Doppler study of the fetal circulation during long-term maternal hyperoxygenation for severe early onset intrauterine growth retardation

C. M. Bilardo, R. M. Snijders, S. Campbell and K. H. Nicolaides

Harris Birthright Research Centre for Fetal Medicine, King's College Hospital, London, UK

ABSTRACT

In 21 severely growth-retarded, hypoxemic fetuses at 22–30 weeks' gestation, the effect of long-term maternal hyperoxygenation on serial Doppler measurements of the fetal descending thoracic aorta mean velocity (V_m), common carotid artery pulsatility index (PI) and umbilical artery PI was investigated. The treatment was continued on average for 4 weeks and delivery, at 26–34 weeks, was decided for fetal or maternal indications. In the subgroup of 12 fetuses that survived, the mean aortic V_m increased within 72 h of maternal hyperoxygenation. This increase continued for 1–8 weeks, after which there was a decrease to pretreatment values. In the subgroup of neonatal deaths (n = 5), there was a non-significant increase in mean aortic V_m. In the subgroup of intrauterine deaths (n = 4), there was a non-significant trend for continuing deterioration in mean aortic V_m throughout the period of maternal hyperoxygenation. The mean carotid PI did not change significantly in any of the subgroups during maternal hyperoxygenation. However, in the subgroup that survived there was a tendency for improvement and in the subgroup of intrauterine deaths a tendency for deterioration. The mean umbilical artery PI did not change significantly in any of the groups or subgroups during maternal hyperoxygenation. Therefore, measurement of aortic V_m is a useful indicator of fetal response to maternal hyperoxygenation and its increase constitutes a favorable prognostic factor.

INTRODUCTION

Intrauterine growth retardation in the presence of impaired uteroplacental or fetoplacental circulations is associated with fetal hypoxemia and acidemia[1,2]. Further-more, there is an associated redistribution in fetal blood flow in favor of the brain and at the expense of the viscera and musculoskeletal system[3,4]. These hemodynamic adjustments can be detected by Doppler studies of the fetal circulation[2,5]. The best indices reflecting this redistribution in fetal hypoxemia are a decreased blood velocity in the fetal descending thoracic aorta and a decreased impedance to flow in the fetal common carotid artery[5].

In some hypoxemic growth-retarded fetuses, maternal hyperoxygenation is associated with return of fetal blood oxygen pressure (pO_2) to within the normal range and with increased blood velocity in the fetal aorta[6]. This study examines the role of Doppler studies in monitoring the fetal hemodynamic response to prolonged maternal hyperoxygenation and the relationship between this response and fetal outcome.

PATIENTS AND METHODS

During a 5-year period (September 1985–December 1990), 407 patients with severely small-for-gestational-age fetuses were referred to our unit at 17–39 weeks' gestation for cordocentesis to determine fetal karyotype and blood gases[7].

The fetal karyotype was abnormal in 73 (18%) and normal in 334 of the cases. In the chromosomally normal group, the umbilical venous or umbilical arterial blood pO_2 was within the 90% confidence intervals of the appropriate reference range for gestation in 90 fetuses and below the 5th percentile in 244 cases. The parents of the chromosomally normal but hypoxemic fetuses were counselled extensively as to the available options depend-

ing on gestational age, estimated fetal size and degree of fetal hypoxemia, and the following decisions were made:

(1) Delivery within 24–48 h of cordocentesis ($n = 91$);

(2) Elective abortion ($n = 15$);

(3) Expectant management ($n = 103$);

(4) Maternal hyperoxygenation ($n = 35$).

In 21 of the group of 35 fetuses managed by maternal hyperoxygenation, serial measurements of the time-averaged, intensity-weighted mean blood velocity (V_m) in the fetal descending thoracic aorta were performed by Doppler ultrasound; additionally, in 18 of the cases, the pulsatility index (PI) in the fetal common carotid artery was measured. The mothers were hospitalized, rested in bed and given humidified oxygen to breath via an MC face mask at the rate of 8 l/min (delivering about 55% of oxygen) continuously, apart from the daily needs of hygiene and alimentation. The Doppler studies were performed twice a week without discontinuing the oxygen administration to the mother. In two of the 35 patients undergoing hyperoxygenation, but none of the 21 who had Doppler studies, therapy was interrupted for 2 days because of maternal hyperemesis. There were no other maternal complications.

