# Elevated Blood Pressure is Associated with Rarefaction of the Retinal Vasculature in Children

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**Purpose.** Retinal vascular fractal dimension ($D_f$) is a measure of the geometric complexity of the retinal microvasculature, and has been associated with diabetic retinopathy. In this study, the authors examined the relationship between blood pressure and retinal $D_f$ in children.

**Methods.** Among 1174 children aged 10 to 14 years who participated in the Singapore Cohort Study of Risk Factors for Myopia, retinal $D_f$ was measured from digital fundus images using a computer-based program following a standardized protocol. Blood pressure was calculated from the average of three separate measurements in a seated position.

**Results.** The analysis shows that retinal $D_f$ was normally distributed, with a mean of 1.4619 (SD, 0.0144). After adjusting for age, sex, height, and retinal arteriolar and venular caliber, smaller retinal $D_f$ was correlated with elevated mean arterial blood pressure ($P = 0.02$), diastolic blood pressure ($P = 0.02$), and possibly systolic blood pressure ($P = 0.06$).

**Conclusions.** Higher blood pressure in children is associated with smaller retinal $D_f$, reflecting rarefaction of the retinal microvasculature. Retinal fractal analysis detects early subtle microvascular effects of elevated blood pressure, and may further the understanding of the genesis of ocular and systemic vascular complications of hypertension. (*Invest Ophthalmol Vis Sci.* 2012;53:470–474) DOI:10.1167/iovs.11-8835

Fractal analysis has been increasingly applied to understanding interindividual variations in the retinal vascular branching pattern.[1–3] Unlike conventional Euclidean measurements such as vessel width or branching angles, fractal analysis measures the degree of geometric complexity of the retinal microvascular network,[2,4] summarized using a single measure known as the fractal dimension ($D_f$). According to Murray's optimality principle, the most efficient retinal vascular network has an ideal branching pattern that creates minimum work for maximum blood flow and perfusion. This ideal network can be represented by an "optimal" $D_f$ value.[2,5]

We have recently developed a computer program to perform fractal analysis of retinal images.[6] Our previous studies in adult populations have shown that variations in retinal $D_f$ are associated with various ocular (e.g., diabetic retinopathy) and systemic (e.g., stroke) vascular diseases that are related to hypertension.[7–14] However, little is known about the direct relationship between blood pressure and the retinal fractal.

In this study, we examined the relationship between blood pressure and retinal $D_f$ in a population of healthy young children, in which the confounding effects of systemic and ocular diseases are minimal. This knowledge might further our understanding of the genesis of ocular and systemic microvascular diseases related to hypertension.

## Methods

### Study Population

The Singapore Cohort Study of Risk Factors for Myopia is a study of 1979 schoolchildren aged 7 to 9 years at baseline in Singapore. Details of the study population have been described in detail elsewhere.[15] In brief, 2913 children were initially recruited for the study with a participation rate of 67.9% (1979 participants). Children from grades 1 and 2 from an eastern school ($n = 660$) and children from grades 1, 2, and 3 from a northern school ($n = 1023$) were invited to participate in November 1999, and children from grades 1, 2, and 3 from a western school ($n = 1230$) were enrolled in May 2001. Children with medical conditions ($n = 94$), such as leukemia and heart disorders, syndrome-associated myopia, or eye disorders, such as cataract, were excluded from the study. Twelve hundred fifty-two participants returned in 2006 for a follow-up examination. The Ethics Committee of the Singapore Eye Research Institute approved the study, and the conduct of the study followed the tenets of the Declaration of Helsinki. Written informed consent was obtained from all parents after the nature of the study was explained.

