Coronary Flow in Neonates with Impaired Intrauterine Growth

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Background: Subclinical myocardial injury has been reported in newborns with fetal weights < 2 SDs for gestational age. Intrauterine growth restriction might affect cardiac function and coronary flow (CF).

Methods: Seventeen newborns with intrauterine growth restriction and 15 age-matched healthy controls were enrolled in the study. Blood flow in the umbilical artery and maternal uterine artery was assessed using Doppler velocimetry. Cardiac function and left anterior descending coronary artery CF were measured using transthoracic Doppler echocardiography at 1 week of age.

Results: The mean growth deviation of the newborns from normal was −2.5 ± 0.2 SDs. Percentage left ventricular shortening fraction was 39 ± 4.3% in patients and 42 ± 4.1% in controls (P = .40), and the mean left ventricular mass index was 86.6 g/m^2 in patients and 73.7 g/m^2 in controls (P < .01). The mean left anterior descending coronary artery diameter was 0.99 ± 0.1 mm in patients and 0.8 ± 0.1 mm in controls (P = .002). The left anterior descending coronary artery flow velocity-time integral was correlated with left ventricular mass index (r = 0.31, P = .007) and with mitral peak E/A ratio (r = 0.74, P = .01). Intrauterine growth restriction was associated with increased peak flow velocity in diastole (34.5 ± 4 vs 19 ± 6 cm/sec in controls, P = .0001), as well as increased CF (37 ± 7.3 vs 8.2 ± 3.0 mL/min in controls, P = .001).

Conclusions: CF is significantly increased in neonates with impaired intrauterine growth. Left ventricular mass index is increased, but systolic and diastolic function remains normal. The clinical significance of increased CF is unclear, but it might lead to decreased CF reserve. (J Am Soc Echocardiogr 2012;25:313-8.)

Keywords: Intrauterine growth restriction, Neonates, Coronary flow, Transthoracic Doppler echocardiography

Impaired intrauterine growth (i.e., intrauterine growth restriction [IUGR]) is defined as weight deviation of >2 SDs below the mean for gestational age.[1] Recent data suggest that newborns with IUGR have increased risk for the development of adult premature cardiovascular disease, syndrome X, hypertension, and type 2 diabetes mellitus.[2,3] Low–birth weight babies have an increased risk for cardiovascular diseases later in life.[4] It has been reported that cardiac troponin I, a marker of myocardial damage, is elevated in growth-restricted babies.[3] Neonatal cardiac damage and abnormal coronary flow parameters may be mechanistic links to the increased rate of coronary artery disease later in life.[5]

There are different clinical causes that may lead to an increase in coronary flow, such as anemia and ductus arteriosus constriction.[6] It has been reported that coronary blood flow in fetuses with IUGR is increased predominantly during diastole compared with systole.[6] Rizzo *et al.*[7] reported that a poor fetal and neonatal outcomes can be predicted by visualization of coronary flow and reverse flow in the ductus venosus in fetuses with IUGR. In general, evaluation of coronary blood flow dynamics provides information on myocardial oxygen delivery and cardiac performance in various clinical conditions.[5]

Experiments in fetal lambs showed that intrauterine hypoxemia for 5 to 8 days led to increased coronary flow.[8] Increased coronary blood flow in human fetuses in patients with uteroplacental insufficiency identifies those at high risk for intrauterine death.[6,9] In our experimental fetal lamb model, acute asphyxia was found to cause a rapid increase in coronary blood flow; not until after a few minutes, when the fetal lamb was on the verge of cardiac arrest, did coronary flow decrease to preasphyxia values.[10] Cerebral flow does not have the early flow augmentation, and it is related only to systolic blood pressure.

The effects of impaired intrauterine growth on cardiac performance and coronary circulation have been incompletely investigated. The aim of this study was to investigate coronary flow parameters and their relationship with cardiac function in neonates with impaired intrauterine growth.

METHODS

Study Subjects

The inclusion criterion was intrauterine growth impairment > −2 SDs from the gestational age–related normal fetal weight. The exclusion criteria were clinical signs of infection or inflammation, significant congenital anomalies, and gestational age < 30 weeks.

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Abbreviations

BFC = Blood flow class

CI = Confidence interval

IUGR = Intrauterine growth restriction

LAD = Left anterior descending coronary artery

LV = Left ventricular

LVM = Left ventricular mass

LVMI = Left ventricular mass index

PFVd = diastolic Peak flow velocity

PI = Pulsatility index

VTI = Velocity-time integral

VTId = diastolic Velocity-time integral

VTIs = systolic Velocity-time integral

A total of 17 neonates with impaired intrauterine growth were studied. Their diagnoses were based on ultrasound examinations performed at a median gestational age of 37 weeks (range, 32–39 weeks). Gestational age–matched (±2 weeks) and age-matched healthy newborns adequate for gestational age ($n = 15$) were used as controls. The neonates were discharged home on day 2 or 3 after birth as per the neonatal unit protocol. Transthoracic Doppler echocardiography was done at 1 week of age for patients and controls, when the ductus arteriosus was spontaneously closed in all.

Written informed consent was obtained from the parents of infants enrolled in the study. The study protocol conformed to the principles outlined in the Declaration of Helsinki.[11] The Lund University ethics committee for human research approved the study, including coronary flow reserve testing with adenosine.