The first Doppler measurements were performed immediately before cordocentesis. With the patients in a semi-recumbent position, flow velocity waveforms were recorded by a pulsed Doppler duplex scanner (Kranzbühler 8130, Berlin, West Germany) from the maternal uterine arteries, from the umbilical artery and from the fetal descending thoracic aorta and common carotid artery, as previously described[2,5]. The high-pass

filter was set at 150 Hz. All recordings were taken in the absence of fetal body or chest movements. For the uterine arteries, the resistance index (RI) was measured and the presence of a diastolic notch was noted. For the umbilical artery the pulsatility index (PI) was measured and the presence of end-diastolic frequencies noted[8]. The fetal aortic V_m and common carotid artery PI were calculated[5].

The results were not disclosed to the clinicians managing the patients and delivery was undertaken for maternal or fetal indications.

Statistical analysis

In each case fetal biometry, blood gases and Doppler results were expressed as the number of standard deviations (SDs) by which the measured values differed from the appropriate normal mean for gestation (Δ value)[1,2,9]. Friedman's analysis of variance and Page's trend test were used to compare four series of Doppler measurements: (A) the measurement taken immediately before cordocentesis; (B) at 24–72 h after the onset of maternal hyperoxygenation; (C) representing the mean value of all measurements obtained during the period of maternal hyperoxygenation (excluding measurements B and D); and (D) taken within 3 days before delivery. The Wilcoxon rank sum test was then used to compare these four groups of measurements for different pregnancy outcome groups.
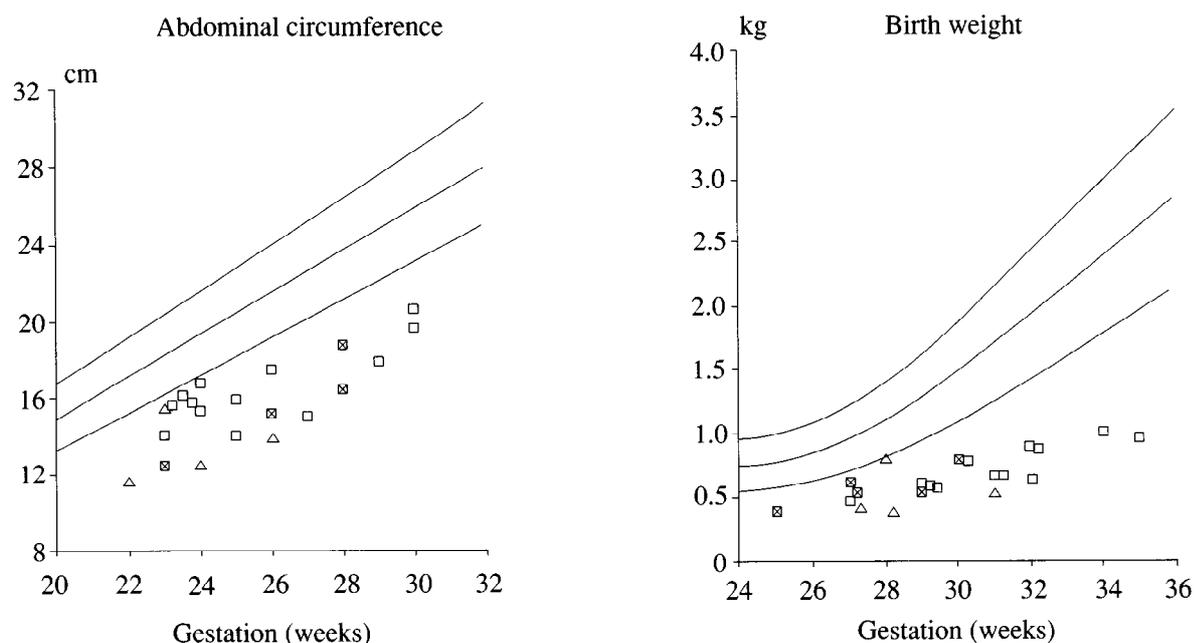

