestational age.

Statistical Analysis

Blood pressure was categorized into quartiles (according to the population distribution in each study) and also analyzed as a continuous variable. Mean retinal arteriolar and venular caliber measurements were compared between age and sex-adjusted blood pressure quartiles using 1-way ANOVA. Changes in retinal arteriolar and venular caliber for each 10-mm Hg increase in systolic, diastolic, and mean arterial blood pressure were determined using multiple linear regressions. Models were initially adjusted for age and sex and then additionally for race, BMI, spherical equivalent refraction, axial length of the eye, birth weight, and gestational age (term or not). Finally, we examined potential effect modifiers in stratified analyses of age, sex, BMI, birth weight, and gestation. All of the probabilities quoted are 2-sided, and all of the statistical analyses were undertaken using SAS version 8 (SAS Institute Inc).

Results

Table 1 shows characteristics of the 2 study populations. As compared with Sydney, Singapore children were older, more likely boys, and of Chinese ethnicity. Singapore children had lower systolic and diastolic blood pressures compared with Sydney children. In Singapore, the percentage of children with head circumference in the 3rd percentile or below was higher compared with Sydney (13% vs 5% respectively)

TABLE 1. Study Populations: The Sydney Childhood Eye Study (Sydney) and the Singapore Cohort Study of the Risk Factors for Myopia (Singapore)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Sydney (n=1572)</th>
<th>Singapore (n=380)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>6.3 (0.4)</td>
<td>7.6 (0.6)</td>
</tr>
<tr>
<td>Sex, male, %</td>
<td>50.8</td>
<td>56.8</td>
</tr>
<tr>
<td>Race, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>64.2</td>
<td>0.0</td>
</tr>
<tr>
<td>Chinese</td>
<td>16.6</td>
<td>92.6</td>
</tr>
<tr>
<td>Other</td>
<td>19.2</td>
<td>7.4</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>99.8 (10.5)</td>
<td>109.9 (14.9)</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>60.3 (10.1)</td>
<td>63.9 (10.2)</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>23.8 (4.5)</td>
<td>33.4 (9.8)</td>
</tr>
<tr>
<td>Height, cm</td>
<td>120.6 (5.7)</td>
<td>136.0 (11.3)</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>16.2 (2.1)</td>
<td>17.7 (3.2)</td>
</tr>
<tr>
<td>Gestational age, term, %</td>
<td>92.2</td>
<td>81.9</td>
</tr>
<tr>
<td>Head circumference, cm</td>
<td>34.8 (1.8)</td>
<td>33.8 (1.4)</td>
</tr>
<tr>
<td>Birth weight, g</td>
<td>3382 (569)</td>
<td>3231 (448)</td>
</tr>
<tr>
<td>Birth length, cm</td>
<td>50.7 (3.1)</td>
<td>49.5 (2.3)</td>
</tr>
<tr>
<td>Spherical equivalent refraction, diopters*</td>
<td>1.30 (0.9)</td>
<td>–2.25 (2.01)</td>
</tr>
<tr>
<td>Axial length, mm*</td>
<td>22.6 (0.7)</td>
<td>24.2 (1.0)</td>
</tr>
<tr>
<td>Retinal arteriolar caliber, μm</td>
<td>159.6 (14.0)</td>
<td>161.8 (14.7)</td>
</tr>
<tr>
<td>Retinal venular caliber, μm</td>
<td>222.3 (18.4)</td>
<td>234.0 (20.4)</td>
</tr>
</tbody>
</table>

Data are mean (SD) or proportions.

*Axial length and spherical equivalent of the eye for which data has been used throughout analysis (this was the right eye in 96.6% of participants).
higher systolic and diastolic blood pressures, higher weight and BMI, were less likely to be born at term, and were more likely to have a myopic refraction and longer axial length. Singapore children had slightly wider retinal arteriolar caliber (161.8 μm versus 159.6 μm) and also wider venular caliber (234.0 μm versus 222.3 μm) than Sydney children. This was largely explained by the higher weight in Singapore children (33 versus 24 kg; data not shown).

Table 2 shows the mean retinal arteriolar and venular caliber by quartiles of systolic, diastolic, and mean arterial blood pressure, adjusted for age and sex. Children with higher blood pressure quartiles had consistently and significantly narrower retinal arteriolar caliber than those with lower quartiles ($P<0.003$ for all of the comparisons). The difference in arteriolar caliber between the first and fourth quartiles (5 μm) was similar for different blood pressure variables in both studies. Blood pressure was not associated with retinal venular caliber in either study ($P>0.2$ for all of the comparisons).