Fetal Doppler Velocimetry and Fetometry

Doppler blood flow registrations were done on a Philips HDI 5000 system with a 5-MHz to 2-MHz transducer (Philips Medical Systems, Bothell, WA). Flow velocity waveforms were recorded in a free-floating midportion of the umbilical artery. Blood flow velocities were obtained from both maternal uterine arteries just above their crossings with the iliac arteries. The Doppler examinations were done transabdominally with the fetus in a quiet state. The angle of insonation was optimized to be as low as possible, never exceeding 45°. The Doppler spectrum was recorded during maternal voluntary apnea. In none of the women were there any discernible uterine contractions. The pulsatility index (PI) of the flow waveforms was calculated according to Gosling *et al.*[12] The ultrasound equipment on the Doppler spectrum recorded from the umbilical artery and maternal uterine arteries calculated PI automatically.

Semiquantitative classification of umbilical artery flow waveform was done as follows: normal blood flow class (BFC), a PI < +2 SDs from the gestational age–related normal PI value; BFC 1, a PI > +2 SDs but <3 SDs from the gestational age–related normal PI; and BFC 2, a PI > +3 SDs from the gestational age–related normal PI. No fetuses with absent or reversed end-diastolic flow (BFC 3) were detected.[13] The maternal uterine artery flow velocity waveforms were considered abnormal if the PI was >1.2 and/or a diastolic notch of the waveforms was present.[14]

For fetal weight determination, the biparietal diameter, mean abdominal diameter, and femur length were measured; the values were used according to the formula of Persson and Weldner.[15] The Swedish standard intrauterine growth curve was used when calculating the birth weight deviation in relation to gestational age–related birth weight.[16]

Standard Transthoracic Doppler Echocardiography

Echocardiographic examinations were done using a Sequoia C512 (Siemens Medical Solutions USA, Inc., Mountain View, CA) with a pulsed-wave Doppler frequency of 7/10 MHz. Standard M-mode and B-mode and Doppler echocardiographic studies were performed to determine the anatomy and function of the heart. Echocardiography was done at 1 week of age, when the ductus arteriosus was spontaneously closed.

The diameter of the aortic ring was measured in a long-axis view using M-mode imaging. Left ventricular (LV) mass (LVM) was calculated from M-mode images as recommended by the American Society of Echocardiography[17]: LVM (g) = 0.8[1.04(diastolic LV internal diameter + diastolic LV septal thickness + diastolic LV posterior wall thickness)^3 − (diastolic LV internal diameter)^3] + 0.6.

LV fractional shortening was computed according to the standard formula.[18] The flow velocity measurements across the aortic valve were averaged over three consequent cardiac cycles. The analysis package of the ultrasound unit was used for manual tracing of the spectral envelope. The velocity-time integral (VTI) was calculated by multiplying the sum of systolic VTI (VTIs) and diastolic VTI (VTId) by heart rate. Aortic root diameter was measured from the longitudinal-axis view on M-mode echocardiography. Cardiac output was calculated as VTIs + VTId × heart rate × π[(aortic root diameter)/2]^2.

Coronary Flow Measurements

After identifying the coronary arteries in a short-axis view of the aortic valve on two-dimensional echocardiography, the left anterior descending coronary artery (LAD) diameter at end-diastole was measured. The calipers were applied to the endothelial borders about 3 mm distal to the bifurcation of left coronary artery. The pulsed-wave Doppler sample volume was placed on the same area and LAD flow velocity registered. The sample volume that gave the best possible quality envelope and pure sound throughout the cardiac cycle was chosen. The velocity scale was decreased to the minimum range and gradually increased until color signals were optimized within the vessel lumen. The color gain was adjusted to provide optimal images. The sample volume was set at 0.5 to 1.0 mm in both depth and width. Measurements were corrected for the angle between the Doppler beam and the direction of coronary flow. The mean angle was 33 ± 8° for the LAD flow measurements. True velocity was defined as the measured velocity divided by the cosine of the angle between the Doppler beam and the direction of the blood flow. Phasic coronary flow was investigated by measuring diastolic peak flow velocity (PFVd), systolic peak flow velocity, VTId, and VTIs. Coronary blood flow was calculated as follows: blood flow (mL/min) = VTIs + VTId × heart rate × π[(coronary diameter)/2]^2.

The protocol for flow measurements is described in more detail elsewhere.[19,20] In brief, the following adjustments were made in the ultrasound machine: space-time was put at a high frame rate (T1) and wall filter at two-thirds (F2), color gain was accustomed to minimize color flow signal scatter (gate 3), and color Doppler mix was on. Pulsed Doppler of 4.5 MHz, a sweep rate of 100 mm/sec, and a velocity range of 15 to 60 cm/sec were used. Measurements were corrected for the angle between the Doppler beam and the coronary flow direction. True velocity was defined as the measured velocity divided by the cosine of the angle between the Doppler beam and the direction of blood. All studies were saved on magneto-optical disks and analyzed later in single-frame-advance mode.

Statistical analyses were performed using StatView version 5.0 (SAS Institute Inc., Cary, NC). The measured variables were analyzed by means of descriptive statistical analyses. P values < .05 were considered statistically significant. Results are presented as mean ± SD and coefficients of variation. Student's t test was used to compare continuous variables. Simple regression analysis was used to test the