Figure 1 Fetal abdominal circumference at presentation and birth weight in 21 severely growth-retarded fetuses treated with maternal hyperoxygenation, plotted on the reference ranges (mean, 95th and 5th percentiles) for gestation. There were four intrauterine ($\triangle$) and five neonatal ($\boxtimes$) deaths; 12 babies survived ($\square$)
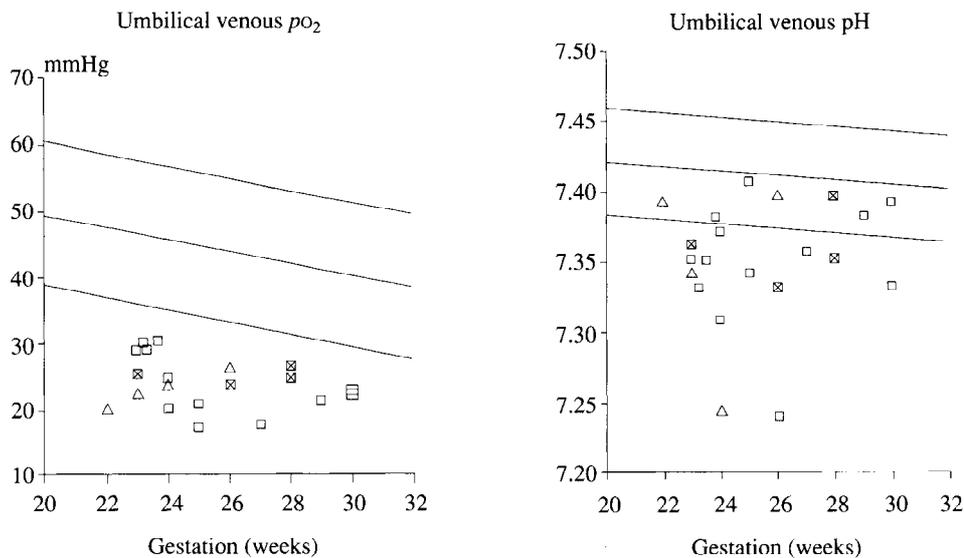
Figure 2 Umbilical venous blood pO_2 and pH in 21 severely growth-retarded fetuses treated with maternal hyperoxygenation, plotted on the reference ranges (mean, 95th and 5th percentiles) for gestation. Subsequently, there were four intrauterine (△) and five neonatal (⊠) deaths; 12 babies survived (□)
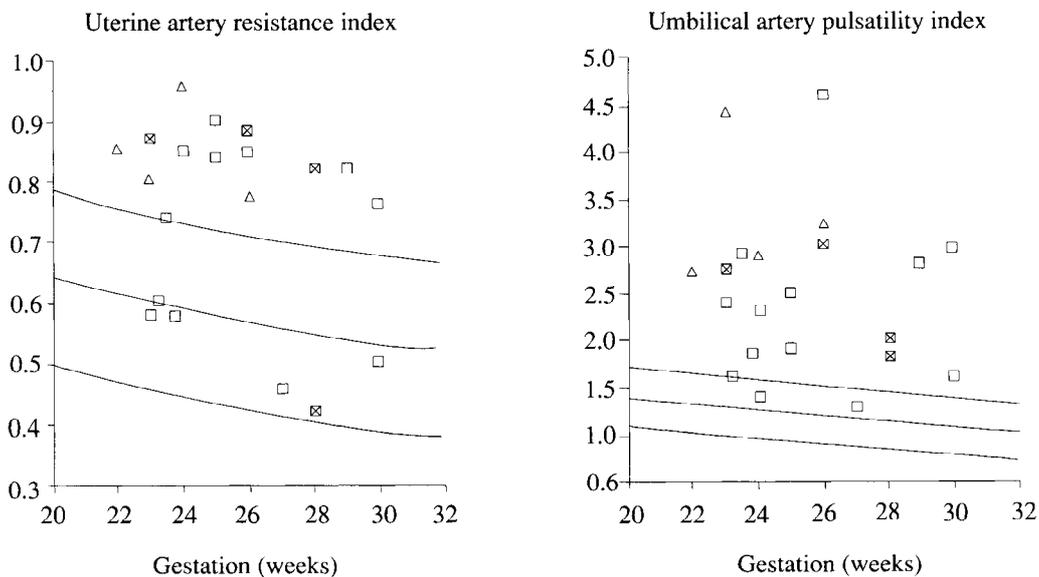
Figure 3 The highest uterine artery resistance index (RI; left) and umbilical artery pulsatility index (PI; right) in 21 severely growth-retarded fetuses treated with maternal hyperoxygenation, plotted on the reference ranges (mean, 95th and 5th percentiles) for gestation. Subsequently, there were four intrauterine (△) and five neonatal (⊠) deaths; 12 babies survived (□)

RESULTS

In the 21 cases treated with maternal hyperoxygenation, the mean gestational age at cordocentesis was 25 weeks (range 22–30 weeks). In all cases the fetal abdominal circumference was below the 5th percentile of our reference range for gestation (Figure 1). The umbilical venous blood pO_2 was below the 5th percentile in all cases, and 14 of the fetuses were acidemic (Figure 2).

