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Relationship between fetal cardiac and extra-cardiac Doppler flow velocity waveforms and neonatal outcome in intrauterine growth retardation

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Summary

In a total of 42 consecutive pregnancies with intrauterine growth retardation (IUGR), Doppler velocimetry was related to neonatal outcome as determined by Apgar score at 1 min, umbilical artery acid-base status and Po_2, number of nucleated red blood cells (NRBC), duration of ventilatory support, and sonographic appearance of cerebral leukomalacia. Doppler flow velocity waveforms were obtained from the ascending aorta (AO), pulmonary artery (PA), internal carotid artery (ICA) and umbilical artery (UA) at 2–3 day intervals until delivery. At cardiac level the peak systolic velocity (PSV) and time-averaged velocity (AV), and at peripheral level the pulsatility index (PI) was determined. As all Doppler parameters were significantly related to gestational age at birth, gestational age was taken into account in the analysis. There was no relationship between Apgar score, acid-base status and Doppler parameters. Low AVAO was related to a low umbilical artery Po_2. Significant correlations were established between PSVPA, AVPA and PIUA, and the duration of neonatal ventilatory support. Infants who died within 22 days after admission to the neonatal intensive care unit (n = 7) displayed a significantly higher PIUA than those who remained alive. The PIUA was also related to the absolute and relative number of NRBCs. No relationship existed between the Doppler parameters and degree of leukomalacia. The present study demonstrates that from all Doppler parameters, the PIUA is most clearly related to neonatal outcome in IUGR.

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Introduction

Doppler flow velocity waveforms from the umbilical artery and fetal descending aorta have been related to adverse outcome, as determined by Apgar scores, umbilical cord acid-base status and admission rate to the neonatal intensive care unit [1–5]. Perinatal asphyxia is likely to predispose infants to cerebral injury such as periventricular haemorrhage (PVH) and periventricular leukomalacia (PVL) [6]. Increased nucleated red blood cell (NRBC) counts have also been related to asphyxia. A cordocentesis study by Soothill et al. [7] suggested a relationship between chronic hypoxia and elevated NRBC counts in intrauterine growth retardation (IUGR). A similar relationship between elevated NRCB counts and growth retardation was established in the neonate [8].

Cardiac flow velocity waveforms have demonstrated reduced peak systolic velocities at outflow tract level in IUGR [9]. No information is available on the significance of these cardiac flow velocities in the prediction of neonatal outcome.

In the present study, therefore, attention was focused on the relationship between both fetal cardiac and peripheral arterial blood flow velocity waveforms and neonatal outcome as determined by: (i) Apgar score at 1 min, umbilical artery acid-base status and oxygen tension, (ii) admission rate to the neonatal intensive care unit and requirement of positive pressure ventilatory support, (iii) nucleated red blood cell counts and (iv) sonographic appearance and degree of periventricular leucomalacia in the neonatal period.

Materials and Methods

Out of 43 consecutive women with IUGR, 42 consented to participate in the study. IUGR was defined as a fundal growth delay of more than two weeks and a deviation of the sonographic fetal upper abdominal circumference to beneath the 10th percentile of the reference curve [10]. Pregnancy duration was determined from the last menstrual period and confirmed by ultrasonic measurements of the biparietal diameter at 14–20 weeks gestation. The study protocol was approved by the Hospital Ethics Committee. Gestational age at the entry into the study ranged from 26 to 35 weeks of gestation (median, 31).

Doppler flow measurements were performed by one observer (I.A.L.G) at 2–3 day intervals until delivery. The last Doppler measurement before delivery was related to neonatal outcome. Doppler data were blinded to the obstetric staff. A combined mechanical sector and pulsed/continuous Doppler system (Diasonics CV 400) with a carrier frequency of 3.5 and 3.0 MHz was used. The sector scanner operates at power outputs of less than 100 mW/cm^2 spatial peak-temporal average in both imaging and Doppler modes by manufacturer's specifications. In each instance, the correct position of the pulsed Doppler gate was ensured by two-dimensional ultrasound both before and after each Doppler tracing was obtained. Maximum flow velocity waveforms were recorded at both cardiac and peripheral level. At cardiac level, Doppler recordings were produced from the fetal ascending aorta (AO) and pulmonary artery (PA). Flow velocity waveforms from the fetal ascending aorta were obtained from the five-chamber view [11]. Fetal pulmonary artery flow velocity waveforms were recorded from the conventional echocardiographic short axis view [11]. The Doppler sample volume was placed in the great vessels immediately distal to the semilunar valves. The angle between the Doppler cursor and the assumed direction of flow was always 10° or less. Sample volume length was between 0.2 and 0.4 cm. Peak systolic velocity (PSV, cm/s), and time-averaged velocity (AV, cm/s) were calculated.