### Retinal Photography and Fractal Analysis

All participants were examined on the school premises by a team of ophthalmologists, optometrists, and research assistants at the 2006 visit. After pupil dilatation with cyclopentolate 1%, digital retinal photographs centered on the optic disc were taken of both eyes using standardized settings.[15]

Fractal analysis was performed on the optic disc-centered retinal photographs using a computer-based program (International Retinal Imaging Software [IRIS-Fractal], version 1; National University of Singapore, Singapore) following a standardized protocol, as described previously.[6,7] For each retinal photograph, one trained grader, masked to participants' characteristics and clinical diagnoses, used the program to measure retinal $D_f$ within a predefined circular region of 3.5 optic disc radii centered on the optic disc. After the program automatically traced all the retinal vessels within this region, the grader checked the tracing with the original photograph and removed occasional artifacts misidentified as vessels (peripapillary atrophy, choroidal vessels, pigment abnormalities, and nerve fiber reflection). The program then performed fractal analysis and calculated retinal $D_f$ using the box-counting approach,[6,7,16] an established method for measuring fractal dimension of structures that are not perfectly self-similar, such as the retinal vasculature. Intragrader reproducibility of measurements using IRIS-Fractal was high, with the grader showing an intraclass correlation

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coefficient of 0.93. The grader also showed high intergrader correlation of 0.97 with other fractal graders in our center using the same images. Retinal vascular caliber was also measured from these photographs, and summarized as central retinal artery equivalent (CRAE) or central retinal vein equivalent (CRVE) using a standardized protocol described elsewhere.[17,18]

### Assessment of Blood Pressure

Blood pressure was measured in the seated position after 5 minutes of rest using an automated sphygmomanometer (Omron HEM 705 LP; Omron Health Care, Inc., Bannockburn, IL) with the appropriate cuff size. The cuff size was selected to ensure that the bladder spanned the circumference of the arm and covered at least 75% of the upper arm without obscuring the antecubital fossa. The average of three separate measurements of systolic and diastolic blood pressure was used for analysis. Mean arterial blood pressure (MABP) was calculated as one-third of the systolic blood pressure (SBP) plus two-thirds of the diastolic blood pressure (DBP).

### Assessment of Other Parameters

Cycloplegic refraction was obtained using calibrated auto refractometers (RK5; Canon, Inc. Ltd., Tochigiken, Japan). Axial length, anterior chamber depth, lens thickness, and vitreous chamber depth measurements were obtained using a biometry ultrasound unit (probe frequency, 10 mHz; Echoscan US-800; Nidek Co. Ltd., Tokyo, Japan). One drop of 0.5% proparacaine was instilled into each eye before ultrasound biometry measurements were made. The average of six values was taken with the SD of the six measurements <0.12 mm.

The parents completed several questionnaires that covered topics including demographic information, parental smoking status, and indicators of socioeconomic status, such as total family income per month, parental education level, and type of housing. The child's birth history, including birth weight, birth length, head circumference, gestational age, and history of jaundice at birth, was obtained from each child's health booklet, completed by medical personnel soon after birth.

### Statistical Analysis

We reported characteristics of adolescents included in the study and compared them between different sex groups. Results were reported as means and standard deviations, with differences tested using the independent *t*-test. Multivariate linear regression models were used to determine the association of mean arterial blood pressure with the retinal vascular fractal dimension, adjusting for potential confounders. Similar models were fitted for systolic and diastolic blood pressure. All statistical analyses were performed using statistical software (SPSS version 17; SPSS Inc., Chicago, IL).

## Results

A total of 1252 subjects were initially included. After excluding 75 participants due to ungradable retinal photographs or incomplete blood pressure measurements, and 3 participants due to outlying values of mean arterial blood pressure, 1174 subjects (94%) were available for final analysis. There were no significant differences in baseline characteristics between the included and excluded groups (data not shown).

Out of 1174 participants, 50.9% were female, and the mean age was 11.91 years. By ethnicity, 71.1% were Chinese, 21.0% Malay, 6.7% Indian, and 1.1% others. Detailed characteristics of the participants stratified by sex are shown in Table 1. In general, boys had a SBP of approximately 8 mm Hg higher than girls, a MABP of approximately 3 mm Hg higher than girls, but similar DBP. There are no significant differences among different races.

Figure 1 shows the distribution of the retinal $D_f$ in our study population. $D_f$ was normally distributed, with a mean of 1.4619 (95% confidence interval [CI], 1.4475–1.4763). There was no significant difference in retinal fractal dimension between the two sex groups ($P = 0.128$).

