PAPERS AND SHORT REPORTS

Doppler studies in the growth retarded fetus and prediction of neonatal necrotising enterocolitis, haemorrhage, and neonatal morbidity

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Abstract

In 82 consecutive cases of intrauterine growth retardation managed by established criteria fetal Doppler studies identified 29 fetuses with absence of end diastolic frequencies in the fetal aorta. These same fetuses were significantly more growth retarded ($p<0.001$) and had an earlier gestational age at delivery ($p<0.001$) than those with end diastolic frequencies present. A subgroup of these cases was analysed in more detail to examine the prognostic value of this phenomenon for the neonate. Two groups of neonates of equivalent gestational age and with a birth weight below 2000 g were compared. There were 26 neonates with absent end diastolic frequencies (group 1) and 20 with end diastolic frequencies (group 2) in the fetal aorta. Those in group 1 were more likely to suffer perinatal death ($p<0.05$), necrotising enterocolitis ($p<0.01$), and haemorrhage ($p<0.05$). Only 4 (15%) of the babies in group 1 had an uncomplicated neonatal period compared with 15 (75%) in group 2 ($p<0.001$).

The circulatory changes identified in these cases may provide a more sensitive measure of critical fetal compromise than current techniques and thus allow the clinician to deliver the fetus before irreversible tissue damage has occurred.

Introduction

Fetal intrauterine growth retardation is strongly associated with perinatal death,[1] neonatal morbidity,[2] and long term handicap.[3] With our increasing ability to prevent intrauterine death avoidance of neonatal morbidity should become both the target and the measure of antenatal care. Adverse sequelae are more apparent in growth retarded fetuses who are delivered prematurely. This group is particularly at risk from hypoxia,[4] and it is this insult which most closely predicts long term handicap.[4,5] Furthermore, the association of reduced head circumference with neurological deficit in these cases[6] shows the considerable prenatal influence on outcome. Thus the early recognition of hypoxia is essential in the prevention of irreversible damage.

The recently described non-invasive investigation of the maternal and fetal circulations by Doppler ultrasound may provide further information about fetal condition and detect hypoxia in advance of current monitoring techniques. One well described aberrant pattern of the blood flow velocity waveform recorded from the aorta and umbilical artery in fetuses with intrauterine growth retardation is a reduction in, and in some cases an absence of, end diastolic frequencies (figure).[6,7] This phenomenon is believed to result from increased peripheral vascular resistance,[8,9] a well described response in sheep and primates exposed to both acute and chronic hypoxia.[10,11]

We have analysed retrospectively the clinical history and outcome of those cases where Doppler blood flow studies of the fetal aorta were carried out in the presence of intrauterine growth retardation. The aim was to assess the prognostic value of this investigation in terms of both obstetric and neonatal outcome and in particular to compare those cases with and without end diastolic frequencies in the fetal aorta. Umbilical and uteroplacental arterial waveforms were also recorded, and these results will be reported more fully elsewhere.

Materials and methods

Data were available from 82 consecutive pregnancies in which the mother was delivered of a growth retarded infant and in which fetomaternal blood flow studies had been carried out within 10 days of delivery. Intrauterine growth retardation was defined as a birth weight below the 10th centile for gestational age with corrections made for both the infant's sex and the mother's parity.[12] Birthweight ratio was calculated for each infant as the actual birth weight divided by the mean expected birth weight with the same corrections applied as above. All pregnancies were dated by ultrasound examination at 16 to 18 weeks of gestation.[13] In each case clinical suspicion of intrauterine growth retardation was confirmed by ultrasound examination

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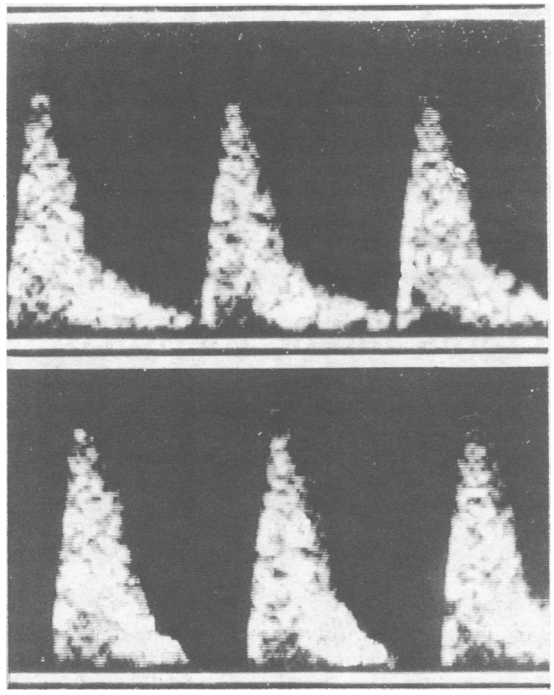
and measurement of the biparietal diameter, head circumference, and abdominal circumference. The ratio of these last two measurements was plotted to see whether asymmetrical or symmetrical growth retardation was present.[14] A subjective assessment of amniotic fluid volume was made simultaneously by an experienced ultrasonographer and the patient classified as having either normal liquor volume or oligohydramnios.



