Doppler measurements of fetal and uteroplacental circulations: Relationship with umbilical venous blood gases measured at cordocentesis

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A pulsed Doppler study of the fetal and uteroplacental circulations was performed on 41 pregnant women with small-for-gestational-age and 10 women with appropriate-for-gestational-age fetuses at 19 to 37 weeks' gestation. Blood gases and pH, measured in umbilical venous samples obtained by cordocentesis within 1 hour of the Doppler studies, were correlated individually and as an "asphyxia" index, to the Doppler and ultrasonographic biometric measurements. Although there were significant correlations between the majority of the ultrasonographic biometric and Doppler measurements with the blood gas results, better correlations were found with the ratio of common carotid artery to descending thoracic aorta mean velocity and pulsatility index. The best predictor of asphyxia was an index comprising aortic mean velocity and the common carotid artery pulsatility index. When this index was abnormal, 89% of fetuses had an asphyxia index 1 SD above the mean and 60% 2 SDs above the mean. A normal index was always associated with normal blood gases. The indices representing the inverse relationship of impedance and velocity in the two major vessels that supply the brain and the abdominal viscera provide the best prediction of the fetal condition because they reflect the hemodynamic response to changes in the partial pressure of respiratory gases. (AM J OBSTET GYNECOL 1990;162:115-20.)

Key words: Doppler ultrasonography, fetal circulation, fetal blood gases, fetal asphyxia, cordocentesis

Animal studies have shown that reduced placental perfusion is associated with intrauterine growth retardation.[1] Furthermore, in fetal hypoxemia there is a redistribution in blood flow with increased blood supply to vital organs, such as the brain, heart, and adrenals, and a simultaneous reduction of perfusion of other organs that include the lungs, gastrointestinal tract, and kidneys.[2] This redistribution of flow is referred to as the "brain-sparing effect."

Doppler ultrasonography has allowed examination of the human fetus in both physiologic and pathologic conditions.[3] Reference ranges for intensity-weighted mean blood velocities and impedance indices (pulsatility index and resistance index) with gestation have been established for the fetal descending thoracic aorta, the common carotid artery, the umbilical artery, and the uteroplacental vessels.[4,5] A series of cross-sectional studies in pregnancies complicated by intrauterine growth retardation have demonstrated that increased impedance in the uteroplacental vessels and in the umbilical artery is associated with hypoxemia and poor perinatal outcome.[6-8] Furthermore, in small-for-gestational-age (SGA) fetuses, there is a correlation between reduced aortic intensity-weighted mean velocity and low fetal

Table I. Equations defining the reference ranges for each variable used in the statistical analysis

Variable	*Equation*	*Source*
Po_2	76.5 − 1.244 G	Soothill et al.[14]
Pco_2	38.29 − exp (11.873 − 0.5961 G)	Soothill et al.[14]
pH	7.38 (constant)	Soothill et al.[14]
UA PI	exp (0.585 − 0.2289 G)	Pearce et al.[5]
UP RI	$\log_e$ − 0.454 − 0.015	Pearce et al.[5]
Ao Vm	−16.27 + 2.706 G − 0.03845 G^2	Bilardo et al.[4]
Ao PI	0.4294 + 0.1118 G − 0.00175 G^2	Bilardo et al.[4]
CC Vm	3.482 + 0.4655 G	Bilardo et al.[4]
CC PI	−0.6613 + 0.3701 G − 0.0075 G^2	Bilardo et al.[4]
CA PI (ratio)	0.4046 + 0.1316 G − 0.0029 G^2	Bilardo et al.[4]
CA Vm (ratio)	0.3059 + 0.00986 G	Bilardo et al.[4]

G, Gestational age; *UA PI*, umbilical artery pulsatility index; *UP RI*, uteroplacental resistance index; *Ao Vm*, aortic mean velocity; *Ao PI*, aortic pulsatility index; *CC Vm*, common carotid artery mean velocity; *CC PI*, common carotid artery pulsatility index; *CA PI*, carotid-aortic pulsatility index; *CA Vm*, carotid-aortic mean velocity.