Table 2 shows the linear regression models used to demonstrate the relationship between retinal $D_f$ and blood pressure, adjusted for potential confounders. In Model 1, after controlling for age, sex, and height, smaller retinal $D_f$ is significantly associated with a higher MABP ($P = 0.009$), SBP ($P = 0.019$), and DBP ($P = 0.015$). Model 2 shows further adjustment for CRAE and CRVE; results were essentially similar, with smaller retinal $D_f$ associated with higher MABP ($P = 0.021$), SBP ($P = 0.064$), and DBP ($P = 0.022$). This inverse correlation is illustrated with the example of MABP in Figure 2 ($P$ for trend = 0.043).

## Discussion

Our study provides normative data on the distribution and mean of the retinal $D_f$ in a sample of healthy children, using a previously validated standardized method of retinal fractal analysis. Our data showed that retinal $D_f$ has a normal distribution, and more importantly, that blood pressure is inversely related to retinal $D_f$. This supports our findings in an earlier pilot study in adults.[6]

Our study further extends work by our group and others who have previously reported that the retinal vascular caliber, particularly arteriolar caliber, is influenced by blood pressure in both adults[19,20] and children.[21] Vessel narrowing is corre-

**Table 1.** Participant Characteristics in the Singapore Cohort Study of Risk Factors for Myopia

| Characteristics | Total ($n$ = 1174) | Boys ($n$ = 576) | Girls ($n$ = 598) | $P$ Value |
|---|---|---|---|---|
| Age, y | 11.91 (1.01) | 11.93 (1.04) | 11.88 (0.99) | 0.372 |
| Systolic blood pressure, mm Hg | 110.41 (13.68) | 114.60 (14.20) | 106.38 (11.84) | <0.001 |
| Diastolic blood pressure, mm Hg | 64.04 (8.51) | 64.42 (8.86) | 63.67 (8.14) | 0.135 |
| Pulse pressure, mm Hg | 46.37 (10.07) | 50.19 (9.83) | 42.70 (8.86) | <0.001 |
| Mean Arterial blood pressure, mm Hg | 79.50 (9.39) | 81.15 (9.91) | 77.91 (8.57) | <0.001 |
| Body mass index | 19.65 (4.03) | 19.76 (4.05) | 19.54 (4.01) | 0.352 |
| Height, cm | 159.21 (9.46) | 162.04 (10.75) | 156.49 (7.03) | <0.001 |
| Weight, kg | 50.24 (12.93) | 52.41 (13.78) | 48.15 (11.70) | <0.001 |
| Birth weight, g | 3163.38 (479.20) | 3193.42 (486.57) | 3134.62 (470.65) | 0.036 |
| Birth length, cm | 49.09 (2.43) | 49.40 (2.36) | 48.79 (2.46) | <0.001 |
| Gestational age, wk | 38.53 (1.74) | 38.53 (1.77) | 38.53 (1.71) | 0.981 |
| Axial length, mm | 23.27 (0.93) | 23.57 (0.91) | 22.98 (0.85) | <0.001 |
| Spherical equivalent refraction, diopters | −0.33 (1.67) | −0.42 (1.76) | −0.22 (1.57) | 0.031 |
| Retinal fractal dimension | 1.4619 (0.0144) | 1.4613 (0.0148) | 1.4626 (0.0141) | 0.135 |

Data are mean (SD). Body mass index calculated as weight (kg)/height ($m^2$).