Doppler flow velocity waveforms recorded from fetal aorta with (top) end diastolic frequencies present and (bottom) end diastolic frequencies absent.

Blood flow measurements were taken from the fetal aorta using a linear array pulsed Doppler duplex (Kranzbuehler), which combines a 3·5 MHz linear array transducer and a 2 MHz pulsed Doppler transducer. The methodology has been fully reported.[7] The time averaged mean velocity was calculated automatically by the spectrum analyser. Furthermore, the display of the Doppler shifted frequencies and their intensity against time permitted calculation of the peak systolic velocity and various qualitative variables. These latter measurements, which include the A/B ratio,[15] resistance index of Pourcelot,[16] and pulsatility index,[17] are simple ratios of peak systolic and end diastolic frequencies and are independent of the angle of insonation. They show increased values when end diastolic frequencies are decreased by a rise in peripheral resistance. All the above qualitative and quantitative variables are independent of gestational age when measured in the third trimester.[7]

The condition of absent end diastolic frequencies was diagnosed when no frequencies were visible above the level of the 150 Hz filter, this being used to exclude low frequency distorting signals from the vessel walls. Thus when the three qualitative measurements were taken from those waveforms with absent end diastolic frequencies the end diastolic value was interpreted as being 150 Hz. Only signals recorded at angles of less than 60 degrees were used for analysis so as to limit the quantitative and qualitative errors inherent in high angle measurements.[15] Serial measurements of aortic blood velocity variables and growth indices were made until delivery took place.

The clinicians were not informed of the results of the Doppler studies. Thus intervention was carried out on the basis of traditional criteria of a halt of fetal growth as measured by ultrasound biometry, or the recording of an abnormal cardiotocogram, or deterioration in the maternal condition.

The neonatal histories were reviewed independently by HG, who was unaware of the blood velocity assessments of individual fetuses. Special note was taken of the following: birth weight; sex; Apgar scores at one and five minutes; initial axillary temperature; arterial or capillary blood pH; base excess and packed cell volume; use of umbilical arterial or venous catheters; age at introduction of enteral feeding; occurrence of respiratory disorders and need for ventilatory support; and presence of thrombocytopenia (platelet count $<60\times10^9$/l), polycythaemia (packed cell volume >0·60), and coagulation problems manifested by bleeding after capillary puncture that was difficult to control and associated with prolonged prothrombin and partial thromboplastin times. Additional evidence of other neonatal problems was recorded including renal failure, oedema, and necrotising enterocolitis, defined as abdominal distension, blood in the stool, and pneumatosis intestinalis or perforation seen in the abdominal radiograph.

Statistical testing was by either Student's *t* test or Fisher's exact probability test (two sided), as appropriate. Results are given as means and standard deviation (SD).

Results

ALL PATIENTS

There was a total of 53 fetuses with discernible aortic end diastolic frequencies and 29 fetuses without. These two groups were similar in all characteristics other than gestational age at delivery and birth weight. Not only were the infants who had absent end diastolic frequencies in utero significantly more premature at delivery (32·1 (3·5) *v* 36·5 (3·4) weeks; $p<0·001$) but their birth weights (1173 (543) *v* 2062 (544) g; $p<0·001$) and birthweight ratios (73·7 (7·8) *v* 58·4 (11·8); $p<0·001$) were also significantly reduced. Therefore, though the absence of end diastolic frequencies indicated a greater predisposition towards intrauterine growth retardation than when they were present, a comparison of both obstetric and neonatal features between the two groups was precluded by the discrepancy in both gestational age and size at birth. To overcome this an upper weight limit of 2000 g was taken. In this way two groups were derived which had similar numbers, maternal characteristics, and gestational ages. These two groups were used to assess the prognostic potential of aortic blood flow velocity waveform analysis.

BABIES LESS THAN 2000 G

Waveform analysis

There were 26 fetuses with end diastolic frequencies absent (group 1) and 20 with end diastolic frequencies present (group 2). Fetuses in group 1 had significantly reduced aortic peak systolic and mean velocities and significantly increased values of qualitative variables (table I).