In 16 of the 21 cases, the highest uterine artery RI was above the 95th percentile (Figure 3), and in 18 of the cases there was an early diastolic notch in the waveform from this vessel. The umbilical artery PI was above the 95th percentile in 19 cases; in 16 of the cases there was absence of frequencies at the end of diastole in the waveform from this vessel, and in an additional two cases

there was reversed flow (Figure 3). The fetal aortic V_m was below the 5th percentile in 17 cases (Figure 4), and the fetal carotid PI was below the 5th percentile in 15 of the 18 cases in which it was measured (Figure 4).

There were four intrauterine deaths after 3–5 (mean 4) weeks of maternal hyperoxygenation (gestation at death 27–31 weeks); although there was cardiotocographic evidence of fetal distress, delivery was not undertaken because the degree of growth retardation was considered to be too severe for postnatal survival. In the remaining 17 cases, delivery by Cesarean section was performed at 26–35 (mean 30) weeks' gestation and after 1–9 (mean 4) weeks of maternal hyperoxygenation. The indications for delivery were antepartum hemorrhage ($n = 3$), severe proteinuric pregnancy-induced hypertension ($n = 4$), and decelerative fetal heart rate pattern
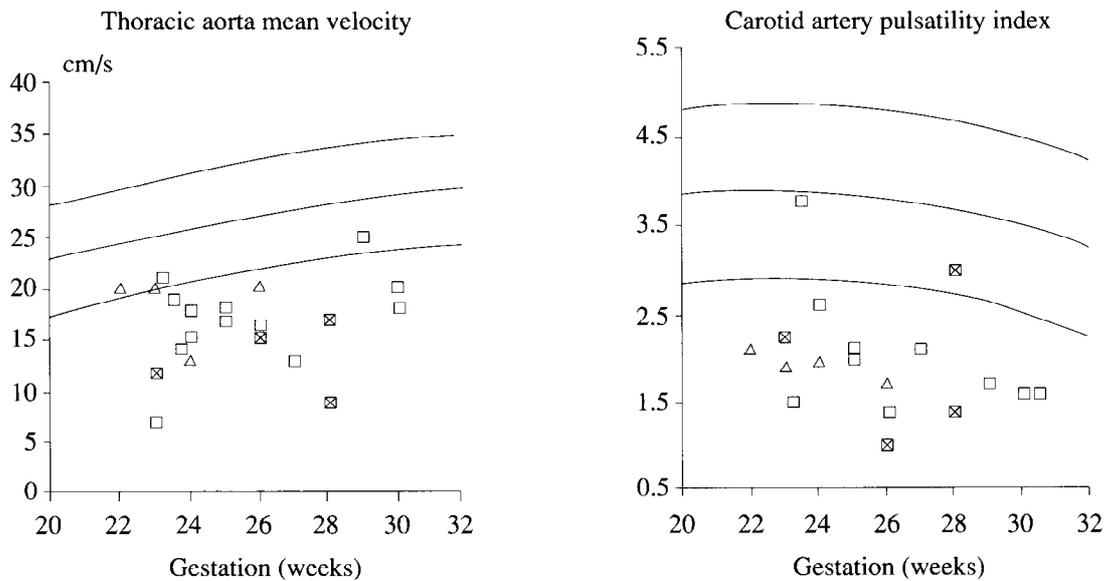
Figure 4 Fetal aortic time-averaged, intensity-weighted mean blood velocity (V_m; left) and carotid artery pulsatility index (PI; right) in 21 severely growth-retarded fetuses treated with maternal hyperoxygenation, plotted on the reference ranges (mean, 95th and 5th percentiles) for gestation. Subsequently, there were four intrauterine (ᴧ) and five neonatal (⊠) deaths; 12 babies survived (□)

