Impaired Vascular Growth in Late Adolescence After Intrauterine Growth Restriction

J. Brodszki, MD, PhD; T. Länne, MD, PhD; K. Maršál, MD, PhD; D. Ley, MD, PhD

Background—Abnormal blood flow in a fetus small for gestational age indicates true fetal intrauterine growth restriction (IUGR). We tested the hypothesis that IUGR with abnormal fetal blood flow is associated with long-term abnormal vascular morphology and function in adolescence.

Methods and Results—In a prospective study, vascular mechanical properties of the common carotid artery (CCA), abdominal aorta, and popliteal artery (PA) were assessed by echo-tracking sonography in 21 adolescents with IUGR and abnormal fetal aortic blood flow and in 23 adolescents with normal fetal growth and normal fetal aortic blood flow. Endothelium-dependent and -independent vasodilatation of the brachial artery was measured by high-resolution ultrasound. After adjustment for body surface area and sex, the IUGR group had significantly smaller end-diastolic vessel diameters than the referents in the abdominal aorta and PA (mean difference, 1.7 mm [95% CI, 0.62 to 2.74] and 0.6 mm [95% CI, 0.25 to 1.02], respectively) (P=0.003 and P=0.002, respectively), with a similar trend in the CCA (P=0.09). A higher resting heart rate was observed in the IUGR group (P=0.01). No differences were found in stiffness or in endothelium-dependent and -independent vasodilatation between the 2 groups.

Conclusions—IUGR caused by placental insufficiency appears to be associated with impaired vascular growth persisting into young adulthood in both men and women. The smaller aortic dimensions and the higher resting heart rate seen in adolescents with previous IUGR may be of importance for future cardiovascular health. (Circulation. 2005;111:2623-2628.)

Key Words: endothelium • pediatrics • fetal growth retardation • vessels • ultrasonics

Low birth weight has been related to mortality from coronary disease and to development of hypertension and diabetes.1–3 During the past decade, evidence has accumulated strengthening the relationship between prevalence of cardiovascular risk factors, such as high body mass index,4 dyslipidemia,5 and glucose intolerance,6 and birth characteristics. The underlying mechanisms are not fully understood and have been attributed to both unfavorable intrauterine environment7 and exaggerated postnatal growth.8

When influences of intrauterine environment and growth are studied, the definition of intrauterine growth restriction (IUGR) is of utmost importance. The presence of abnormal fetal blood flow in subjects with birth weight small for gestational age identifies true IUGR due to placental dysfunction. Increased placental impedance will reduce fetal aortic end-diastolic flow and may even cause flow reversal, thus compromising the fetal cardiovascular function.9 Chronic changes in fetal hemodynamics may form the substrate for later abnormality.

We tested the hypothesis that IUGR with abnormal fetal blood flow is associated with abnormal vascular morphology and function in adolescence.

Methods
The subjects belonged to 2 cohorts examined prospectively during fetal life over a 3-year period at the Department of Obstetrics and Gynecology in Malmö in 1982 to 1985: one cohort consisted of strictly normal subjects participating in a study on fetal physiology,10 and the other examined subjects because of suspicion of IUGR.11 A total of 149 subjects (85%) from these 2 cohorts were followed up at the age of 7 years.12 From the latter follow-up cohort, all subjects chosen were born at full term with the most severe degree of abnormality of fetal aortic blood flow, ie, with absent or reverse diastolic flow and/or with weight deviation at birth ≥2.5 SD below the mean weight of the normal population. The 21 subjects constituted the study group. The group of referents comprised individuals randomly selected among those who had normal intrauterine blood flow and birth weight appropriate for gestational age at birth.

All subjects were examined serially with ultrasound biometry and Doppler velocimetry of aortic blood flow during the last trimester of pregnancy. The blood flow velocity waveforms of the fetal aorta were transformed into a semiquantitative variable, blood flow class (BFC), according to the degree of reduction of the diastolic component of the waveform. Four BFC were defined: BFC 0 (normal), with positive flow throughout the heart cycle and normal pulsatility index13,14; BFC I, with positive flow throughout the heart cycle and pulsatility index greater than the mean ±2 SD of normal; BFC II, with undetectable end-diastolic velocity; and BFC III, with absence of positive flow throughout the major part of diastole or reverse flow in diastole. Fetal aortic BFC was defined according to the result of

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From the Departments of Obstetrics and Gynecology (J.B., K.M.) and Pediatrics (D.L.), University Hospital of Lund, Lund University, Lund; and Department of Medicine and Care, Linköping University, Linköping (T.L.), Sweden.