TABLE I—*Waveform analysis. Values are means (SD in parentheses)*

	Group 1 (end diastolic frequencies absent; n=26)	Group 2 (end diastolic frequencies present; (n=20)
Measurement to delivery interval (days)	1·96	3·30
Aortic blood velocity (cm/s)	18·3 (4·8)	29·0 (8·2)***
Peak aortic blood velocity (cm/s)	81·0 (17·0)	100·0 (21·0)**
A/B ratio aorta flow velocity waveform	14·7 (5·1)	7·8 (2·2)***
Resistance index aorta flow velocity waveform	0·92 (0·03)	0·86 (0·04)***
Pulsatility index aorta flow velocity waveform	2·41 (0·32)	1·99 (0·31)***

** $p<0·01$. *** $p<0·001$.

Maternal characteristics

There were no significant differences between the two groups in either maternal characteristics or maternal complications of pregnancy (table II). The same number of mothers in each group (eight) had received dexamethasone before delivery.

Fetal and neonatal characteristics

There was a significantly increased incidence of asymmetrical intrauterine growth retardation in group 1, and oligohydramnios was also more frequently associated with these pregnancies, though the trend was not significant (table II). Decelerations were seen in 17 (65%) of the antepartum cardiotocograms recorded from group 1 fetuses, prompting caesarean section in all these cases. The same phenomenon was seen in only 3 (15%) of the group 2 fetuses, a highly significant difference. Gestational age at delivery was not significantly different between the two groups, though the mean in group 1 was 1·3 weeks less than that in group 2 (table III). Birth weight and birthweight ratio were highly significantly reduced in those fetuses with absent end diastolic frequencies. We noted an increased number of neonates in group 1 with depressed Apgar scores at both one and five minutes, though this did not reach statistical significance. Despite these adverse features, blood pH, base excess, packed cell volume, and initial

TABLE II—*Maternal characteristics and complications of pregnancy. Except where stated otherwise, figures are numbers (percentages) of patients*

	Group 1 (n=26)	Group 2 (n=20)
Maternal characteristics		
Mean maternal age in years (SD)	24·8 (5·0)	25·4 (5·2)
Mean maternal height in cm (SD)	161 (6)	159 (6)
Mean maternal weight in kg (SD)	55 (7)	62 (17)
Nulliparous	15 (58)	15 (75)
Single	12 (46)	7 (35)
Smokers	8 (31)	4 (20)
White	18 (69)	18 (90)
Pregnancy complications		
No maternal disease	16 (2)	14 (70)
Pregnancy induced hypertension	6 (23)	5 (25)
Chronic hypertension	4 (15)	1 (5)
Oligohydramnios	9 (35)	3 (15)
Abnormal antepartum cardiotocogram prompting lower segment caesarean section	17 (65)	3 (15)***

***p<0·001.

TABLE III—*Characteristics of neonate. Except where stated otherwise, values are means (SD in parentheses)*

	Group 1 (n=26)	Group 2 (n=20)
Gestation at delivery (weeks)	31·8 (2·9)	33·1 (2·6)
Birth weight (g)	1045 (394)	1465 (338)***
Birthweight ratio	0·57 (0·12)	0·71 (0·09)***
No (%) with birth weight <5th centile	23 (88)	7 (35)***
No (%) with asymmetrical intrauterine growth retardation	23 (88)	9 (45)**†
Sex (M:F)	14:12	10:10
Initial temperature (°C)	36·0 (0·85)	36·1 (0·51)
No (%) with Apgar score <6 at:		
1 minute	17 (65)	10 (50)
5 minutes	7 (27)	1 (5)
Initial pH	7·287 (0·16)	7·264 (0·16)
Initial base deficit (mmol(mEq)/l)	7·5 (5·8)	7·9 (6·8)
Packed cell volume	0·56 (0·085)	0·55 (0·062)

**†p<0·005. ***p<0·001.

axillary temperature were similar in the two groups. The sex ratio was also similar.

There were seven deaths in the neonatal period in group 1 plus two further, late deaths (table IV). The early deaths were due to pulmonary haemorrhage (one case), pulmonary infection (one), pulmonary haemorrhage and renal failure (one), intraventricular haemorrhage and pneumothorax (one), bronchopulmonary dysplasia (one), and necrotising enterocolitis (two). The late deaths were due to hepatoblastoma in one case and unknown aetiology in the second. All these deaths occurred in infants weighing less than 1000 g at birth. The only death in group 2 was due to severe respiratory distress and pulmonary interstitial emphysema in an infant weighing 950 g. Though there was a trend towards more frequent neonatal death in group 1, this was not statistically significant. Combining all deaths in the two groups resulted in a significant difference, but this should be interpreted with caution owing to the nature of the two late deaths in group 1.

