Fetal Growth Restriction in Preterm Infants and Cardiovascular Function at Five Years of Age

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Objectives We have previously reported an increased cardiac workload in newborn preterm small (SGA) infants, but not in infants appropriate for gestational age (AGA). We hypothesized that these cardiovascular changes will persist at follow-up at 5 years of age.

Study design We assessed blood pressure, echocardiography, and skin perfusion with laser Doppler flowmetry in 22 SGA (821 ± 248 g, 28.5 ± 2.5 gestational weeks) and in 25 AGA (1065 ± 241 g, 27.6 ± 0.8 weeks) preterm children at age 5 years. Laser Doppler flowmetry also was used in 13 control children (3982 ± 425 g, 40.4 ± 1.8 weeks).

Results The preterm children in both the SGA and AGA groups had similar higher systolic blood pressures, increased interventricular septum thicknesses, and smaller left ventricular end-diastolic diameters compared with population reference values. Maximal endothelium-independent perfusion to sodium nitroprusside was higher and maximal endothelium-dependent perfusion to acetylcholine reached a plateau earlier in the AGA preterm group than in the control group.

Conclusions Prematurity may impair cardiovascular function independently of intrauterine growth restriction. Altered cardiac dimensions and differences in perfusion responses may reflect increased cardiac afterload. *(J Pediatr 2007;151:494-9)*

Being small size at birth, especially when combined with accelerated weight gain in childhood, is associated with an increased risk for cardiovascular morbidity.[1,2] Further, low gestational age is associated with increased systolic blood pressure (BP) in early adulthood,[3] and low birth weight with impaired endothelial function.[4] Endothelial function is modulated by vasoactive substances, but the endothelium also regulates vascular tone, permeability, cellular transmigration, smooth muscle cell proliferation, and platelet aggregation.[5] Endothelial dysfunction in childhood leads to cardiovascular diseases,[6,7] but the pathophysiological mechanisms remain unidentified. Whether intrauterine growth restriction in prematurely born children causes an increased risk for cardiovascular morbidity is unknown.

In this prospective cohort study of small (SGA) and appropriate for gestational age (AGA) very low birth weight (<1500 g) preterm infants, SGA infants had cardiac hypertrophy and elevated initial left ventricular output during the first week of life as signs of increased cardiac workload and compromised capacity for hemodynamic adaptation.[8] Similarly, increased aortic wall thickness, suggesting an increased intrauterine cardiac workload, has been reported in full-term growth-restricted infants at birth.[9] We hypothesized that SGA children with increased cardiac workload perinatally would show persisting workload and signs of endothelial dysfunction at age 5 years. Furthermore, we studied the relationship of perinatal risk factors and postnatal growth to cardiovascular and endothelial function.

We assessed the macrocirculation with echocardiography and BP, and cutaneous microvascular blood flux with non-invasive laser Doppler flowmetry (LDF). In LDF, the reflection of Doppler shift in the illuminated area of the superficial microcirculation is proportionate to the number of blood cells and their perfusion velocity expressed as arbitrary perfusion units (PU).[10] LDF combined with iontophoresis can be used to assess the skin perfusion response to a charged drug delivered locally through the skin by a direct low-intensity electric current.[11] Cholinergic endothelium-dependent skin perfusion has been assessed with acetylcholine (ACh), which induces endothelial vasoactive production, and endothelium-independent perfusion with sodiumnitroprusside (SNP), a nitric oxide donor

ACh	Acetylcholine	LDF	Laser Doppler flowmetry
AGA	Appropriate for gestational age	PU	Perfusion units
AUC	Area under the curve	SGA	Small for gestational age
BP	Blood pressure	SNP	Sodium nitroprusside
IVS	Interventricular septum		

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Table I. Perinatal characteristics of preterm small and appropriate for gestational age and term-born control children

	SGA (n = 22)	AGA (n = 25)	Control (n = 13)
Maternal gestational diabetes mellitus, n (%)	3 (14)	4 (16)	1 (8)
Maternal smoking during pregnancy, n (%)	1 (5)	4 (16)	0
Antenatal steroids, n (%)	17 (78)	18 (72)	0
Pre-eclampsia, n (%)	11 (50)	2 (8)*	0
Vaginal delivery, n (%)	3 (14)†	13 (52)	11 (85)
Gestational age, weeks	28.5 ± 2.5	27.6 ± 0.8	40.4 ± 1.8
Birth weight, g	821 ± 248	1065 ± 241*	3982 ± 425
Male gender, n (%)	15 (68)	15 (60)	6 (46)
Oxygen dependency at 36 gestational weeks, n (%)	12 (55)	13 (52)	0
Postnatal dexamethasone, n (%)	7 (32)	6 (24)	0

*$P \leq .001$, SGA group versus AGA group.
†$P < .05$, SGA group versus AGA group or control group.

causing smooth muscle relaxation.[11] LDF responses to drug provocations on the same recording site are reproducible.[12] ACh-induced perfusion change in LDF correlates with the brachial artery flow-mediated vasodilation,[13] a method to study shear-stress-induced endothelium-mediated vasodilation.