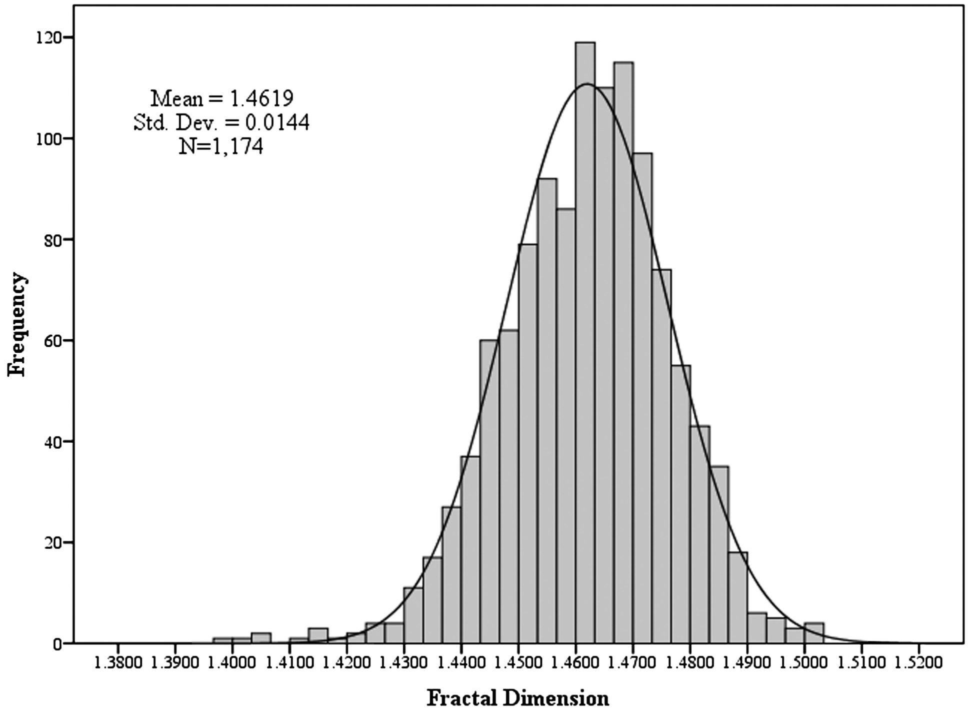


**FIGURE 1.** Distribution of retinal fractal dimension.

lated with $D_f$, as it reduces the geometric complexity the microvascular network. However, our analysis showed that the association between elevated blood pressure and lowered retinal $D_f$ remained strong, even after adjusting for retinal vascular caliber (Model 2). This shows that the relationship between blood pressure and $D_f$ are independent of its effects on retinal vessel caliber.

From clinical and experimental data, we now know that microvascular changes in elevated blood pressures can be grouped into two main processes: vessel remodeling and network rarefaction.[22–24] Remodeling pertains to the structural changes to the resistance of arterioles culminating in vessel narrowing. The microcirculation is in a state of chronic vasoconstriction, due to local physiological myogenic reflexes. This results in eutrophic inward remodeling of vessels, with an increase in media-to-lumen ratio and decreased vessel diameter.[25] The extent of vascular remodeling can be determined by measuring the retinal vessel caliber. On the other hand, rarefaction is a separate concept relating to the reduced spatial density of the microvascular network through vessel destruction and insufficient angiogenesis.[23,24] These changes are simultaneously present in all vascular beds,[25] and changes in the retina can represent the state of the microcirculation in general.[26,27] The retinal $D_f$ characterizes the branching network, and a decrease in the retinal $D_f$ indicates loss of complexity and microvascular rarefaction. Therefore, $D_f$ introduces additional, unique information about the retinal vasculature.

Apart from structural changes, deviation from the optimal $D_f$ value also indicates functional changes in blood flow. Vascular branching patterns follow Murray's principle of minimum work, which minimizes energy expenditure from shear stress on the vessel wall.[5,28] Blood flow-induced shear stress strongly influences the growth and remodeling of arteriolar trees,[28,29] reflected in changes in the retinal $D_f$.

Although vessel remodeling is recognized as a consequence of hypertension, the causality relationship between rarefaction and hypertension is less clear.[22,23] Current evidence suggests that rarefaction is both a primary defect and a downstream consequence of hypertension.[23,24] Regardless, our study in normal children proposes that microvascular rarefaction can be detected early, among children in higher quartiles of blood pressure, using retinal fractal analysis. Our data does not include children with overt clinical hypertension, but population studies have shown that elevated blood pressure tracks from childhood to adulthood and predicts essential hypertension.[30–32] Children with retinal rarefaction may represent a subpopulation with a greater risk of developing hypertension in adulthood, although further studies are still required to confirm this.