In linear regression models controlling for age and sex, retinal arteriolar caliber decreased by 1.64 to 2.11 μm for
TABLE 3. Linear Regression Models of Retinal Vascular Caliber and Blood Pressure

<table>
<thead>
<tr>
<th>Per 10 mm Hg Increase in:</th>
<th>Retinal Arteriolar Diameter (μm)</th>
<th>Retinal Venular Diameter (μm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic blood pressure</td>
<td>Mean Δ (95% CI)*</td>
<td>P</td>
</tr>
<tr>
<td>Sydney</td>
<td>Age and sex†</td>
<td></td>
</tr>
<tr>
<td></td>
<td>−2.11 (−2.76 to −1.45)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Multivariable‡</td>
<td></td>
</tr>
<tr>
<td></td>
<td>−2.08 (−2.79 to −1.38)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Singapore</td>
<td>Age and sex†</td>
<td></td>
</tr>
<tr>
<td></td>
<td>−1.64 (−2.63 to −0.66)</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>Multivariable‡</td>
<td></td>
</tr>
<tr>
<td></td>
<td>−1.43 (−2.59 to −0.27)</td>
<td>0.016</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td>Age and sex†</td>
<td></td>
</tr>
<tr>
<td></td>
<td>−1.46 (−2.14 to −0.78)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Multivariable‡</td>
<td></td>
</tr>
<tr>
<td></td>
<td>−1.47 (−2.16 to −0.78)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean arterial blood pressure</td>
<td>Age and sex†</td>
<td></td>
</tr>
<tr>
<td></td>
<td>−2.14 (−3.59 to −0.69)</td>
<td>0.004</td>
</tr>
<tr>
<td></td>
<td>Multivariable‡</td>
<td></td>
</tr>
<tr>
<td></td>
<td>−2.30 (−4.00 to −0.59)</td>
<td>0.008</td>
</tr>
</tbody>
</table>

*β-Coefficient (95% confidence intervals) of blood pressure variables (per 10 mm Hg), in linear regression models or retinal arteriolar or venular caliber.  
†Adjusted for age and sex.  
‡Adjusted for age, sex, race, BMI, axial length, spherical equivalent refraction, term birth, and birth weight.

Discussion

We found in 2 populations of children aged 6 to 8 years that higher blood pressure was significantly and monotonically associated with retinal arteriolar narrowing. On average, while controlling for age, sex, race, BMI, refraction, and birth parameters, each 10-mm Hg increase in systolic blood pressure and mean arterial blood pressure was associated with a 1.43- to 2.08-μm and 2.0- to 2.4-μm narrower retinal arteriolar caliber, respectively. In stratified analysis for the mean arterial blood pressure, this effect was seen in children aged 6, 7, or 8 years; in boys and girls; in those with higher or lower BMI and birth weight; and in term or preterm children. Blood pressure had no consistent effects on retinal venular caliber. The pattern and magnitude of the associations were consistent across the 2 cohorts.

Our principal finding, that higher blood pressure was associated with retinal arteriolar narrowing in children, is supported by numerous studies in adult populations, mostly aged ≥40 years.12–17 These studies have shown consistently that retinal arteriolar narrowing is not only associated with higher concurrent blood pressure levels but also with higher past blood pressure levels measured ≥9 years earlier.12,13 The current study suggests that the influence of blood pressure may extend from early childhood. Although our findings raise the possibility that adverse vascular effect of elevated blood pressure may occur early in life, it is also important to note that the observed narrowing of retinal arterioles could also be a functional phenomenon caused, for example, by sympathetic activity. Furthermore, in adult normotensive individuals, retinal arteriolar narrowing has been shown to predict the future development of hypertension independent of other factors in 4 separate cohorts.15–17,33 The Rotterdam study, for example, reported that retinal arteriolar narrowing was asso-
associated with higher risk of incident hypertension (odds ratio per SD decrease in retinal arteriolar caliber: 1.38; 95% confidence interval: 1.23 to 1.55). Thus, retinal arteriolar narrowing, at least in adults, is a preclinical marker of hypertension risk. Whether retinal arteriolar narrowing in children also predicts future hypertension in adulthood is not known.

There are very few studies on retinal signs associated with blood pressure in children for comparison. These have been largely confined to small clinic-based samples of children with essential hypertension, using qualitative methods to document retinal signs. Daniels et al, for example, reported a high prevalence (41%) of retinal arteriolar narrowing, as detected from direct ophthalmoscopy, in children and adolescents with essential hypertension. Our current study shows that retinal arteriolar narrowing, detected using a quantitative technique, is associated with higher blood pressure levels in community-based samples of healthy children.

The magnitude of the effect of higher blood pressure on retinal arteriolar narrowing in our childhood samples appears around two thirds of that observed in adult populations. For example, in a population-based study in white adults aged 43 to 84 years, each 10-mm Hg increase in mean arterial blood pressure was associated with a 2.2% decrease in arteriolar caliber, while controlling for other factors. In our current study, a similar increase in mean arterial blood pressure was associated with a 1.5% decrease in arteriolar caliber. These differences in magnitude are not unexpected and are explained by the shorter cumulative exposure of the retinal vasculature to higher blood pressure levels in children, as compared with the effects of greater lifetime blood pressure load on the development of retinal arteriolar narrowing in adults.