Correspondence to Jana Brodszki, MD, Department of Obstetrics and Gynecology, University Hospital of Lund, SE-221 85 Lund, Sweden. E-mail jana.brodszki@gyn.lu.se

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the last Doppler measurement before the delivery. Results from the Doppler velocimetry were not available to the clinicians, ie, they did not influence the clinical management and timing of delivery.

For the present study, 44 adolescents were examined. Operators blinded to the group identity examined the endothelial function and vascular mechanical properties of large arteries on the same day. The subjects were examined during morning hours in a quiet, temperature-controlled room after 12 hours of fasting. Smokers were instructed not to smoke for at least 12 hours before the vascular studies.

**Vascular Mechanical Properties**

Dynamic properties of large arteries were assessed by echo-tracking sonography. This technique provides, in addition to vessel diameters, indirect measures of arterial elastic properties, which are derived from diameter changes of arteries in response to the change in distending pressure. We used an echo-tracking system (Diamove, Teltec AB) capable of detecting vessel wall movements of <10 μm and with a time resolution of 1.15 ms. The echo-tracking instrument measures the instant distance between vessel walls perpendicular to the longitudinal axis of the vessel. Details of the technique and measurement procedure have been described previously. Three consecutive recordings of pulsatile diameter changes were obtained from the abdominal aorta, the common carotid artery (CCA), and the popliteal artery (PA). The abdominal aorta was imaged from the epigastrium, and the measurements were performed ~2 cm under the xiphoid process. The CCA was imaged from behind the sternocleidomastoid muscle, and measurements were performed 2 cm proximal to the bifurcation. Measurements of the PA were performed in the central part of the popliteal fossa.

Arterial blood pressure was measured by auscultation with a sphygmomanometer on the right arm at baseline and after each recording of pulsatile diameter changes.

Stiffness (β) was defined as $\beta = \ln(P_{\text{syst}}/P_{\text{diast}})/(D_{\text{syst}}-D_{\text{diast}})/D_{\text{diast}}$, where $P_{\text{syst}}$ and $P_{\text{diast}}$ are the maximum systolic and diastolic pressures in millimeters of mercury, respectively, and $D_{\text{syst}}$ and $D_{\text{diast}}$ are the corresponding vessel diameters in millimeters. Pulse pressure (ΔP) is the difference between the systolic and diastolic pressures. Stiffness (β) was calculated offline from the diameter curves, and a high value of β denotes a stiffened arterial wall. The coefficients of variation for repeated vessel diameter measurements were 5.7%, 4.1%, and 5.5% for the abdominal aorta, the CCA, and the PA, respectively. The corresponding coefficients of variation for stiffness of the aorta, the CCA, and the PA were 9.8%, 11.5%, and 12.3%, respectively. The variabilities in the blood pressure measurement were 3.3% and 3.5% for the systolic and diastolic blood pressure, respectively.

**Endothelial Function**

Endothelial function was assessed as described by Celermajer et al. Changes in the brachial artery diameter in response to reactive hyperemia were measured with an Acuson apparatus equipped with a 7.0-MHz linear array transducer. The subjects rested for 10 minutes before the ultrasound scanning. The right brachial artery was visualized in a longitudinal section ~5 to 8 cm above the elbow. The transducer was mounted in a stereotaxic clamp to maintain the same position throughout the examination. Flow increase in the brachial artery was achieved by placing a pneumatic cuff on the forearm and inflating to 250 mm Hg for 4 minutes. The artery was scanned continuously from 30 seconds before to 150 seconds after cuff deflation. Images for offline analysis were frozen 4 to 8 seconds after cuff deflation. After administration of nitroglycerine, the brachial artery was scanned for 10 minutes.

Offline, the brachial artery diameter was measured as the distance between the leading edge of the lumen-intima interface of the anterior wall and the leading edge of the lumen-intima interface of the posterior wall. Automated edge detection software was used. Measurements were performed at the end of diastole, coinciding with the R wave of the ECG. Brachial artery diameters were obtained at baseline and at 1 minute after cuff deflation. Similarly, brachial artery diameters before and 4 minutes after nitroglycerine administration were recorded. Flow-mediated dilatation was derived from the brachial artery diameter increase at the respective time interval in relation to the baseline diameter and expressed as a percentage.

The Committee for Research Ethics at Lund University approved the study, and informed consent was obtained from each subject.

