Evidence of Arteriolar Narrowing in Low-Birth-Weight Children

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Background—Cardiovascular disease may have its origins in utero, but the influence of in utero growth on microvascular structure in children is unknown. We hypothesized that poor in utero growth is associated with narrower arteriolar caliber, which may help explain the established association of low birth weight with hypertension and cardiovascular disease in adulthood.

Methods and Results—We examined the relation of birth weight and other markers of in utero growth to microvascular caliber in the retina in a population-based study of 1369 6-year-old children in Sydney, Australia (Sydney Childhood Eye Study). Birth weight, birth length, and head circumference were obtained from parental records. Retinal arteriolar and venular calibers were measured from digitized retinal photographs by a validated computer-assisted method. Lower birth weight, shorter birth length, and smaller head circumference were associated with narrower retinal arteriolar caliber. Each kilogram decrease in birth weight was associated with a 2.3-μm (95% CI 0.6 to 3.9, \( P = 0.01 \)) narrower retinal arteriolar caliber after controlling for age, gender, ethnicity, height, body mass index, axial length, mean arterial blood pressure, and prematurity. Similar associations were observed between shorter birth length and smaller head circumference with narrower retinal arteriolar caliber.

Conclusions—Children who had lower birth weight, shorter birth length, and smaller head circumference had narrower retinal arteriolar calibers. These data support the concept that poor in utero growth may have an adverse influence on microvascular structure. (Circulation. 2008;118:518-524.)

Key Words: microcirculation ■ arteries ■ hypertension ■ angiogenesis

Cardiovascular disease is the leading cause of death in the developed world.\(^1\) A large body of literature shows that susceptibility to cardiovascular disease may have etiological origins in utero and in infancy.\(^2,3\) Epidemiological data have linked markers of poorer early life growth, such as lower birth weight and smaller head circumference, with higher blood pressure in childhood\(^2,5-9\) and risk of cardiovascular disease in adulthood.\(^10\) These findings are the foundation of the fetal/developmental origins of adult disease hypothesis, which suggests early growth and nutritional factors program various physiological and anatomic changes that are adaptive in early life (eg, during infancy) but are maladaptive in later life.\(^5,3,11\)

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Nevertheless, the exact structural vascular changes that are affected by poor early growth are unclear. Low birth weight has been linked with structural and functional abnormalities in large arteries\(^12-14\) and increased carotid atherosclerosis\(^15,16\) both in childhood and adulthood, which may be a potential pathway that predisposes to earlier-onset cardiovascular disease. Alternatively, early growth may affect small vessel structure and function, but there are scant data to support this, largely because of limited methods to assess the human microcirculation and because of difficulties in minimizing confounding from hypertension or diabetes mellitus, both of which have profound microcirculatory effects.

We have developed reliable, computer-based techniques to measure retinal microvascular caliber from retinal photographs and have shown that narrowed retinal arterioles are a marker of both future hypertension and cardiovascular risk in adult populations.\(^17-23\) In the present study, we test the hypothesis that low birth weight and other markers of poor early life growth (shorter birth length and smaller head circumference) are associated with narrower retinal arteriolar caliber in a population-based sample of 6-year-old children. We suggest that this population is ideal to test this hypothesis, because children have
few potentially confounding vascular diseases or traditional risk factors.

Methods

Study Population
The Sydney Myopia Study was the first stage of a series of population-based eye surveys (collectively known as the Sydney Childhood Eye Study) to examine the prevalence and associations of eye diseases across a range of ages. This study examined grade 1 school children (mostly age 6 years) attending 34 primary schools across the Sydney metropolitan region selected during 2003 to 2004 by random cluster sampling. From 2238 eligible children, 1740 (78%) with parental consent underwent a thorough, comprehensive medical history questionnaire and eye examination that included retinal photography. This study is based on 1369 children (78.7%) who had data on birth parameters and gradable retinal photographs. The University of Sydney Human Research Ethics Committee and the Department of Education and Training, both in Sydney, Australia, approved the study. It was conducted according to the tenets of the Helsinki Declaration. Written informed consent was obtained from all parents with verbal assent from the children.