Table 1 Standard deviation scores (Δ) for abdominal circumference, umbilical venous pO_2, pH, umbilical artery pulsatility index (PI), time-average, intensity-weighted aortic mean blood velocity (V_m) and common carotid PI in the group of fetuses that survived and those that either died *in utero* or in the neonatal period

	Survivors		Neonatal death		Intrauterine death	
	Median	Range	Median	Range	Median	Range
Gestation (weeks)	24 ± 3	23 30	25 ± 6	23 28	23 ± 4	22 26
Δ abdominal circumference	−4.8	−8.0 −1.9	−5.5	−7.7 −4.1	−6.6	−8.1 −2.1
Δ pO_2	−2.5	−3.7 −2.0	−2.4	−2.7 −1.7	−2.7	−4.3 −2.0
Δ pH	−2.5	−4.7 −0.3	−2.5	−6.6 −0.7	−2.1	−6.6 −0.8
Δ umbilical PI	4.5	0.5 10.0	7.8	3.5 18.6	8.2	5.0 10.9
Δ aortic V_m	−2.9	−5.2 −1.3	−3.3	−5.8 −3.3	−1.9	−3.8 −1.3
Δ carotid PI	−3.5	−4.0 −0.1	−4.0	−4.8 −1.3	−3.3	−3.6 −2.9

Table 2 Standard deviation scores (Δ) for umbilical pulsatility index (PI), time-averaged, intensity-weighted aortic mean blood velocity (V_m) and common carotid artery PI at different stages of maternal hyperoxygenation (A = before; B = within 72 h; C = mean over the total period without measurements A, B and D; D = within 3 days of delivery) in the total group of fetuses and in the subgroups of different outcomes

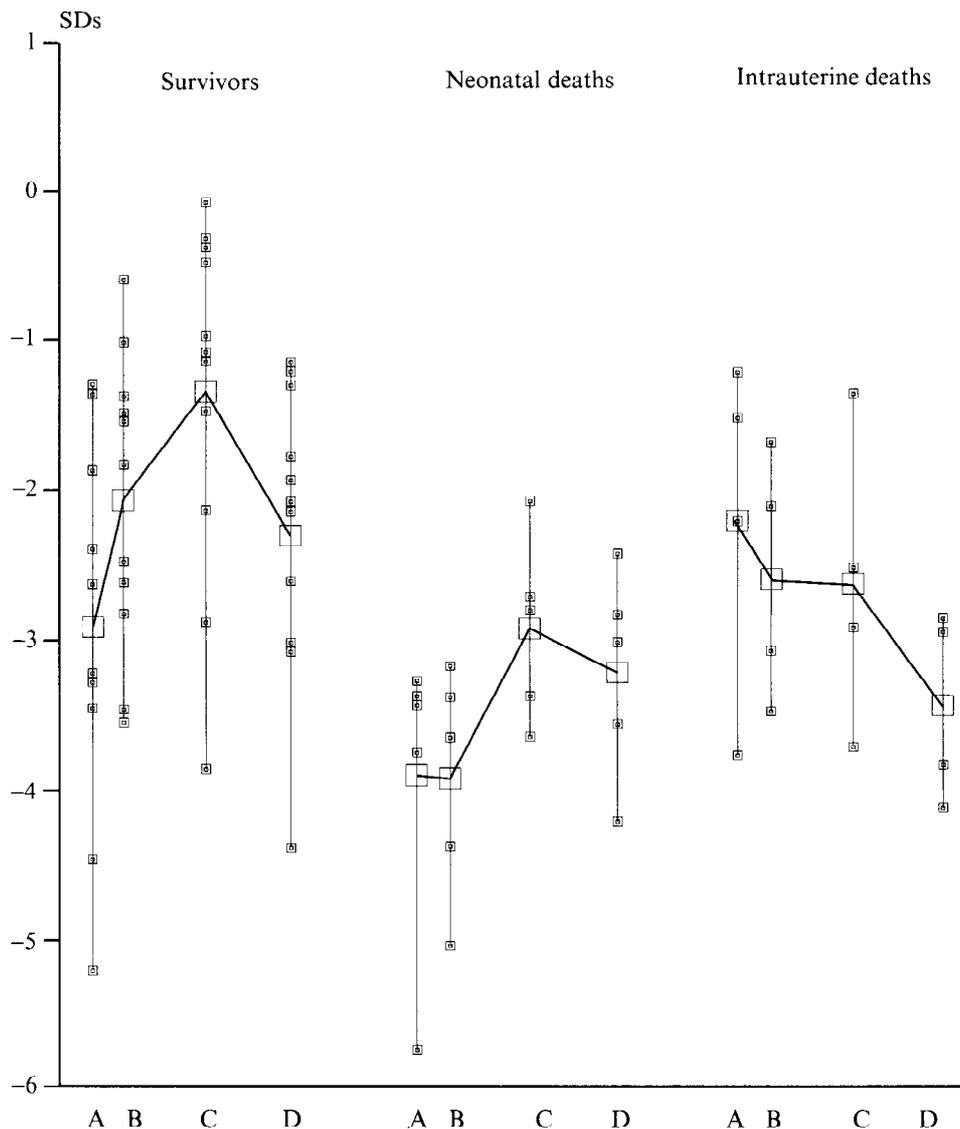|	Mean standard deviation score			
	Total (n = 21)	Survivors (n = 12)	Neonatal death (n = 5)	Intrauterine death (n = 4)
Δ Umbilical artery PI				
A	6.8	4.5	7.8	9.7
B	6.5	5.0	6.7	9.5
C	5.4	4.4	6.5	6.7
D	6.8	6.4	10.3	8.8
Δ Aortic V_m				
A	−3.2	−2.9	−3.5	−1.9
B	−2.6	−2.0	−3.7	−2.6
C	−2.1	−1.1*	−2.8	−2.8
D	−2.9	−2.1*	−3.1	−3.4
Δ Common carotid PI				
A	−3.3	−3.2	−4.0	−3.3
B	−3.2	−3.2	−3.1	−3.3
C	−2.8	−2.5	−3.2	−3.2
D	−3.2	−2.8	−3.2	−3.9*