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Table II. Correlation of ultrasonographic biometric and Doppler measurements with fetal blood gases, pH, and asphyxia index

	Po_2		Pco_2		*pH*		*Asphyxia*	
Measurement	*r*	*RSD*	*r*	*RSD*	*r*	*RSD*	*r*	*RSD*
ΔAC	0.28	8.9	−0.48	6.0	0.49	0.050	−0.48	22.1
ΔHC	0.32	8.9	−0.44	6.2	0.37	0.049	−0.44	22.8
ΔHC/AC	−0.30	9.0	0.37	6.4	−0.44	0.047	0.42	23.0
ΔUP RI	−0.58	7.7	0.35	6.5	−0.33	0.049	0.48	22.4
ΔUA PI	0.52	8.0	−0.40	6.4	0.49	0.043	−0.54	21.1
ΔAo Vm	0.51	8.0	−0.59	5.6	0.54	0.044	−0.62	19.7
ΔAo PI	−0.47	8.3	0.57	5.7	−0.57	0.043	0.61	20.0
ΔCC Vm	−0.28	9.0	0.41*	6.4	0.38*	0.040	−0.43	23.0
ΔCC PI	0.63	7.3	−0.43	6.2	0.51	0.045	−0.60	20.2
$\Delta CC/Ao_{Vm}$	0.63*	7.4	0.62*	5.4	0.57*	0.043	−0.68	19.0
$\Delta CC/Ao_{PI}$	0.66	7.1	−0.54	5.8	0.55	0.043	−0.66	19.3
Ao-CC index	0.62	7.4	−0.58	5.6	0.58	0.043	−0.67	18.7

Δ, Difference between obtained measurement and normal mean value for gestational age; *r*, correlation coefficient; *RSD*, residuals S-D; *AC*, abdominal circumference; *HC*, head circumference; *HC/AC*, head to abdominal circumference ratio; *UP RI*, uteroplacental resistance index; *UA PI*, umbilical artery pulsatility index; *Ao Vm*, aortic intensity-weighted mean velocity; *CC*, common carotid artery; *CC/Ao Vm*, ratio of *CC* and *Ao Vm*; *CC/Ao PI*, ratio of *CC* and *Ao PI*; *Ao-CC* index, aortic-carotid score created by principal component analysis.

*Required quadratic term in the regression: r is the square root of the index of determination r^2. $r = 0.28$, significant at $p = 0.05$. $r = 0.36$, significant at $p = 0.01$. $r = 0.45$, significant at $p = 0.001$.

Po_2 levels. The absence of end-diastolic frequencies in the aortic flow velocity waveforms is associated with a high incidence of neonatal complications affecting those organs that suffered from the redistribution of flow (i.e., necrotizing enterocolitis, pulmonary hemorrhage, coagulopathy).[9] More recently Doppler studies have also demonstrated that in growth-retarded fetuses the cerebral perfusion is increased.[10, 11]

This study examines the relationship between Doppler measurements of velocity and impedance in the common carotid artery and fetal blood gases. A comparison is also made between the various ultrasonographic biometric and Doppler measurements of uteroplacental and fetal circulation in their ability to predict fetal oxygenation.

Patients and methods

Doppler studies of the fetal and uteroplacental circulation were performed 30 to 60 minutes before cordocentesis in 51 patients referred to our center for fetal assessment at 19 to 37 weeks' gestation. The study was cross-sectional. All fetuses had an ultrasonographic scan and in 41 cases the fetal abdominal circumference was below the 2.5th percentile of our normal range; cordocentesis was performed for fetal karyotyping and determination of acid-base status.[12] In the remaining 10 cases the abdominal circumference was within the normal range for gestation, and the indication for fetal blood sampling was prenatal diagnosis (toxoplasmosis, $n = 2$; rapid karyotyping for failed amniocentesis or placental biopsy cultures, $n = 3$; presence of ultrasonographic markers for chromosomal disorders, $n = 4$; blood grouping, $n = 1$). All fetuses were subsequently determined to be chromosomally normal and not to be affected by the condition investigated. Gestational age was established by Naegele's rule and from an ultrasonographic measurement of the fetal biparietal diameter at 16 to 18 weeks. The SGA fetuses were classified on the basis of the head circumference/abdominal circumference ratio into symmetric and asymmetric types if this ratio was below or above the 97.5th percentile, respectively, of our normal range.