Birth Parameters Assessment
Parents were sent a comprehensive 193-item questionnaire to complete or had this administered at a telephone interview. The parents of all Australian children are provided with a health record booklet for its integrity. All authors have read and agree to the manuscript as written.

Retinal Photography and Measurement of Retinal Vessel Caliber

The first and fifth Korotkoff sounds were used to detect systolic and diastolic blood pressure, respectively. Mean arterial blood pressure was calculated as one third of the systolic plus two thirds of the diastolic blood pressure. Height in meters was measured with children standing, without shoes. Weight in kilograms was measured with a standard portable weighing machine, calibrated before study commencement. Body mass index was calculated as weight divided by height squared (kg/m²). The ocular refractive status was measured by autorefraction (model RK-F1, Canon) and converted to spherical equivalent, and axial length was obtained by laser interferometry (IOL-Master, Zeiss, Oberkochen, Germany).

Statistical Analyses

We examined the relationship of birth weight and other markers of early life growth (birth length and head circumference) to retinal vessel calibers using logistic and multiple linear regression techniques. We constructed models adjusted for age (continuously in weeks), gender, ethnicity, prematurity, body mass index, height, axial length (last 3 continuously) and mean arterial blood pressure (continuously). We modeled retinal vessel caliber as a categorized variable (in quartiles) and continuously, and we repeated analyses after excluding children who had been born very prematurely. We calculated the effect on arteriolar caliber per 1-SD decrease in birth weight, birth length, and head circumference, respectively. We also examined the relationship of birth weight with systolic and diastolic blood pressure in multiple linear regression models. SAS version 9.1 (SAS Institute, Cary, NC) was used for all analyses. The authors had full access to the data and take full responsibility for its integrity. All authors have read and agree to the manuscript as written.

Results

The demographic, birth weight, and other perinatal characteristics of children in this sample are described in Table 1. Children with low birth weight were similar to their peers of normal or higher birth weight for characteristics including parental socioeconomic status, parental age, and education level. Children with low birth weight were more likely, however, to be first born, be twins or triplets, or be delivered by Caesarian section.

At birth, children in this population had a mean birth weight of 3382 g (95% CI 3352 to 3412 g), mean body length of 50.7 cm (95% CI 50.5 to 50.8 cm), and mean head circumference of 34.8 cm (95% CI 34.7 to 34.9 cm). Mean retinal arteriolar and venular calibers were 162.7 μm (95% CI 161.9 to 163.4 μm) and 226.8 μm (95% CI 225.9 to 227.8 μm), respectively. Mean age was 349 weeks (95% CI 348 to 350 weeks); 50.4% were male; and mean height, body mass index, and blood pressure were 120.6 cm (95% CI 120.3 to 120.9 cm), 16.2 kg/m² (95% CI 16.1 to 16.3 kg/m²), and 73.3 mm Hg (95% CI 72.9 to 73.9 mm Hg), respectively. In univariate analyses, age (in months) was not associated with arteriolar caliber, whereas gender was. Arterioles were 3.4 μm (95% CI 2.0 to 4.7 μm, P=0.0001) narrower in boys than in girls. A 1-mm increase in axial length was associated with 4.9-μm (95% CI 3.7 to 6.0 μm) narrower arterioles. Before adjustment for age, gender, and other factors, each 1-kg decrease in birth weight was associated with 1.8-μm (95% CI 0.1 to 3.6 μm, P=0.04) narrower retinal arterioles. Premature birth was associated with 3.8-μm (95% CI 1.1 to 6.4 μm, P=0.007) narrower arterioles, and each 1-SD decrease in birth length and head circumferences was associated with 0.9-μm (95% CI –0.1 to 1.9 μm, P=0.07) and 1.0-μm (95% CI 0.1 to 1.8 μm, P=0.03) narrower arterioles, respectively.