Peripheral arterial Doppler studies were focused on the fetal umbilical artery (UA) [12] and the fetal internal carotid artery (ICA) [13]. The pulsatility index (PI) was calculated for both the umbilical artery and internal carotid artery. PI is derived by dividing the difference between the peak systolic and end-diastolic velocity by the mean velocity over the entire cardiac cycle [14].

All Doppler studies at cardiac and peripheral level were performed with the patient in the semirecumbent position and during periods of fetal apnoea, because high amplitude fetal breathing movements modulate blood flow velocity waveforms. All flow velocity waveforms were recorded on hard copies. A microcomputer (Olivetti M24) linked to a graphics tablet was used for analysis of the Doppler recordings. An average of four consecutive flow velocity waveforms with the highest velocity and of similar appearance was used to establish each value.

Neonatal outcome was expressed by Apgar score at 1 min, umbilical artery pH, base excess (BE, mEq/l) and oxygen tension (Po_2, KPa).

Thirty-three infants were admitted to the neonatal intensive care unit (NICU) of the Sophia Children's Hospital and 5 infants were referred to the NICU of a district hospital.

A nucleated red blood cell count (NRBC) was performed in 26 infants admitted to the NICU of the Sophia Children's Hospital. Total white blood cell count (WBC) was determined within 12 h after birth and the number of NRBCs was calculated from examination of the blood smear for the differential WBC count. The WBC count was then corrected for the NRBC count. NRBCs were determined as NRBCs per 100 WBCs and as absolute NRBC counts by multiplying the (corrected) WBC count by the percentage of NRBCs.

Cerebral scans were performed in 28 infants admitted to the NICU of the Sophia Children's Hospital at 2/3, 6/7 and 10/11 days after delivery. These were performed through the anterior fontanelle using a Diasonics scanner (ADA 400), with a 7.5 MHz transducer by one observer (W.B.). Abnormal ultrasound findings were classified into three groups: PVL stage II, cystic periventricular leukomalacia characterized by intense bilateral flaring of the periventricular areas followed by polycystic degeneration; PVL stage I, flaring without visible cystic changes but followed by ventricular dilatation; PVL stage 0, flaring alone [15]. For further analysis, the infants were judged according to their severest degree of leukomalacia as documented during the first 11 days of postnatal life.

Multiple regression analysis was used to investigate simultaneously the relationship of the Doppler measurements and gestational age with pregnancy outcome. The Mann-Whitney *U*-test was used for comparing the Doppler data with the results of the brain scans, and postnatal deaths. $P = 0.05$ (two-sided) was considered the limit of statistical significance.

Results

Birth weight (median, 1055 g) varied between $P < 2.3$ and $P = 25$ (median, $P = 5$) according to Kloosterman's Tables corrected for maternal parity and fetal sex (Table I) [16]. There was one intrauterine death. Five women were delivered vaginally. Thirty-six women were delivered by caesarean section, 28 of which because of fetal distress as determined by the fetal cardiotocogram. In the remaining eight women, caesarean section was performed because of partial abruptio placentae ($n = 2$), severe pre-eclampsia ($n = 4$) or gestational age of 36 weeks or more ($n = 2$). The time delay between the last Doppler measurement and delivery varied between 0 and 6 days (median, 1). One woman was excluded from the study because of a time delay of 20 days, leaving 40 patients for further analysis. The time delay between the entry of the study and delivery varied between 1 day and 7 weeks (median 2.5 weeks). The success rate for obtaining acceptable blood flow velocity waveforms (last measurement) in the umbilical artery, internal carotid artery, ascending aorta and pulmonary artery was 100%, 95%, 93% and 88%, respectively. PIUA and PIICA were situated outside the reference curves (± 2 S.D.) [17,18] in 78% and 87%, respectively. For the PSVAO and PSVPA the percentages were 63 and 84. No reference charts are available for the AVAO and AVPA. All Doppler parameters significantly correlated with gestational age at birth. A negative correlation was established for the PIUA, and PIICA ($r = -0.32$ and $r = -0.40$, respectively), whereas a positive correlation was established for the PSVAO, AVAO, PSVPA, and AVPA ($r = +0.49$, $r = +0.36$, $r = +0.56$, and $r = +0.47$, respectively).