A duplexed system consisting of a 2 MHz pulsed Doppler probe attached at a fixed angle of 53 degrees to a 3 MHz linear array transducer (Kranzbuhler-ADR 5000, Berlin) was used for the Doppler studies. Flow velocity waveforms were recorded from the major branches of the uteroplacental vessels, umbilical artery, fetal descending thoracic aorta, and common carotid artery as previously described.[3-5] The Doppler sonograms were considered for measurements when there were no fetal gross body or chest movements and the fetal heart rate was between 120 and 140 beats per minute. The high-pass filter was set at 150 Hz. The duration for the Doppler investigation in each patient was approximately 40 minutes (range, 20 to 60 minutes). For velocity determinations a representative pair of cardiac cycles was selected from the flow velocity waveforms of the aorta and of the common carotid artery, and the angle of insonation of the vessel was measured on the frozen image of the linear array display; this angle was always kept below 55 degrees. The mean velocity was calculated automatically by a built-in computer from the intensity-weighted means of the

Table III. Means and SDs for each variable considered in the study, corrected for gestational age

Variable	*N*	*Mean*	*SD*	*SE*	*Minimum*	*Maximum*
P_{O_2}	51	−15.46	9.24	1.29	−35.01	5.23
P_{CO_2}	51	3.74	6.82	0.96	−9.34	25.21
pH	50	−0.03	0.05	0.01	−0.14	0.06
Asphyxia index	50	26.30	25.00	3.50	−29.40	84.30
AC	51	−5.31	3.41	0.48	−11.40	5.40
HC	50	−2.92	2.26	0.32	−7.20	1.50
HC/AC	50	0.15	0.12	0.02	−0.25	0.39
UP RI	50	0.71	0.18	0.02	0.35	0.96
UA PI	51	−1.27	1.37	0.19	−7.51	0.88
Ao Vm	51	−6.51	4.82	0.67	−16.00	4.71
Ao PI	51	0.39	0.56	0.08	−0.78	1.86
CC Vm	51	2.70	4.75	0.66	−7.13	14.40
CC PI	51	−1.33	0.87	0.12	−2.89	0.50
CC/Ao Vm	49	0.32	0.32	0.04	−0.26	1.01
CC/Ao PI	49	−0.66	0.63	0.09	−1.51	1.00
Ao-CC index	51	−12.10	7.70	1.10	−25.90	5.57

See Tables I and II for abbreviations.

Doppler-shifted frequencies of two consecutive cardiac cycles. Velocity measurements were repeated twice and the mean of the two measurements was considered. The coefficient of variation for mean velocity measurements in the aorta and in the common carotid artery were 6% and 12%, respectively.[4] The pulsatility index, as defined by Gosling, was measured in all fetal flow velocity waveforms as previously described.[4] The coefficient of variation for this measurement is 10% for the aorta, 8% for the common carotid artery, and 7% for the umbilical artery.[4, 5] In flow velocity waveforms from the uteroplacental vessels, the resistence index, as defined by Pourcelot, was calculated on three consecutive cardiac cycles.

The umbilical venous P_{O_2} (n = 51), P_{CO_2} (n = 51), and pH (n = 50) were measured by a blood gas analyzer (Radiometer ABL 330, Copenhagen, Denmark) immediately after cordocentesis in samples collected in heparinized syringes, and the values were compared to those of our reference ranges.[13] Identification of the umbilical cord vessel sampled was made at the time of cordocentesis by the intravascular injection of 0.4 ml of normal saline solution.[12] Because of the larger size of the umbilical vein this vessel is more often sampled, and in this study we have considered the data obtained from umbilical venous samples only.

Statistical analysis

In normal pregnancy measurements of fetal size, blood gases, and Doppler parameters change with gestational age.[4, 5, 13] To allow for this effect, each measurement in this study was subtracted from the normal mean for gestational age and expressed as difference (Δ). Table I shows the equations to define the reference ranges for each Doppler and blood gas variable considered in the study. For the ultrasonographic biometric measurements, the normal means were derived from the normal ranges used in our ultrasonography unit.