**Statistical Analysis**

Normality of the continuous data was assessed by Shapiro-Wilk test. Differences between the IUGR group and the referent group were evaluated with Student t test, Mann-Whitney test, or χ² test, as appropriate. The effect of IUGR on vascular variables was evaluated by linear regression analysis. Adjustment for potential confounders was performed. A significant difference was considered present if $P<0.05$.

**Results**

**Clinical Characteristics**

The median age of both study groups was 18 years (range, 16 to 19 years). There was no significant difference in the sex distribution between the 2 groups ($P=0.78$). Twenty-one of the subjects (11 women and 10 men) were small for gestational age at birth, with a median deviation of weight at birth of ~31% (range, ~42% to ~22%) from the gestational age– and gender-related mean at a mean gestational age of 270 days (Table 1). Two had fetal aortic BFC I, 10 BFC II, and 9 BFC III. The remaining 23 subjects (13 women and 10 men) had a normal aortic BFC and birth weight appropriate for gestational age (median weight deviation, ~2% [range, ~10% to 22%] at a mean gestational age of 278 gestational days) (Table 1). Clinical characteristics at birth are given in Table 1. There were no differences in maternal variables such as maternal age, parity, and maternal pregnancy weight gain (data not shown).

Age, weight, and height at follow-up in the IUGR group and referent group are given in Table 1. There was no significant difference in weight, height, and body surface area of the IUGR group compared with the referent group.

There were no significant differences between the IUGR group and referents in systolic blood pressure, diastolic blood pressure, pulse pressure, and mean arterial pressure either before or after adjustment for height (Table 2). The IUGR group had a significantly higher resting heart rate than referents ($P=0.01$).

Smoking habits in both groups were similar, with 4 smokers in the IUGR group and 5 smokers in the referent group ($P=0.82$). All of the participants were healthy without any significant past medical history. There was 1 parental history of hypertension in the IUGR group.

**Mechanical Properties of Large Arteries**

The IUGR group had significantly smaller end-diastolic vessel diameters in the abdominal aorta and PA ($P=0.001$ and $P=0.002$, respectively) (Table 3). The mean abdominal aorta, CCA, and PA vessel diameters correlated with body surface area and sex (abdominal aorta, $r=0.46$, $P=0.002$ and $r=0.36$, $P=0.02$, respectively; CCA, $r=0.32$, $P=0.04$ and $r=0.38$, $P=0.01$, respectively; PA, $r=0.36$, $P=0.02$ and $r=0.4$, $P=0.007$, respectively). After adjustment for body surface area and sex, subjects in the IUGR group had significantly smaller end-diastolic abdominal aorta and PA...
diameters ($P=0.003$ and $P=0.002$, respectively), with a similar trend in the CCA ($P=0.09$) (Table 3). There were no differences between the 2 groups in stiffness ($\beta$) in the 3 vascular regions. The stiffness of the aorta in the IUGR group was $4.9\pm3.3$ (SD) (range, 2.2 to 16.9) compared with $4.3\pm0.9$ (range, 2.7 to 6.6) in the referent group ($P=0.5$); of the CCA, $4.1\pm1.3$ (SD) (range, 2.2 to 8.2) compared with $4.3\pm1.0$ (SD) (range, 2.5 to 6.7) ($P=0.4$); and of the PA, $10.5\pm9.2$ (range, 3.2 to 43.3) compared with $10.3\pm3.4$ (range, 5.7 to 17.5) ($P=0.1$).

**Endothelial Function**

At 1 minute after cuff deflation, there was no significant difference in flow-mediated dilatation between the IUGR and referent group ($P=0.85$) (Table 4). Nitroglycerine-induced dilatation was similar in both groups ($P=0.46$). Baseline brachial artery diameters were comparable between the 2 groups ($P=0.57$). There were no significant differences between the 2 groups in blood flow at baseline or during hyperemia (Table 4). Flow-mediated dilatation at 1 minute after cuff deflation was not associated with IUGR, baseline vessel diameter, sex, age, smoking, or use of contraceptives. Exclusion of smokers did not significantly affect the results.

**TABLE 2. Blood Pressure in Adolescents With IUGR** and Referents

<table>
<thead>
<tr>
<th></th>
<th>IUGR (n=21)</th>
<th>Referents (n=23)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic BP, mm Hg</td>
<td>$114\pm11$</td>
<td>$111\pm9$</td>
<td>0.59</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>$67\pm7$</td>
<td>$67\pm6$</td>
<td>0.79</td>
</tr>
<tr>
<td>MAP, mm Hg</td>
<td>$83\pm8$</td>
<td>$82\pm7$</td>
<td>0.93</td>
</tr>
<tr>
<td>Pulse pressure, mm Hg</td>
<td>$47\pm7$</td>
<td>$44\pm7$</td>
<td>0.32</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>$71\pm9$</td>
<td>$64\pm7$</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Values are mean±SD. BP indicates blood pressure; MAP, mean arterial pressure.