**TABLE 2.** Linear Regression of Fractal Dimension with Blood Pressure

| | Model 1 | | | | Model 2 | | | |
|---|---|---|---|---|---|---|---|---|
| | | 95% CI for Beta | | | | 95% CI for Beta | | |
| | **Standardized Beta** | **Lower Bound** | **Upper Bound** | ***P* Value** | **Standardized Beta** | **Lower Bound** | **Upper Bound** | ***P* Value** |
| Mean arterial blood pressure, mm Hg | −0.083 | −0.145 | −0.021 | 0.009 | −0.074 | −0.137 | −0.011 | 0.021 |
| Systolic Blood Pressure, mm Hg | −0.078 | −0.142 | −0.013 | 0.019 | −0.062 | −0.128 | 0.004 | 0.064 |
| Diastolic Blood Pressure, mm Hg | −0.074 | −0.134 | −0.014 | 0.015 | −0.071 | −0.131 | −0.010 | 0.022 |

Model 1 adjusted for age, sex, and height. Model 2 adjusted for age, sex, height, CRAE, and CRVE.

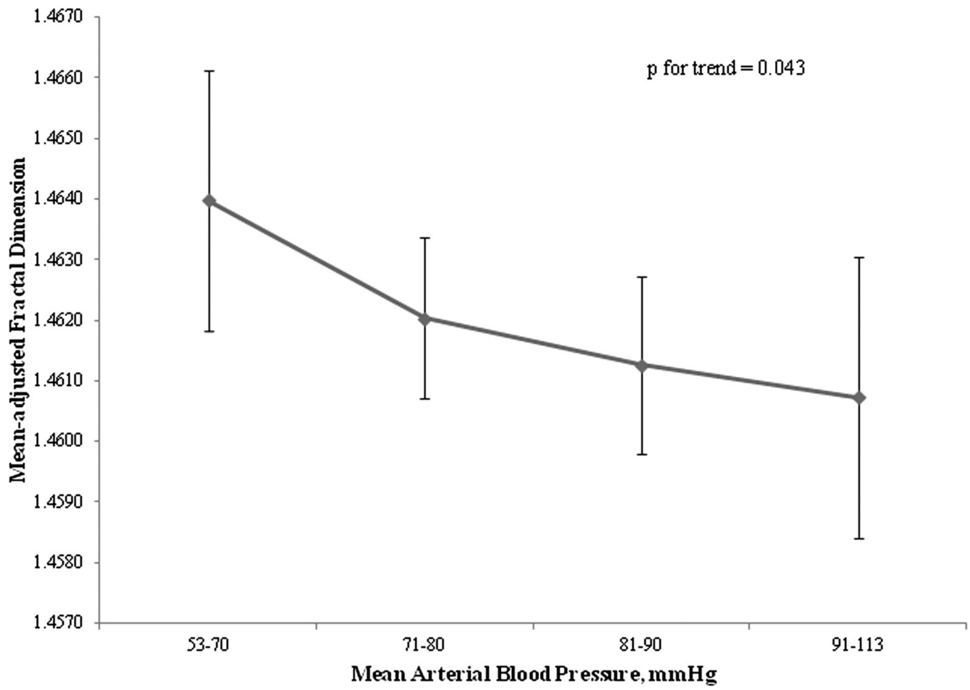


**FIGURE 2.** Average retinal fractal dimension in quartiles of mean arterial blood pressure.

Strengths of our study include the use of a standardized protocol to calculate fractal dimensions using a computer program with minimal user input, as well as a reliable method of measurement of the systemic and ocular information. The retinal image grader was blinded to the study participants, and statistical analysis took possible confounding factors into consideration. The use of fractal measurements in quantifying the retinal vascular branching pattern has certain advantages. It is a dimensionless measure, and is therefore independent of magnification within a certain range, unlike measurements of caliber and tortuosity. It is also a global reflection of various parameters of the retinal vascular network, and not just a single measure. However, our study is not without limitations. The fractal analysis program is not infallible in tracing the retinal branching pattern, as described elsewhere.[6] Briefly, it may pick up artifacts like peripapillary atrophy as vessels (false positive) or miss out on minor vessels due to lack of contrast (false negative). False positives are easily identified and removed by trained graders. While graders cannot add their own trace, false negatives do not occur as frequently, and images with missing major vessels are excluded from analysis.

Our study is the first to demonstrate that that children with high-normal blood pressure have smaller retinal $D_f$, reflecting early microvascular rarefaction. It also suggests that these subtle retinal vascular geometric changes can be detected in a quantitative manner from an early age. The potential of retinal fractal analysis as a novel tool to assess the risk of hypertensive ocular and systemic vascular diseases deserves further investigation.

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