Measurement of Other Variables

We measured blood pressure on the school premises using a standard protocol. After the children had rested for 5 minutes, blood pressure was measured while they were seated using an automated digital oscillometric sphygmomanometer (model HEM 907, Omron Healthcare, Bannockburn, Ill) with appropriate cuff size (bladder length ~80% and width at least 40% of the arm circumference, covering the upper arm but not obscuring the antecubital fossa).
Children with full data (n=1369) were similar to those with incomplete records (n=371) in terms of age, gender, height, body mass index, mean arterial blood pressure, birth weight, body length, head circumference, and prematurity birth. (P>0.05).

The Figure shows the relationship of birth weight categories and retinal vessel caliber in the 6-year-old childhood sample after adjustment for age, gender, ethnicity, body mass index, height, axial length, prematurity, and mean arteriolar blood pressure. Lower birth weight was associated with narrower retinal arteriolar caliber. (P for trend=0.01). Birth weight was not associated with retinal venular caliber. Other birth parameters, such as prematurity, shorter birth length, and smaller head circumference, were also related to narrower retinal arteriolar caliber (Table 2). These parameters were not associated with venular caliber.

Further analyses modeled several birth parameters continuously, which confirmed our earlier observations (Table 3). Decreasing birth weight, shorter birth length, and smaller head circumference were all associated with narrower retinal arterioles. After adjustment for all variables, there was a 1.28-μm narrowing in arteriolar caliber per 1-kg decrease in birth weight, 1.00-μm narrowing in arteriolar caliber per 1-SD decrease in birth weight, birth length, and head circumference, respectively. Children with low birth weight and those who were born prematurely had a 3.73- and 3.43-μm narrower retinal arteriolar caliber, respectively. In this fully adjusted model, each 1-kg decrease in birth weight was associated with 2.23-μm (95% CI 0.57 to 3.92 μm, P=0.01) narrowing in mean retinal arteriolar caliber.

We performed several subsidiary analyses. After the exclusion of premature children of <33 weeks (n=12), associations were similar. Each 1-SD decrease in birth weight, birth length, and head circumference remained significantly associated with arteriolar narrowing after multivariable adjustment: 1.27 μm (95% CI 0.36 to 2.18 μm, P=0.008), 1.12 μm (95% CI 0.22 to 2.02 μm, P=0.016), and 1.16 μm (95% CI 0.35 to 1.96 μm, P=0.006), respectively, for the 3 birth parameters. Each 1-kg decrease in birth weight was associated with a 2.23-μm (95% CI 0.63 to 3.83 μm, P=0.008) narrowing in mean retinal arteriolar caliber.

We also examined the previously reported association of birth weight and blood pressure and observed that each 1-kg decrease in birth weight was associated with 1.83-mm Hg (95% CI 0.91 to 2.76 mm Hg, P=0.0003) higher systolic and 1.64-mm Hg (95% CI 0.63 to 2.65 mm Hg, P=0.002) higher diastolic blood pressure, respectively, for all children. The magnitude of this association was only slightly attenuated after the exclusion of premature children.

### Discussion

In this population-based study, we showed that 6-year-old children with lower birth weight, shorter birth length, and smaller head circumference had significantly narrower retinal arterioles than those with higher birth weight, longer birth length, and larger head circumference. The relationship was strong, had a gradient of effect, and persisted after adjustment for confounding factors. Its demonstration in children free of adult cardiovascular disease and risk factors argues against the effects of these factors as potential confounders. The present data also show lower birth weight to be related to higher blood pressure in these children, consistent with other studies.9

These findings in children are compatible with findings in adult populations that narrower retinal arteriolar caliber is a marker of increased risk for hypertension and cardiovascular disease.17,18 The present data thus support the hypothesis that microvascular arteriolar structure, considered a major deter-