Table I presents data on Apgar scores at 1 min and postnatal umbilical artery pH, BE, and Po_2. No correlation could be established between Apgar score at 1 min and the Doppler parameters. No correlation existed between the Doppler flow velocity parameters from the internal carotid artery and pulmonary artery, and

TABLE I

Data on neonatal outcome.

	Median	Range	*n*
Gestational age at birth (weeks)	32	28 to 37	40
Birth weight (g)	1055	395 to 2030	40
Apgar at 1 min	6	1 to 10	40
pH	7.20	6.82 to 7.33	40
BE	−7.0	−0.9 to −24.2	39
Po_2 (kPa)	1.37	0.48 to 2.53	24

postnatal umbilical artery pH, BE and Po_2. PIUA was significantly related to pH and BE. However, this relationship disappeared when taking into account gestational age. PSVAO and AVAO were significantly correlated with Po_2 ($r = +0.44$, $P = 0.04$; $r = +0.57$, $P = 0.007$, respectively). When gestational age was taken into account, this relationship only remained significant for AVAO.

Eighteen neonates required positive pressure ventilation. Duration of ventilation varied between 1 and 38 days (median, 8 days). All flow parameters except for the PIICA correlated significantly with the duration of ventilation. After multiple regression taking into account gestational age, this correlation only remained significant for the PSVPA ($r = -0.46$, $P = 0.006$), AVPA ($r = -0.54$, $P = 0.001$), and PIUA ($r = +0.42$, $P = 0.007$). There were seven postnatal deaths; one infant died immediately after birth, and six infants died within 22 days after admission to the NICU. These neonates displayed a significantly higher PIUA (mean 4.07, S.D. 1.58) compared to those who remained alive (2.05, S.D. 1.39; $P < 0.001$). After multiple regression, taking into account gestational age, this correlation remained significant ($P = 0.01$).

NRBC/100 WBC varied between 11.5 and 3350 (median, 125), absolute NRBC count ranged between 0.6×10^9 and 164×10^9/l (median, 7.7×10^9). Because of the skewed distributions, the logarithm of both NRBC counts and absolute number of NRBC was used in the analysis. Both the NRBC/100 WBC and absolute NRBC count were significantly correlated with PIUA ($r = 0.64$, $P < 0.001$, and $r = 0.61$, $P \leq 0.001$, respectively). Taking into account gestational age, the correlation remained significant ($P = 0.001$).

Brain scans were performed in 28 infants, 19 of which showed no abnormalities. A subdural haemorrhage was seen in one infant. PVL stage 0, I and II were seen in 2, 2 and 4 infants, respectively. Doppler flow velocity waveforms from infants with PVL stage I and II were not significantly different from those with PVL stage 0 or from those with normal scans.

Discussion

The majority of reports agree upon a possible role of Doppler flow velocity waveforms in the surveillance of high-risk pregnancies [1–5]. These studies reveal relationships with pregnancy outcome in various obstetric populations. However, as the majority of clinical endpoints and Doppler parameters are age-related, one may question as to whether Doppler flow velocity waveforms provide additional information about adverse perinatal outcome. Indeed, in the present study, the greater number of correlations of Doppler parameters with neonatal outcome disappear when correcting for gestational age.