**Discussion**

The mechanical properties of large arteries are recognized as an important factor influencing cardiac load and blood pressure regulation. Alterations detected in childhood and adolescence are likely to have an impact on cardiovascular health in adult life. In our study the IUGR group showed a decreased diameter of large arteries. There was a strong correlation between the aortic diameter and body habitus. Differences in body size between the 2 groups could have affected the results; however, a substantial decrease in diameter of central elastic arteries (abdominal aorta) and the muscular PA was still present after correction for body surface area and sex.

Obviously, the measuring technique is of importance when the findings are interpreted. The echo-tracking technique measures the luminal interfaces of the B-mode image of the anterior and posterior arterial wall. Theoretically, this means that an increased thickness of the intima and media of the arterial wall might lead to an underestimation of the diameter. The thickness of the intima and media was not evaluated in this investigation, but a significant increase or manifest atherosclerotic narrowing of the lumen in this young cohort of individuals seems improbable. Thus, the finding that individuals exposed to IUGR have smaller vessel diameters in central elastic arteries (abdominal aorta, CCA) and in the muscular PA in proportion to their body size than individuals with normal fetal growth seems plausible. Interestingly, in the brachial artery, which is a muscular artery, the diameter was not affected. Recently, the observation was published that the PA, although a muscular artery, appears to have wall properties and behavior of a central elastic artery. This suggests that normal, age-dependent growth of elastic arteries is more sensitive to effects of restricted fetal growth than is the growth of muscular arteries, which could possibly be mediated by a reduction in the deposition of elastin, as proposed by Martyn and Greenwald.
The cohort of this study is of particular interest because data on fetal aortic blood flow velocity waveforms were available. It has been shown that hemodynamic changes in the fetal descending aorta parallel those in the umbilical artery.\(^25\) In growth-restricted fetuses with abnormal fetal aortic velocity waveforms, reduced blood flow to the peripheral circulation and lower mean blood flow velocities and volume blood flow in the descending aorta are seen.\(^11,26\) It is further known that the volume and pattern of flow through a developing structure influence its growth.\(^27\) Thus, the changes in fetal hemodynamics present in all our studied subjects with IUGR may have formed the substrate for later abnormality. Matrix metalloproteinases, a large family of proteases with crucial importance for angiogenesis and adaptive arterial remodeling,\(^28,29\) have been found to be upregulated and activated in the arterial wall in response to shear stress.\(^30\) Fetal volume blood flow in the IUGR subjects of this study was decreased.\(^31\) Decrease in volume blood flow and subsequent decrease in shear stress might have influenced the matrix metalloproteinase system. Therefore, it would be reasonable to assume a hypotrophic remodeling of the vascular system.

When human fetal vessels were studied in growth-restricted fetuses, smaller descending aortic dimensions and reduced growth velocity of the aorta were observed.\(^31,32\) It was further observed that reduction of somatic growth in IUGR was accompanied by a reduction in the peripheral vascular bed size.\(^31\) However, after correction for estimated fetal weight, the fetal aortic vessel diameters were found to be comparable to those of the normally grown fetuses, thus indicating that the discrepancy between body habitus and vessel size observed in our study may possibly be a phenomenon occurring after birth.

Data on postnatal vascular dimensions in humans who were subjected to growth restriction are limited. Our data confirm the report by Ley et al,\(^33\) who found significantly lower aortic diameters after correction for body surface area in 9-year-old children with IUGR. However, Martin et al\(^34\) did not find any significant differences in the aortic and carotid dimensions of 9-year-old children with low birth weight. In the latter study, almost one third of the study group were not lean at birth. The difference in defining IUGR may account for the discrepant findings of the 2 aforementioned studies. In a separate investigation, the retinal vasculature of our study and referent groups was examined.\(^35\) The finding of a reduced number of retinal branching points in the IUGR group in combination with the results from our study suggests a general impairment of vascular growth.