There were seven definite cases of necrotising enterocolitis (table IV), all occurring in group 1. In five instances pneumatosis intestinalis was recognisable on abdominal radiography, and in two other cases a perforation had occurred with free gas visible in the peritoneal cavity. One further probable case of necrotising enterocolitis showed distended, featureless loops of bowel but no pneumatosis and was not therefore included for statistical analysis as a case of necrotising enterocolitis. In five of the seven cases an umbilical arterial catheter was inserted for blood sampling. None of the infants had umbilical venous catheterisation. Four of the remaining babies in group 1 had umbilical arterial catheters, five having venous catheters. Of the babies in group 2, three had indwelling arterial catheters. None had umbilical venous catheterisation. Similar proportions of neonates in groups 1 and 2 began enteral feeding within two days. None of the group with necrotising enterocolitis had polycythaemia, but two infants were noted as having initial hypothermia within the first hour after birth. The mean age at onset was 21 days. Six of the babies with necrotising enterocolitis weighed less than 1000 g at birth and had preceding or coexisting respiratory problems. Three of the infants with necrotising enterocolitis died, two as a direct result of this condition.

TABLE IV—*Neonatal outcome. Figures are numbers (percentages) of patients*

	Group 1 (n=26)	Group 2 (n=20)
Total deaths in first year	9 (35)	1 (5)*
Neonatal deaths	7 (27)	1 (5)
Necrotising enterocolitis	7 (27)	0**
Respiratory distress syndrome	11 (42)	5 (25)
Thrombocytopenia	8 (31)	3 (15)
Coagulation disorder (normal platelet count)	3 (12)	0
Pulmonary, gastrointestinal, and intraventricular haemorrhage	6 (23)	0*
Renal failure	2 (8)	0
Patent ductus arteriosus	2 (8)	2 (10)
None of the above complications	4 (15)	15 (75)***

*p<0·05. **p<0·01. ***p<0·001.

Eleven of the infants in group 1 and five in group 2 had the respiratory distress syndrome, all needing increased fractional inspired oxygen and most needing ventilatory support. Two infants in each group had a patent ductus arteriosus. Thrombocytopenia occurred more commonly in group 1. Severe haemorrhage (including peritoneal haemorrhage, pulmonary haemorrhage, or intraventricular haemorrhage), peripheral oedema, and severe renal failure were seen only in group 1.

We tried to assess whether the duration of absent end diastolic frequencies or the severity of the condition might predict an even poorer neonatal outcome. With many fetuses in this group already having absent end diastolic frequencies when first seen the actual duration of the phenomenon in the individual fetus was unknown. We arbitrarily extracted those cases with known absence of end diastolic frequencies for more than 14 days (n=13) and found a neonatal death rate of 54% (seven cases) and a rate of necrotising enterocolitis of 31% (four). There was no significant difference between the gestational ages of this subgroup and the remaining cases in group 1.

Increased severity was defined as loss of end diastolic frequencies for more than 30% of the cardiac cycle. There were nine such infants, among whom 5 (56%) died in the neonatal period, one further infant having renal failure, one suffering necrotising enterocolitis, and only two neonates having an uncomplicated course. Hence both increased duration of fetal life with absent end diastolic frequencies and an increased proportion of the cardiac cycle without frequencies seemed to be associated with a poorer prognosis.

Other clinical variables were used in an attempt to predict neonatal death and necrotising enterocolitis in the study cases but neither an abnormal cardiotocogram, nor oligohydramnios, nor a predicted birth weight of less than the 5th centile, nor asymmetrical intrauterine growth retardation proved as sensitive as the finding of absent end diastolic frequencies in the fetal aorta.

Discussion

Though caution should be exercised when results in animals are extrapolated to man, they may provide clues for the pathological basis of our findings. Studies in sheep and primates have shown a pronounced redistribution of fetal blood flow in response to acute and chronic asphyxia.[10,11] Selective vasoconstriction—probably mediated in the main by α adrenergic innervation[18]—results in a decreased blood flow to lungs, intestines, kidneys, skin, and muscle. The cerebral, myocardial, and adrenal blood supply is increased, the placental circulation being maintained until the onset of a more severe degree of hypoxia. If we postulate that a similar mechanism is operative in the human fetus our findings can more readily be interpreted.