*significant change; $p < 0.05$

Figure 5 Changes in fetal aortic time-averaged, intensity-weighted mean blood velocity (V_m) during maternal hyperoxygenation in the three outcome groups. In the subgroup of 12 fetuses that survived, the mean aortic V_m increased significantly within 72 h of maternal hyperoxygenation and this increase was maintained for 1–8 weeks before decreasing to pretreatment values. In the subgroup of neonatal deaths there was a non-significant increase in mean aortic V_m. In the subgroup of intrauterine deaths there was a non-significant trend for continuing deterioration

($n = 10$). Five infants died in the neonatal period and 12 are alive and now, at 1–4 years old, they are developing normally. The gestation at delivery and birth weight are shown in Figure 1.

At the time of cordocentesis, there were no significant differences in gestational age, Δ abdominal circumference, ΔpO_2, Δ pH, Δ aortic V_m or Δ umbilical artery and common carotid PI between the group of fetuses that survived and those that either died *in utero* or in the neonatal period (Table 1).

In the subgroup of 12 fetuses that survived, the mean aortic V_m increased significantly for 1–8 weeks, after which there was a decrease to pretreatment values ($Z = 3.09$, $p < 0.01$ and $Z = -2.13$, $p < 0.05$, respectively). In the subgroup of neonatal deaths ($n = 5$), there was a non-significant increase in mean aortic V_m and in the subgroup of intrauterine deaths ($n = 4$), there was a non-significant trend for continuing deterioration in mean aortic V_m throughout the period of maternal

hyperoxygenation (Figure 5, Table 2; $Z = 1.78$, $p < 0.08$ and $Z = -1.74$, $p = 0.08$, respectively). The mean carotid PI and the umbilical artery PI did not change significantly in any of the subgroups (Figures 6 and 7, Table 2). However, in the subgroup that survived there was a tendency for improvement of common carotid PI and in the subgroup of intrauterine deaths a tendency for deterioration ($Z = 1.63$, $p = 0.10$ and $Z = -1.91$, $p = 0.06$, respectively).