METHODS

Subjects

In a regional tertiary neonatal intensive care unit, Hospital for Children and Adolescents of Helsinki University Hospital, very low birth weight SGA and AGA infants were enrolled from 1998 to 2000.[8] Gestational age was determined with ultrasound scanning examinations before the end of 20 weeks of gestation. A birth weight SD score ≤ -2 SD[14] was used as SGA criterion, reflecting growth restriction during the latter half of pregnancy. Extensive echocardiography was performed repeatedly by 1 cardiologist (T.B.) in 61 infants during the 2 first weeks of life,[9] and 9 infants underwent routine echocardiography.

Of the 70 preterm children at 5 years, 45 of their parents (64%) consented to echocardiography and LDF, and 2 parents (3%) consented to LDF only. Of 25 full-term infants born at the same time in the same hospital recruited as a control group, 13 families (52%) gave their consent to LDF assessment. The perinatal characteristics of the children are shown in Table I. The mean birth weight SD of the children in the SGA group (N = 22) was −2.2 (range, −5.1-−2.0) and that of the children in the AGA group (N = 25) was −0.3 (range, −1.4-1.0). In the preterm children, pre-eclampsia was associated with lower birth weight SD ($P = .002$). The study was approved by the Ethics Committee for Pediatrics, Adolescent Medicine, and Psychiatry, Hospital District of Helsinki and Uusimaa.

Echocardiography and Blood Pressure

Echocardiography (Acuson Sequoia C 512, tranducers 4 and 5 MHz, Acuson, US, Mountain View, CA) was performed by 1 cardiologist (T.B.) with a within-observer variability of 5.8%. The left and right ventricular dimensions, thickness and motion of the ventricular walls, left ventricular ejection fraction, and fractional shortening were measured. The dimensions were adjusted to body surface area.[16] The internal diameter of the aortic annulus and the flow velocity integral of the ascending aorta were measured for the calculation of left ventricular output. The same pediatric cardiologist (T.B.) performed all echocardiographic measurements with a within-observer variability of 5.8%. BP was measured after echocardiography (20-minute rest) from the right upper arm with a Dinamap Critikon (model 1846SX/P, Critikon Inc., Tampa, FL) in a recumbent position. Healthy control subjects were not recruited for echocardiography and BP measurements, because well-described age-adjusted normal values were calculated with published data.[15,16]

Laser Doppler Flowmetry

The LDF recordings were performed at a temperature of 22° to 23°C. The child was sitting with 1 arm at a time immobilized with pillows listening to a fairy tale. The right forearm was used for physiological provocations, thereafter the left for acetylcholine (ACh, Sigma-Aldrich Ab, Stockholm, Sweden), and finally the right forearm for sodium nitroprusside (SNP, Sigma-Aldrich Ab) provocations. After cleaning with 70% alcohol, skin perfusion was measured on the proximal volar side of the forearm where no large veins were seen. The illuminated skin area was 1 mm^2, the probe temperature was 32°C, and a single spot laser-Doppler ultrasound scanner with a wavelength of 780 nm was used (Periflux 5000 Perimed AB, Järfälla, Sweden). The same investigator (K.M.) performed all LDF recordings with coefficient of variation of 17% for basal perfusion on different forearm sites and 20% for the maximal ACh and SNP perfusion.

After a baseline measurement at 32°C for 2 minutes (probe PF 457, Perimed AB), arterial occlusion was applied for 2 minutes, inducing a suprasystolic pressure with a pneumatic cuff. The peak perfusion during the post-occlusive hyperemia, the time-to-peak after cuff release, and the relative perfusion change during the reactive hyperemia (percentage of the peak-baseline difference in relation to baseline) were measured. After the original baseline perfusion was achieved, the perfusion change to local warming from 32° to 44°C was assessed.

Iontophoretical transdermal drug provocations were performed at 32°C with 2% ACh, using anodal current of 0.1 mA for 20 seconds 6 times at 40-second intervals (drug delivery probe PF 481, drug delivery electrode PF 383, dispersive electrode PF 384, Perimed AB). Endothelium-inde-

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