### Table 1. Characteristics of Participants by Birth Weight

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Birth Weight ≥2500 g (n=1280)</th>
<th>Low Birth Weight ≤2499 g (n=83)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sociodemographic factors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, wk</td>
<td>348 (347–350)</td>
<td>350 (346–355)</td>
<td>0.43</td>
</tr>
<tr>
<td>Male gender</td>
<td>650 (50.5)</td>
<td>40 (48.2)</td>
<td>0.68</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>845 (65.7)</td>
<td>55 (66.3)</td>
<td>0.92</td>
</tr>
<tr>
<td>East Asian</td>
<td>196 (15.2)</td>
<td>16 (19.3)</td>
<td>0.32</td>
</tr>
<tr>
<td>Other</td>
<td>245 (19.1)</td>
<td>12 (14.4)</td>
<td>0.30</td>
</tr>
<tr>
<td>Both parents employed</td>
<td>696 (56.7)</td>
<td>45 (57.7)</td>
<td>0.87</td>
</tr>
<tr>
<td>Home ownership</td>
<td>915 (74.1)</td>
<td>60 (75.0)</td>
<td>0.86</td>
</tr>
<tr>
<td>Parental education (university)</td>
<td>630 (52.5)</td>
<td>42 (56.0)</td>
<td>0.56</td>
</tr>
<tr>
<td>Perinatal factors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at birth, y</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maternal</td>
<td>30.8 (30.5–31.1)</td>
<td>31.6 (31.0–32.8)</td>
<td>0.18</td>
</tr>
<tr>
<td>Paternal</td>
<td>33.8 (33.5–34.2)</td>
<td>34.5 (33.2–35.9)</td>
<td>0.38</td>
</tr>
<tr>
<td>Caesarean birth</td>
<td>229 (18.3)</td>
<td>33 (40.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Twins or triplets</td>
<td>17 (1.4)</td>
<td>22 (27.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Firstborn child</td>
<td>535 (41.6)</td>
<td>48 (57.8)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Data are given as No. (%) of each group or mean (95% CI).
minant of peripheral vascular resistance,29,30 may be "programmed" early in life and could thereby influence the risk of adult hypertension and cardiovascular disease. We further speculate that intrauterine influences such as nutritional restriction, of which low birth weight and other birth parameters are proxy markers, may result in structural circulatory changes, which are adaptive in fetal life but maladaptive in childhood and adulthood, and subsequently predispose individuals to cardiovascular disease; however, mechanisms relating the microcirculatory changes we observed in childhood to future cardiovascular risk are unknown, and therefore, the present data must be interpreted cautiously.

The present findings are of particular relevance because retinal arteriolar narrowing is a known target end-organ effect of blood pressure and may be a preclinical marker of hypertension, diabetes mellitus, and cardiovascular risk. We have previously shown in adults that narrower retinal arterioles predict by many years the onset of clinical hypertension,22,23 diabetes mellitus,31 and coronary heart disease,2,23 which highlights the contribution of microvascular disease to these disorders. The present results thus complement and extend to small arterioles the substantial existing literature documenting associations of low birth weight with abnormalities of the large arteries such as reduced aortic dimension14 and compliance,13 increased wall thickening,32 narrower coronary arteries,33 and increased carotid atherosclerosis.15,16 Smaller head circumference and shorter birth length are associated with higher blood pressure9,34 and subsequent cardiovascular disease in adulthood,10,35 and the present study is among the first, and the largest to date, to report associations of these birth parameters with structural abnormalities of the microcirculation. We also observed the relationship of low birth weight with higher systolic blood pressure of similar magnitude to many other studies in children and adolescents.8,9 Both low birth weight and retinal arteriolar narrowing are potential subclinical markers for cardiovascular risk. The presence of both factors may indicate a need for closer monitoring, lifestyle modifications, and other interventions in this small subgroup.

In adults, there are reported associations of self-recalled low birth weight with arteriolar narrowing,36 impaired vasoconstriction of the brachial artery,37 and abnormalities in retinal arteriolar branching patterns that suggest "rarefaction" or loss of microvascular branches.38 These findings support the present results, although it should be emphasized that studies in adults could be confounded by preexisting hypertension or diabetes,38 as well as by concerns about the use of self-recalled birth weight collected many years later. The presence of cardiovascular risk factors in childhood has been shown to track into adulthood, where their effects may be amplified.39,40 This supports the concept that microvascular abnormalities in childhood track into adulthood, where they may predispose to hypertension and other adult conditions.