Not only were the babies in group 1 more severely growth retarded but, in addition, this was often asymmetrical and associated with oligohydramnios and abnormal cardiotocogram recordings. That the neonatal acid base state was not severely abnormal in either group, however, suggests that traditional management had resulted in the timely delivery of all babies. Nevertheless, the circulatory redistribution associated with absent end diastolic frequencies, albeit a protective response, may have caused irreversible tissue damage in those in whom it was severe or prolonged. The increased mortality and morbidity in these neonates may be understood to be a consequence of this mechanism.

Evidence of reduced end diastolic frequencies in group 1 is a plausible explanation for the disproportionate number of babies with necrotising enterocolitis. This condition has been thought to be predisposed to by hypoxia and ischaemia,[19] and the splanchnic circulation is particularly affected by the resulting redistribution of blood flow. The presence of hypothermia in two cases, of the respiratory distress syndrome in five cases, and of an umbilical

arterial catheter in five may have further predisposed these infants to the development of necrotising enterocolitis.[20]

A consequence of reduced blood flow to the lungs is reduced production of surfactant.[21] Hypoxia also predisposes to pulmonary vasoconstriction[22] and failure to absorb lung liquid. This might account for the greater number of cases of respiratory disease seen in babies in group 1, with the associated complications of interstitial emphysema, pneumothorax, patent ductus arteriosus, and intraventricular haemorrhage. Similarly, reduction of blood flow and resultant hypoxia in a number of fetal tissues might explain the findings of thrombocytopenia, coagulopathy, and bleeding, which are recognisable components of disseminated intravascular coagulation—a known consequence of hypoxia.[23] Curtailed blood flow to skin, muscle, and kidneys and consequent hypoxic damage would account for the severe peripheral oedema and renal failure seen in two babies in group 1.

Traditional criteria for assessing fetal health correlate well with asphyxia and therefore by definition alert the physician to severe compromise that is already present. The results of such an approach in our cases shows the need to devise other methods which would allow earlier diagnosis of critical fetal compromise before irreversible damage occurs. The assessment of fetal blood flow might form the basis of such a method. Though these blood flow findings are evident as much as three weeks in advance of an abnormal cardiotocogram, and the persistence of this phenomenon heralds a poorer outcome, the time scale of these events has not been clearly elucidated. When deciding the optimal time for delivery of such a compromised fetus a fine balance must be struck between the risks of prematurity and the sequelae of the circulatory effects described above. More detailed studies of the evolution and momentum of these changes in waveform pattern and possibly the use of additional techniques such as ultrasound guided fetal blood sampling[24] are likely to advance our management of these high risk pregnancies.

We acknowledge the support of the Rank Foundation, Action Research for the Crippled Child, and Birthright.

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(Accepted 1 September 1986)

Snoring as a risk factor for ischaemic heart disease and stroke in men

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Abstract

The association of snoring with ischaemic heart disease and stroke was studied prospectively in 4388 men aged 40-69. The men were asked, in a questionnaire sent to them, whether they snored habitually, frequently, occasionally, or never. Hospital records and death certificates were checked for the next three years to establish how many of the men developed ischaemic heart disease or stroke: the numbers were 149 and 42, respectively. Three categories of snoring were used for analysis: habitual and frequent snorers (n=1294), occasional snorers (n=2614), and non-snorers (n=480). The age adjusted relative risk of ischaemic heart disease between habitual plus frequent snorers and non-snorers was 1·91 ($p<0·01$) and for ischaemic heart disease or stroke, or both, 2·38 ($p<0·001$). There were no cases of stroke among the non-snorers. Adjustment for age, body mass index, history of hypertension, smoking, and alcohol use did not significantly decrease the relative risks, which were 1·71 ($p>0·05$) for ischaemic heart disease and 2·08 ($p<0·01$) for ischaemic heart disease and stroke combined. At the beginning of follow up in 1981, 462 men reported a history of angina pectoris or myocardial infarction. For them the relative risk of ischaemic heart disease between habitual plus frequent snorers and non-snorers was 1·30 (NS); for men without previous ischaemic heart disease 2·72 ($p<0·05$).

Snoring seems to be a potential determinant of risk of ischaemic heart disease and stroke.

Introduction

Heavy snoring, which is almost always present in obstructive sleep apnoea, seems to be associated with arterial hypertension.[1-6] During sleep patients with apnoea may develop hypoxaemia and hypercapnia in association with increased pulmonary and systemic arterial pressure and increased susceptibility to cardiac arrhythmias.[7-11] The cardiac index decreases during an apnoeic episode and increases appreciably at the resumption of ventilation.[12] There is