Principal component analysis was used to create from the data an "asphyxia" index that would gather as much information as possible on fetal well-being as expressed by individual measurements of P_{O_2}, P_{CO_2}, and pH.[14] This index is defined by the following equation: Asphyxia = $-\Delta P_{O_2} + 1.43\ (\Delta P_{CO_2}) - 180.2\ (\Delta pH)$. The index encompassed 77% of the combined variance of blood gases and pH. Similarly, by means of principal component analysis a Doppler "aortic-carotid" index, combining the two most reproducible measurements of the central fetal circulation, i.e., aortic mean velocity (AoVm) and common carotid artery pulsatility index (CCPI), was defined by the equation: Aortic-carotid index = Δ Ao VM + 4.2 (ΔCCPI). The combined variance of the two Doppler measurements encompassed by the index was 82%.

Multiple regression analysis (computer program BMDP9R, P. Royston, London) was used to determine the ability of each Doppler and ultrasonographic parameter, both singly and in all possible combinations, to predict fetal P_{O_2}, P_{CO_2}, and pH individually, and then combined in the asphyxia index. Combined Doppler measurements included the ratios between common carotid and aortic velocities and pulsatility indexes and the aortic-carotid index.

Results

The correlation coefficients and the residuals SD of the fetal blood gases, pH, and asphyxia index, regressed on each Doppler and ultrasonographic measurement, are shown in Table II. The mean values for these parameters, expressed as Δ values, are listed in Table III. Among the individual Doppler measurements, considered in a rank order, the predictors that

Table IV. Percentiles of asphyxia index for given values of aortic mean velocity and common carotid pulsatility index adjusted for gestation and expressed as values

	Ao Vm (Δ)								
CC PI (Δ)	*−15.0*	*−12.5*	*−10.0*	*−7.5*	*−5.0*	*−2.5*	*0.0*	*2.5*	*5.0*
−3.00	100.0	100.0	99.9	99.7	99.1	97.8	95.3	90.7	83.5
−2.75	100.0	99.9	99.8	99.5	98.7	97.0	93.7	88.0	79.6
−2.50	100.0	99.9	99.7	99.2	98.1	95.8	91.6	84.9	75.2
−2.25	100.0	99.9	99.6	98.9	97.3	94.3	89.1	81.2	70.4
−2.00	99.9	99.8	99.3	98.4	96.3	92.4	86.1	77.0	65.1
−1.75	99.9	99.6	99.0	97.7	94.9	90.1	82.6	72.3	59.5
−1.50	99.8	99.4	98.6	96.7	93.2	87.3	78.6	67.1	53.8
−1.25	99.7	99.2	97.9	95.5	91.1	84.0	74.1	61.7	47.9
−1.00	99.5	98.8	97.1	93.9	88.5	80.2	69.1	56.0	42.1
−0.75	99.3	98.2	96.0	91.9	85.3	75.9	63.8	50.2	36.5
−0.50	98.9	97.5	94.6	89.5	81.7	71.1	58.2	44.3	31.1
−0.25	98.4	96.5	92.7	86.6	77.6	65.9	52.4	38.6	26.2
0.00	97.8	95.1	90.5	83.2	73.0	60.3	46.5	33.1	21.6
0.25	96.9	93.5	87.8	79.2	67.9	54.6	40.8	28.0	17.6
0.50	95.7	91.4	84.5	74.8	62.5	48.8	35.2	23.3	14.0

See Tables I and II for abbreviations. Underlined values are beyond the 95th percentile for normal fetuses.

Δ Ao Vm and Δ CC PI are calculated by subtracting the normal expected mean for gestation from the measured Doppler value. The normal expected values for *Ao Vm* and *CC PI* from 20 to 42 weeks' gestation are listed below. For example, a fetus at 20 weeks' gestation with an *Ao Vm* of 17.5 cm/sec ($\Delta Ao\ Vm = -5$) and a *CC PI* of 0.99 ($\Delta CC\ PI = -2.75$) has a 98.7% chance of having an asphyxia index above the 95th percentile of its normal range.