Narrower arterioles detected from retinal photographs could indicate the presence of more generalized vessel changes, such as vasoconstriction or arteriosclerosis (medial hyperplasia and mural thickening) possibly related to endothelial dysfunction.17,41 This hypothesis would be consistent with work that reports associations of low birth weight with impaired endothelial dysfunction in children aged 9 to 11 years,15 which tracks into early adult life.42 We note that there was only a 3% to 4% difference in arteriolar caliber across the range of birth weight and other markers of early growth. Similarly small degrees of retinal arteriolar narrowing have been shown to predict the risk of hypertension and cardiovascular diseases in adults.17,18 However, it should be emphasized that the long-term clinical significance of this level of retinal arteriolar narrowing detected during childhood is unclear. The few studies to specifically examine arteriolar caliber in children indicate that narrower arteriolar caliber is linearly related to higher ambient blood pressure43 and greater body mass index.44 Whether retinal arteriolar narrowing detected in childhood predicts greater risk of hypertension and obesity in adulthood is yet to be determined. Our own study will pursue these and other questions by following this cohort into young adulthood. Further animal studies are required to test the hypothesis that poor in utero growth

Figure. Relationship of birth weight to retinal arteriolar and venular calibers. Values are adjusted for age, gender, ethnicity, height, body mass index, axial length, mean arterial blood pressure, and prematurity. Vertical bars represent 95% CIs.
influences microvascular structure by experimental manipulation of in utero growth and birth weight in animal models and the examination of whether this results in structural arteriolar changes.

The present study has several strengths, including its large population-based, random-cluster–selection sample with high response (78%), documented data on birth parameters, and the use of validated techniques to measure arteriolar caliber. As in other observational studies relating the effects of early life exposures to later disease, confounding from unmeasured factors, however, could have influenced our findings. This possibility is less likely given our healthy childhood sample with little burden of adult cardiovascular disease and its risk factors, as well as the statistical adjustment for important confounders such as body mass, blood pressure, and prematurity. Genetic or socioeconomic factors could confound associations of birth weight and arteriolar caliber, although recent data indicate that these potential confounders are unlikely to be important. The measurement of retinal vessel caliber is influenced by ocular and camera factors such as magnification, but these should be common to both arterioles and venules. The lack of association with venular caliber and adjustment for refractive measures (ocular axial length) in the analysis suggest that such factors are unlikely to explain our findings. Finally, although our overall sample size was large, the number of children with low birth weight was substantially smaller. Nonetheless, the microvascular changes we observed spanned the entire continuum of birth weight and

<table>
<thead>
<tr>
<th>Birth weight, g</th>
<th>n</th>
<th>Retinal Arteriolar Caliber</th>
<th>Retinal Venular Caliber</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very low (&lt;2000)</td>
<td>23</td>
<td>156.9 (150.9–162.8)</td>
<td>229.6 (220.5–238.8)</td>
</tr>
<tr>
<td>Low (2000–2499)</td>
<td>60</td>
<td>162.4 (158.3–166.6)</td>
<td>231.3 (228.6–234.1)</td>
</tr>
<tr>
<td>Normal or high (≥2500)</td>
<td>1286</td>
<td>165.6 (163.9–167.2)</td>
<td>232.0 (230.7–233.4)</td>
</tr>
</tbody>
</table>

*Adjusted for age, gender, ethnicity, height, body mass index, axial length, mean arterial blood pressure, and prematurity (except gestational age, which was not adjusted for prematurity). *P* for trend where the variable is modeled continuously.