Beside smaller vascular dimensions in proportion to body size, we found a higher resting heart rate in the IUGR group. An increased heart rate may influence cardiovascular regulation and lead to consequences negative for the cardiovascular system. High resting heart rate has been related to development of coronary atherosclerosis, cardiovascular events, and death.\(^36-38\)

We expected a decreased flow-mediated dilatation of the brachial artery in the IUGR group. However, we could not confirm the finding of impaired endothelial function that has

### TABLE 3. Vascular Data and Effects of IUGR on Vascular Size

<table>
<thead>
<tr>
<th></th>
<th>Referents (n=23)</th>
<th>IUGR (n=21)</th>
<th>Unadjusted</th>
<th>Adjusted†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>B</td>
<td>95% CI</td>
<td>P</td>
<td>B</td>
</tr>
<tr>
<td>Aorta</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diastolic vessel diameter, mm</td>
<td>13.0±1.7</td>
<td>11.2±1.7</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CCA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diastolic vessel diameter, mm</td>
<td>6.5±0.5</td>
<td>6.3±0.6</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>PA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diastolic vessel diameter, mm</td>
<td>6.1±0.6</td>
<td>5.4±0.7</td>
<td>...</td>
<td>...</td>
</tr>
</tbody>
</table>

Values are mean±SD. B indicates mean difference between IUGR and referent groups. *Student t test; †adjusted for body surface area and gender.

### TABLE 4. Brachial Artery Study of Endothelial Function

<table>
<thead>
<tr>
<th></th>
<th>IUGR (n=21)</th>
<th>Referents (n=23)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline vessel diameter, mm</td>
<td>3.1±0.5</td>
<td>3.1±0.5</td>
<td>0.57</td>
</tr>
<tr>
<td>Baseline blood flow, mL/min</td>
<td>108 (27 to 614)</td>
<td>93 (31 to 526)</td>
<td>0.59</td>
</tr>
<tr>
<td>Reactive hyperemia, %</td>
<td>492±277</td>
<td>490±279</td>
<td>0.93</td>
</tr>
<tr>
<td>FMD 1 minute, mm</td>
<td>0.091 (−0.230 to 0.373)</td>
<td>0.065 (−0.038 to 0.239)</td>
<td>0.65</td>
</tr>
<tr>
<td>FMD 1 minute, %</td>
<td>3.3 (−0.8 to 13.1)</td>
<td>2.4 (−1.3 to 8.2)</td>
<td>0.85</td>
</tr>
<tr>
<td>Nitroglycerine-induced dilatation, %</td>
<td>14.6±6.5</td>
<td>15.8±6.1</td>
<td>0.46</td>
</tr>
</tbody>
</table>

Values are mean±SD or median (range). FMD indicates flow-mediated vasodilatation. *Mann-Whitney test.
been reported in children and young adults of low birth weight.34,39–41 Our findings are similar to those of McAllister et al.,42 who did not find any difference in endothelium-dependent and -independent vasodilatation in young healthy adults with either low or normal birth weight at term. Endothelial function was assessed with the use of a well-established method and following the guidelines for the ultrasound assessment of endothelium-dependent flow-mediated vasodilatation of the brachial artery.43 All referents were healthy and without any drug therapy, and exclusion of smokers did not affect the results. However, because of the limited size of the groups, type II error cannot be excluded. Despite the fact that we did not find a reduced flow-mediated dilatation of the brachial artery in the IUGR group, the wide response range of flow-mediated dilatation in the IUGR might suggest an alteration of vascular function. In response to reactive hyperemia, some individuals of the IUGR group responded with a 0.23-mm vessel diameter reduction, whereas others responded with a maximal dilatation of 0.37 mm.

Certain limitations in the present study should be recognized. As mentioned above, the small sample size in our study limits the possibility of detecting moderate effects. However, the sample size could not be enlarged because all individuals available with the most severe degree of IUGR and abnormality of fetal blood flow were chosen from the original cohort, which, to date, is the largest long-term follow-up cohort on IUGR. Multiple comparisons may raise the possibility of a type I error. However, hypertrophic vascular remodeling, ie, changes in fetal blood flow forming the substrate for vascular abnormality later in life, would seem plausible as an explanation of the present findings. This is the first study examining the relationships between growth in utero and vascular variables later in postnatal life in which data on fetal hemodynamics were available. Our findings indicate that IUGR with abnormalities in fetal blood flow were chosen from the original cohort, which, to date, is the largest long-term follow-up cohort on IUGR. Multiple comparisons may raise the possibility of a type I error. However, hypertrophic vascular remodeling, ie, changes in fetal blood flow forming the substrate for vascular abnormality later in life, would seem plausible as an explanation of the present findings.

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Acknowledgments

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References


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