Flow velocity waveforms in the fetal descending aorta and umbilical artery have been related to fetal acid-base status and oxygen tension prenatally and at delivery [1,2,5,17,19–21]. In pregnancy populations suspected of IUGR, contradictory results have been reported: Wladimiroff et al. [17] and Ferrazzi et al. [19] found a correlation between pH at delivery and PI in the umbilical artery, whereas McCowan et al. [20] did not. This may be explained by differences in study populations, effect of the process of birth on acid-base status or the limited number of patients. No significant relationship has been reported between the PI in the fetal thoracic descending aorta and pH [1]. Our data indicate that the correlation between PIUA and pH is mainly determined by gestational age. Similar results have been reported by Bekedam et al. [21] who compared IUGR fetuses with end-diastolic velocities in the umbilical artery with those without end-diastolic velocities. After matching for gestational age and birth weight the difference between the two groups in pH and Po_2 disappeared. A relationship between flow velocity waveforms in the umbilical artery [22] and in thoracic descending aorta [23] and fetal Po_2 and pH has been established in cordocentesis studies. Our observation of a correlation between the time-averaged velocity in the fetal ascending aorta and Po_2 at delivery is in agreement with the findings made at cordocentesis. It has been suggested [23] that these correlations may be related to increased placental vascular impedance or redistribution of blood flow during hypoxemia. In IUGR, reduced peak systolic velocities in the ascending aorta and pulmonary artery have been associated with raised vascular resistance at fetal trunk and placental level, whereby the afterload to the left ventricle is also determined by cerebral vascular resistance [9]. PI values in the internal carotid artery suggest a reduced vascular resistance at cerebral level in all but one of the fetuses. The positive correlation between time-averaged velocities in the ascending aorta and umbilical artery Po_2 may, therefore, may be explained by differences in placental vascular impedance. Since Doppler data from the umbilical artery and pulmonary artery were not related to umbilical artery Po_2, the meaning of this relationship is not clearly understood. The lack of any correlation between cardiac and extra-cardiac flow velocity waveforms and Apgar score may be determined by the crudeness of the scoring system.

Of interest is that low time-averaged and peak-systolic velocities in the pulmonary artery, and a high PI in the umbilical artery are associated with an increased duration of ventilatory support in the 18 neonates in the NICU. The PI in the umbilical artery reflects downstream impedance, and therefore umbilical placental resistance. As mentioned earlier, a similar relationship has been assumed for peak systolic velocities in the pulmonary artery, whereby reduced velocities are associated with increased vascular resistance. This suggests that besides gestational age, impaired placental function may be a determinant of requirement of positive pressure ventilation.

The PIUA seems to be clearly related to neonatal outcome, which is also demonstrated by the positive correlation between PIUA and neonatal mortality. Hackett et al. [24] and Bekedam et al. [21] found an increased mortality in IUGR fetuses with absent end-diastolic velocities compared to those with end-diastolic velocities in the umbilical artery. In contrast to our findings, no significant difference in mortality was found when selecting a subgroup matched for gestational age and birth weight [21]. In this respect one may hypothesize about a possible reduction in postnatal deaths if timing of delivery would have been based on umbilical artery Doppler surveillance. In a randomized trial, Omzigt [25] found a reduction in late fetal deaths in the Doppler group compared to the control group. However, no differences in neonatal mortality and differences of clinical interest in neonatal morbidity could be demonstrated.

A perinatal increase in nucleated red blood cell counts (NRBC counts) has been reported in growth retardation [7,8]. It has been suggested that increased NRBC counts may be related to chronic perinatal hypoxemia. This is in support of the positive correlation between the number of NRBCs per 100 WBC and the absolute number of NRBC, and PIUA, reflecting raised placental vascular resistance and therefore impaired placental perfusion.

Cerebral injury may be one of the neonatal complications in IUGR. Extensive cystic leukomalacia (PVL) is associated with cerebral palsy later in infancy [6]. Cystic leukomalacia is often preceded by so-called flaring, which are echodense periventricular areas. The prognosis of transient flaring or flaring not followed by the development of periventricular cysts (PVL stage 0) appears to be relatively good [26]. Therefore, in the present study infants with PVL stage 0 and normal scans were compared to those with PVL stage I or II. Scans were only performed in the first two weeks postnatally, as changes related to prenatal hypoxemia appear during this period (W.B., pers. commun.). Only six out of 28 infants undergoing serial brain scans displayed leukomalacia stage I or II. This may explain the lack of any correlation between the Doppler parameters and sonographically determined neonatal leukomalacia.

Although some of the obtained relationships only apply to neonates requiring intensive care, it can be concluded that from all Doppler parameters, the PIUA is most clearly related to neonatal outcome in IUGR.

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