Gestational age (wk)	*Aortic mean velocity (cm/sec)*	*Common carotid PI (units)*
20	22.5	3.74
21	23.6	3.80
22	24.7	3.85
23	25.6	3.88
24	26.5	3.90
25	27.4	3.91
26	28.1	3.89
27	28.8	3.87
28	29.4	3.82
29	29.9	3.77
30	30.3	3.69
31	30.7	3.61
32	31.0	3.50
33	31.2	3.39
34	31.3	3.26
35	31.4	3.11
36	31.3	2.95
37	31.2	2.77
38	31.1	2.58
39	30.8	2.37
40	30.5	2.15
41	30.1	1.91
42	29.6	1.66

showed the highest correlations with the asphyxia index were the Δaortic mean velocity, Δaortic pulsatility index, and Δcommon carotid artery pulsatility index. The predictive ability of the individual Doppler measurements was greater if the ratios of common carotid to aortic velocity and pulsatility index were considered. The best combined predictor of asphyxia (i.e., that with the lowest residuals SD and the highest coefficient correlation value) was the aortic-carotid index (Fig. 1). The 50 individual values and the 95% intervals for the variation among individuals around the regression line of the asphyxia index on the aortic-carotid index are shown in Fig. 1. In 38 fetuses the aortic-carotid index was at least 2 SDs below the normal mean; in all these cases the fetal asphyxia index was above the normal mean. In 34 cases (89% of the cases with abnormal aortic-carotid index) it was 1 SD above and in 23 (60%) it was 2 SDs above the normal mean. All fetuses with a normal aortic-carotid index ($n = 12$) had normal blood gas results (no false negatives). Multiple regression analysis did not improve the prediction of blood gases, pH, or asphyxia index above that of the best

single predictor in each case; therefore linear regressions only are presented.

Table IV shows the prediction of percentiles of asphyxia index obtained from the aortic mean velocity and common carotid artery pulsatility index measurements adjusted for gestational age.

Comment

Doppler ultrasonographic investigation facilitates the recognition of circulatory changes that occur in the human fetus under physiologic and pathologic conditions. This study examines the relationship between Doppler findings and the state of fetal oxygenation.

Impaired uteroplacental perfusion, as demonstrated by the increased impedance to flow in the uteroplacental circulation, is significantly correlated with fetal hypoxemia. This supports the findings from histopathologic studies that in some pregnancies with SGA fetuses there is a failure of the normal development of maternal placental bed arteries into low resistance vessels, and the concept that one of the causes of fetal growth retardation is poor maternal blood supply leading to fetal malnutrition.[15] Therefore reduced oxygen supply to the intervillous space results in fetal hypoxemia. Increased uteroplacental resistance index correlates significantly with fetal hypoxemia, but not necessarily with hypercapnia and acidosis because these are more closely related to the metabolic response to hypoxia and to damage to the vasculosyncytial membrane.

Whereas study of uteroplacental flow velocity waveforms provides information about the maternal side of the intervillous space, studies of flow velocity waveforms from the umbilical artery represent the fetal side of the exchange mechanism. Increased placental resistance may result from reduction in the number of placental terminal capillaries and small muscular arteries in the tertiary villi,[16] or from vasoconstriction mediated by the hypoxia-induced release of vasoactive substances. Thus the increase in pulsatility index correlates with the degree of fetal asphyxia and explains why increased resistance in the umbilical artery is associated with poor perinatal outcome. However, umbilical artery pulsatility index shows a weaker correlation with fetal asphyxia than the Doppler measurements of central fetal circulation, which are more directly related to fetal oxygenation.

Aortic mean velocity and common carotid artery pulsatility index are among the best individual predictors of fetal asphyxia. These are also the most reproducible Doppler measurements of the fetal circulation.[4] The finding that common carotid arterial mean velocity is a weaker predictor than common carotid pulsatility index may be caused by inaccuracies in the measurement of the angle of insonation to the vessel.