<table>
<thead>
<tr>
<th>Birth length, cm</th>
<th>n</th>
<th>Retinal Arteriolar Caliber</th>
<th>Retinal Venular Caliber</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st Quartile, &lt;49.3</td>
<td>370</td>
<td>163.5 (161.2–165.8)</td>
<td>231.0 (228.9–233.1)</td>
</tr>
<tr>
<td>2nd Quartile, 49.3 to 51.0</td>
<td>241</td>
<td>165.2 (162.6–167.9)</td>
<td>234.7 (232.1–237.4)</td>
</tr>
<tr>
<td>3rd Quartile, 51.1 to 52.5</td>
<td>322</td>
<td>164.5 (162.0–167.0)</td>
<td>231.6 (228.4–234.7)</td>
</tr>
<tr>
<td>4th Quartile, ≥52.5</td>
<td>305</td>
<td>165.1 (162.3–167.9)</td>
<td>231.3 (229.2–235.3)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Head circumference, cm</th>
<th>n</th>
<th>Retinal Arteriolar Caliber</th>
<th>Retinal Venular Caliber</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st Quartile, &lt;34.0</td>
<td>251</td>
<td>164.0 (161.0–166.9)</td>
<td>232.0 (229.2–234.7)</td>
</tr>
<tr>
<td>2nd Quartile, 34.0 to 34.9</td>
<td>241</td>
<td>164.6 (161.8–167.5)</td>
<td>232.7 (229.7–235.8)</td>
</tr>
<tr>
<td>3rd Quartile, 35.0 to 35.9</td>
<td>241</td>
<td>164.8 (162.0–167.5)</td>
<td>231.6 (228.7–234.5)</td>
</tr>
<tr>
<td>4th Quartile, ≥36.0</td>
<td>279</td>
<td>166.4 (163.6–169.2)</td>
<td>232.2 (228.5–235.8)</td>
</tr>
</tbody>
</table>

| Birth weight, per SD (569 g) decrease | −1.28 (−2.23 to −0.32) | 0.01 | 0.12 (−0.86 to 1.09) | 0.80 |
| Low birth weight (≤2499 g) | −3.73 (−7.09 to −0.38) | 0.03 | −1.24 (−4.62 to 2.14) | 0.46 |
| Birth length, per SD (3.1 cm) decrease | −1.00 (−1.89 to −0.12) | 0.03 | −0.62 (−1.72 to 0.48) | 0.26 |
| Head circumference, per SD (1.8 cm) decrease | −1.24 (−2.09 to −0.38) | 0.006 | −0.05 (−1.09 to 1.00) | 0.93 |

*Adjusted for age, gender, ethnicity, height, axial length, body mass index, mean arterial blood pressure, and prematurity.
showed a linear pattern of association, which further supports the validity of our findings.

In summary, we tested and confirmed the hypothesis that low birth weight and other markers of poorer early growth are related to narrower retinal arteriolar caliber in 6-year-old children. Our results thus suggest a potential mechanism by which poor early life growth may impact adversely on the microcirculation. We speculate that this mechanism may explain, at least in part, an increased susceptibility to the development of hypertension and cardiovascular disease among persons of low and low-normal birth weight.

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Disclosures
None.

References
CLINICAL PERSPECTIVE

Low birth weight and other markers of poor in utero growth are associated with increased risk of adult cardiovascular disease. We hypothesized that a potential mechanism underlying this phenomenon is poor in utero growth that could adversely influence microvascular structure. We tested this hypothesis by examining the relation of birth weight and other markers of in utero growth to retinal microvascular caliber in a population-based study of 1369 children aged 6 years attending 34 schools in Sydney, Australia. Lower birth weight, shorter birth length, and smaller head circumference were all associated with narrower retinal arteriolar caliber. Each kilogram decrease in birth weight was associated with a 2.3-µm (95% CI 0.6 to 3.9, \( P = 0.01 \)) narrower retinal arteriolar caliber after controlling for age, gender, ethnicity, height, body mass index, axial length, mean arterial blood pressure, and prematurity. These data support our study hypothesis, and we thus speculate that the adverse influence of poor in utero growth on microvascular structure may explain in part the documented increased susceptibility to development of hypertension and cardiovascular disease among persons with low and low-normal birth weight. Our results highlight the influences of early life environment on the development of microvascular structural changes. They have potential implications for medical interventions during gestation. Because both low birth weight and retinal arteriolar narrowing are potential subclinical markers of future cardiovascular risk, the presence of both factors may indicate a need for closer monitoring, lifestyle modifications, and other interventions in this subgroup.
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