Cardiac Function and Arterial Biophysical Properties in Small for Gestational Age Infants: Postnatal Manifestations of Fetal Programming

Arvind Sehgal, FRACP[1,2], Tejas Doctor, MD[1], and Samuel Menahem, FCSANZ[2,3]

Objective To investigate the differences in cardiac function and arterial biophysical properties between term-born appropriate for gestational age (AGA) infants and small for gestational age (SGA) infants. Our hypothesis was that adaptation to intrauterine growth restriction induces changes in cardiac and arterial indices.

Study design This was a prospective observational echocardiographic evaluation of cardiac and arterial indices in SGA infants and AGA infants. Demographic and echocardiographic data were compared between 20 inborn term SGA infants with birth weight <3rd percentile for gestational age and 20 AGA infants.

Results The Ponderal index was significantly lower and blood pressure was significantly higher in the SGA infants compared with the AGA infants. Left ventricular output was lower in the SGA infants (170 ± 31 mL/kg/min vs 197 ± 39 mL/kg/min). Diastolic dysfunction was greater in the SGA infants (ie, reduced E and A wave velocities, higher E/A ratio [1.08 ± 0.16 vs 0.85 ± 0.07], and prolonged isovolumic relaxation time [73 ± 6.2 ms vs 62.6 ± 3.6 ms]). Aortic intima-media thickness was significantly greater in the SGA infants (822 ± 105 μm vs 694 ± 52 μm), as were arterial wall stiffness index and input impedance.

Conclusion Cardiac function and arterial biophysical properties were altered in the SGA infants. The findings complement the information on the association between in utero growth and cardiovascular morbidity in later life. *(J Pediatr 2013;163:1296-1300)*.

Intrauterine growth restriction (IUGR) is associated with a higher incidence of perinatal complications and long-term morbidity, and complicates approximately 5%-10% of all pregnancies.[1] The circulatory adaptation to altered nutrient and oxygen delivery results in preferential perfusion to fetal vital organs (ie, brain, heart) as a consequence of selective modulation of vascular resistance. On fetal ultrasound, alterations of fetal cardiac indices (systolic and diastolic functions) and coronary perfusion are almost preterminal manifestations.[2] Growth-restricted fetuses with normal umbilical Doppler measurements also exhibit features of myocardial dysfunction.[3] There is biochemical evidence of subclinical myocardial injury in the form of increased atrial natriuretic peptide and cardiac troponin levels in umbilical cord blood.[4,5] Functional and biochemical cardiac damage and abnormalities in coronary blood flow may suggest pathways leading to cardiovascular morbidities in childhood and adulthood.

Arterial stiffness and distensibility may provide indices of early vascular changes that predispose to the development of further vascular disease. Increased carotid and aortic intima-media thickness (aIMT) have been reported in infants, children, and young adults born small for gestational age (SGA).[6-8] Various echocardiographic measures of biophysical properties (eg, stiffness index, distensibility, compliance) have emerged as important predictors of coronary artery disease and cerebrovascular accident in adults.[9-12] Compromised in utero growth may possibly induce primary vascular remodeling, which might explain the increased predisposition to cardiovascular disease in adult life.

Data on the impact of compromised in utero growth on cardiac function and vascular indices during the postnatal period are extremely limited. Altin et al[13] reported impaired systolic function (reduced stroke volume and left ventricular output [LVO]) and diastolic function (elevated E/A wave ratio) in term infants with mild growth restriction. In the present study, we examined the hypothesis that, in term neonates, adaptation to IUGR induces changes in both cardiac and arterial indices. We evaluated the association between IUGR and echocardiographic functional measurements in the early postnatal period. We aimed to investigate the differences in cardiac function and arterial biophysical properties between term-born appropriate for gestational age (AGA) and SGA infants.

AGA	Appropriate for gestational age
aIMT	Aortic intima-media thickness
BP	Blood pressure
EDT	E wave deceleration time
IUGR	Intrauterine growth restriction
IVRT	Isovolumic relaxation time
LA:Ao	Left atrial:aortic root ratio
LVO	Left ventricular output
PWD	Pulsed wave Doppler
SGA	Small for gestational age
VTI	Velocity time integral

From the [1]Monash Newborn, Monash Children's Hospital; [2]Department of Pediatrics, Monash University; and [3]MonashHeart, Southern Health, Melbourne, Australia

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Methods

Twenty inborn term asymptomatic infants with birth weight <3rd percentile for gestational age (according to local percentile charts[14]) were recruited as cases. These infants were compared with 20 term-born AGA infants. Infants with congenital malformations, chromosomal abnormalities, signs of intrauterine infection, or born to mothers with diabetes, hypertension, or hypercholesterolemia were excluded. None of the SGA infants had abnormal fetal Doppler velocimetry values. Doppler studies of the middle cerebral arteries were performed to assess for cerebral blood flow redistribution. The median gestational age at the latest assessment was 28 weeks (range, 24-38 weeks).