However, the altered fetal blood P_{O_2}-P_{CO_2} homeostasis is better represented by the inverse relationship of resistance and velocities in the descending thoracic aorta and common carotid artery rather than by the measurement of only one of them. This suggests that the human fetus responds to hypoxia in a similar fashion to that described in animals. Thus in hypoxia there is an increase in the blood supply to the brain and reduction in the perfusion of the gastrointestinal tract, kidneys, and lower extremities.[2] Although knowledge of the factors governing circulatory readjustments and their mechanism of action is incomplete, it appears that partial pressures of oxygen and carbon dioxide play a role, presumably through their action on chemoreceptors. Previous studies have attempted to make use of knowledge obtained from animal studies of hypoxia-induced centralization of flow by examining the ratio of the umbilical artery to the internal carotid artery pulsatility index in relation to growth retardation.[10, 11] However, unlike the situation of the descending thoracic aorta, the umbilical arterial flow velocity waveforms are primarily influenced by the state of resistance in the placental microcirculation and not by the fetal chemoreceptor activity.

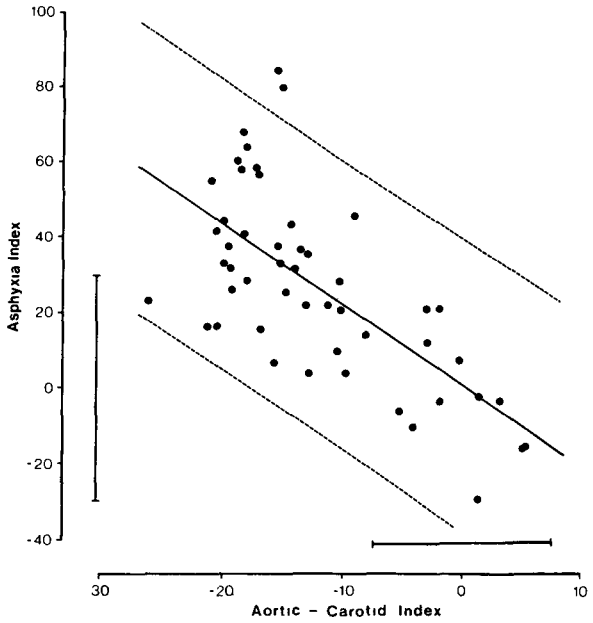

Fig. 1. Individual values (n = 50) and 95% intervals for the regression line of fetal asphyxia index [$-\Delta P_{O_2}$ + 1.43 (ΔP_{CO_2}) − 180.2 (ΔpH)] versus Doppler aortic-carotid index [Δaortic mean velocity + 4.2 (Δcommon carotid artery pulsatility index)]. The two *vertical* and *horizontal lines* represent the normal range (mean ± SD) for the asphyxia index and the aortic-carotid index, respectively. A normal aortic-carotid index was always associated with normal fetal blood gases (n = 12). When this index was abnormal, 89% of the fetuses had an asphyxia index 1 SD above the normal range and 60% 2 SDs above the mean.

The ultrasonographic biometric measurements are weaker predictors of the fetal condition than Doppler measurements and, surprisingly, the symmetry or asymmetry of the growth pattern does not improve the correlation. These findings are compatible with the concept that growth retardation is only one of the causes of fetal "smallness," and the degree of smallness depends on the severity of the growth-retarding insult and on the original growth potential of the individual fetus. Therefore it is not surprising that Doppler ultrasonography constitutes a more accurate method of diagnosing fetal asphyxia than the widely used biometric methods.

The correlations between Doppler measurements and fetal condition imply that the degree of abnormality of the Doppler findings parallels the severity of fetal compromise. Nonetheless, there is still a substantial amount of random variation, which can be seen as "scatter" around the regression line in Fig. 1. This could be partly a result of technical inaccuracies in the Doppler measurements or the biologic variation in the responsiveness of the individual fetus to the same stimulus.

When the aortic-carotid index was abnormal, 60% of fetuses were severely asphyxiated, whereas a normal ratio was always associated with good fetal oxygenation. Furthermore, the simple combination of common carotid artery pulsatility index and aortic mean velocity measurements can be used to establish the probability of a given fetus being hypoxemic and acidemic.

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