The lack of influence from blood pressure on retinal venular caliber in children is consistent with previous adult studies that show that venular caliber is not associated with hypertension and is in keeping with clinical observations in hypertensive patients. The distinct differences in the association between arterioles and venules also increase the likelihood that the relationship of higher blood pressure and retinal arteriolar narrowing in our study is not confounded by unexplained ocular factors (eg, intraocular pressure), which should be common to both arterioles and venules.

Our study provides further evidence that the risk of cardiovascular disease may have its origins early in life, which has implications in cardiovascular disease prevention. Studies now indicate that higher childhood blood pressure levels are “tracked” to higher blood pressure later in life and are independently associated with atherosclerosis in the carotid and femoral arteries and cardiovascular mortality in adults. In the Bogalusa Heart Study, autopsy studies on 93 persons 2 to 39 years of age show that the extent of atherosclerosis in the aorta and coronary arteries was strongly related to blood pressure levels. Other studies in children with essential hypertension have described subclinical indicators of target end organ damage, such as left ventricular hypertrophy. The current study demonstrates that, in healthy children, even mildly elevated blood pressure is associated with structural retinal vascular changes and that this effect is continuous across the range of blood pressure.
Because narrower retinal arterioles may predict subsequent cardiovascular events in adults, our findings in children may, therefore, form the basis for early preventive action and support measures to address modifiable risk factors in children with higher blood pressure (e.g., overweight and low physical activity). Several potential limitations of this study should be discussed. First, there were some systematic differences between characteristics of the children from the 2 cohorts. For example, blood pressure, weight, and BMI were higher in Singapore children. This heterogeneity prevented pooling of the data sets. However, the study populations appear to be reasonably representative of childhood populations. For example, the blood pressure levels in our 2 childhood cohorts are similar to those recorded for 5- to 7-year-old children in the United Kingdom, 9-year-old children in Denmark, and 8-year-old children in the United States. Second, the cross-sectional setting of our study prevented a direct inference of causality between blood pressure and development of retinal arteriolar narrowing. This would require prospective data. Third, unknown sources of variability cannot be excluded and may have introduced additional biases. For example, the instruments and protocols for measuring blood pressure were different in the 2 studies. The consistency of the pattern and magnitude of the findings between the 2 cohorts, however, reduces the likelihood that these biases are substantial. Finally, retinal arteriolar narrowing in children could simply reflect the normal autoregulatory reflex in response to higher blood pressure. Whether these are permanent structural changes would need to be evaluated in longitudinal studies, which are currently in planning. However, longitudinal data in adult populations suggest that retinal arteriolar narrowing is not frequently reversible (P Mitchell and TY Wong, unpublished data, 2006).

**Disclosures**

None.

**References**


10. Barker DJ, Osmond C, Golding J, Kuh D, Wadsworth ME. Growth in utero, childhood levels of blood pressure are consistently and monotonically associated with narrowing of the retinal arterioles and small arteries, independent of body size, birth parameters, and other factors. This suggests that effects of elevated blood pressure may manifest early in life.

**Acknowledgments**

We thank Angela Cheng and Kathy Rose for coordinating these studies.

**Sources of Funding**

This research is supported by the National Health and Medical Research Council, Australia, grant 253732 (P.M.), the National Medical Research Council, Singapore, NMRC/0695/2002 (S.S.M.), the Biomedical Research Council (T.Y.W.), the SingHealth Foundation (T.Y.W.), and the Science Technology and Innovation Grant, Victoria, Australia (T.Y.W.). This work was also supported by a Stichting Donderfonds grant, Emmen, the Netherlands (K.d.H.). The funding agencies had no role in the conduct of the study; data collection, management, analysis, and interpretation of the data; or preparation, review, or approval of the article.

**Perspectives**

Blood pressure levels have increased substantially among children and adolescents over the last decade. Our study, conducted in 2 population-based samples, demonstrates that childhood levels of blood pressure are consistently and monotonically associated with narrowing of the retinal arterioles and small arteries, independent of body size, birth parameters, and other factors. This suggests that effects of elevated blood pressure may manifest early in life.

**Blood Pressure and Retinal Vessel in Children**

**Blood Pressure and Retinal Vessel in Children**


Blood Pressure and Retinal Arteriolar Narrowing in Children
Paul Mitchell, Ning Cheung, Kristin de Haseth, Bronwen Taylor, Elena Rochtchina, F. M. Amirul Islam, Jie Jin Wang, Seang Mei Saw and Tien Y. Wong

Hypertension. 2007;49:1156-1162; originally published online March 19, 2007; doi: 10.1161/HYPERTENSIONAHA.106.085910
Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2007 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/49/5/1156

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Hypertension can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Hypertension is online at:
http://hyper.ahajournals.org/subscriptions/