At our institution, a list of deliveries over the past 24 hours is generated daily. The SGA infants were identified from this list. The next AGA infant on the list after an SGA infant was approached to participate in the study. Infants were in the postnatal ward and, in accordance with institutional practice, were discharged with their mothers after 2 days for vaginal deliveries and ~5 days for cesarean deliveries. Gestational age was calculated based on first trimester ultrasound examinations. The study was approved by our Institutional Research Ethics Board, and informed parental consent was obtained for all infants.

Baseline neonatal characteristics, including weight, length, ponderal index, sex, Apgar scores, and mode of delivery, were recorded. The Ponderal index was calculated by 2 methods: (1) weight (kg)/(length [m])^3 and (2) Rohrer ponderal index: 100 × weight (g)/(length [cm])^3. The latter was plotted on percentile charts published by Lubchenco et al.[15] Noninvasive blood pressure (BP) measurements were obtained using an appropriate-sized cuff on the right arm with the infant in a quiet state and positioned supine on a cot at the level of the sphygmomanometer (model M3046A; Philips, Boeblingen, Germany). The average values of 2 readings were recorded.

Two-dimensional echocardiography was performed at day 2-5 of postnatal life, to allow for ductal closure and the establishment of a stable transition from fetal to extrauterine physiology. All echocardiography recordings were performed by a single operator (A.S.) using the Vivid 7 Advantage cardiovascular ultrasound system (GE Medical Systems, Milwaukee, Wisconsin) with 7.5- and 10-MHz high-frequency probes. Data on flow velocity, velocity time integral (VTI), and arterial indices were analyzed.

Systolic Ventricular Performance

LVO was measured from an apical 5-chamber view.[16] Right ventricular output was calculated by applying pulsed wave Doppler (PWD) to the pulmonary artery from an oblique long-axis approach to obtain the flow waveform and trace the pulmonary artery VTI. Ventricular output was calculated as follows: [(VTI) × (heart rate) × (cross-sectional area)] indexed to body weight. The pulmonary artery cross-sectional area was measured from the high left parasternal window, and the aortic cross-sectional area was measured from the left atrial/aortic root ratio (LA:Ao) images. Left atrial and aortic root dimensions were measured in a continuous sweep from the left ventricle to the aortic root at a position where the aortic valve cusps were well visualized.[17] This measurement served as a marker of chamber dilatation. Left ventricle dimensions for fractional shortening were measured using M mode from a parasternal long-axis view at the level just distal to the mitral valve leaflet tips at end-diastole.

Diastolic Performance

Left ventricular diastolic performance was evaluated from PWD interrogation of transmitral flow. Specifically, the peak velocities of the early passive wave (E wave) and the late active wave (A wave) were measured to calculate the E/A ratio. E wave deceleration time (EDT) was measured from the maximum E point to the baseline. Isovolumic relaxation time (IVRT) was measured from the end of the aortic wave to the beginning of the mitral E wave. Diastolic dysfunction was characterized by reduced E and A wave velocities, increased E/A ratio, and prolonged EDT and IVRT. Tissue Doppler measurements were not performed. All PWD measurements were calculated from the average of 3 consecutive cardiac cycles.

Arterial Indices

The aIMT was measured in a straight, nonbranched 1-cm longitudinal segment of the abdominal aorta using high-resolution ultrasound as described previously.[6,18] The image was focused on the dorsal arterial wall, and gain settings and high-resolution boxes were used to optimize image quality. The aIMT was measured at end-diastole using ultrasound calipers. Arterial wall stiffness index (β index) was calculated using the following formula: ln (systolic BP/diastolic BP)/[(AAOs − AAOd)/AAOd], where AAOs and AAOd are internal aortic dimensions in systole and diastole, respectively. Input impedance (Zi; dynes·s/cm^5) was calculated by the following formula: pulse pressure/peak flow (1 mm Hg = 1333 dynes/cm^2), where pulse pressure is systolic BP − diastolic BP and peak flow is maximal aortic velocity × aortic valve annulus cross-sectional area. Arterial pressure-strain elastic modulus (Ep; mm Hg) was calculated as (systolic BP − diastolic BP)/[(AAOs − AAOd)/AAOd].[19] Systemic vascular resistance (dynes/s/cm^5) was calculated as follows: (mean BP − right atrial pressure)/LVO, with an estimated right atrial pressure value of 5 mm Hg.[20] The measurements for aMIT were made offline by 2 observers (A.S. and T.D.) independently. The maximum of 3 measurements for each observer were recorded, and the average of the 2 observers' values was used.

Statistical Analyses

Because this was a hypothesis-generating study providing preliminary data, a sample size of convenience was chosen. Descriptive statistics were used to characterize baseline clinical and echocardiography characteristics. Parametric and nonparametric data were analyzed using SPSS version 18 (IBM, Armonk, New York) and are presented as