After 24–72 h of maternal hyperoxygenation, the aortic V_m increased in 13 cases (Figure 8). In this group of responders there were ten survivors and three deaths (one intrauterine and two neonatal). No change or decreased aortic V_m was observed in eight cases. In this group there were two survivors and six deaths (three intrauterine and three neonatal). An increase in carotid PI was observed in only five of the 18 cases in which it was measured; two infants survived and three died in the neonatal period.
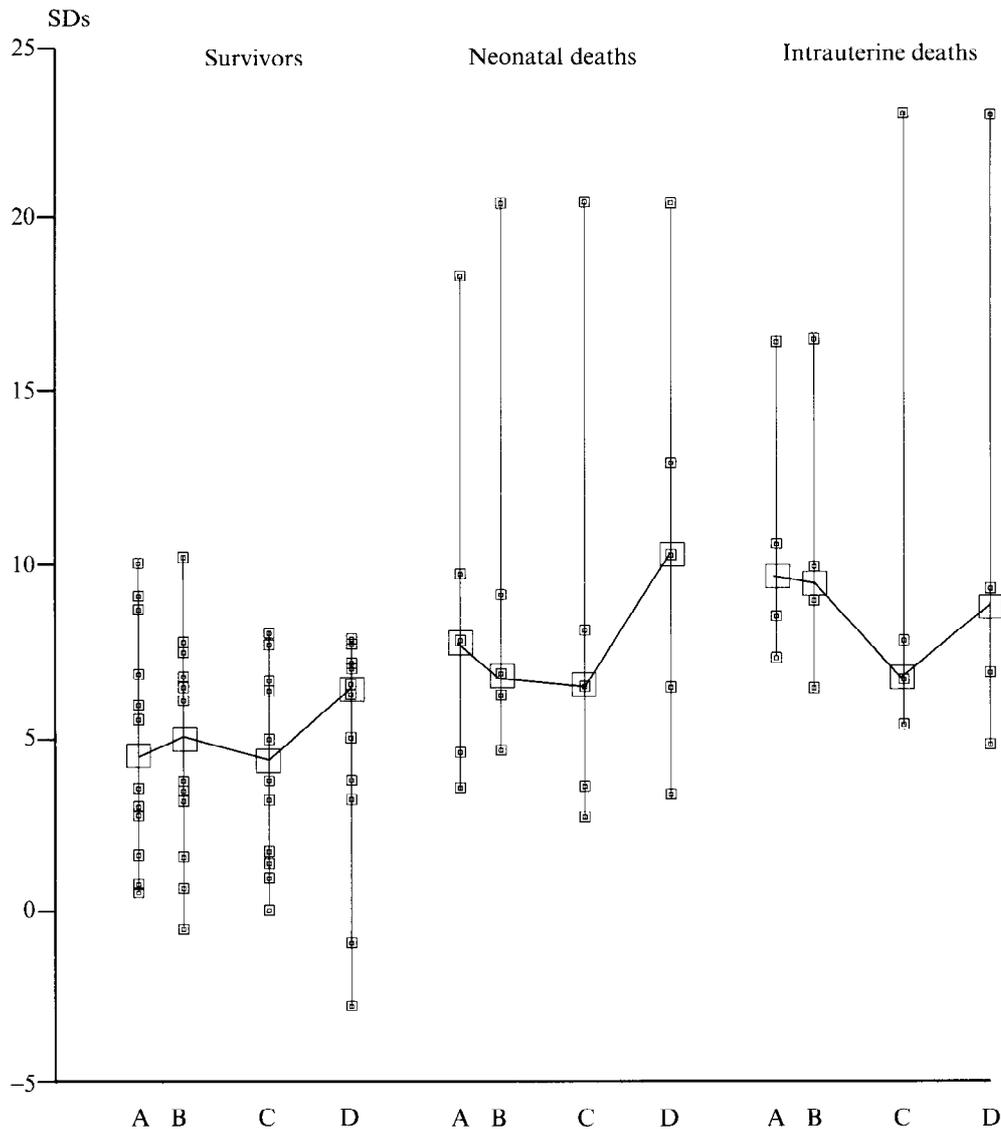
Figure 6 Changes in umbilical artery pulsatility index (PI) during maternal hyperoxygenation in the three outcome groups. The mean umbilical artery PI did not change significantly during maternal hyperoxygenation in any of the three groups. In the two fetuses with highest umbilical PI, there was persistent reversed flow at the end of diastole

DISCUSSION

In this group of hypoxemic, chromosomally normal, severely growth-retarded fetuses, the most likely cause of growth retardation was impaired uteroplacental and/or fetoplacental perfusion, as indicated by the increased impedance to flow in the uterine artery and umbilical artery. It was, therefore, reasonable to assume that, since the most likely cause of fetal hypoxemia was reduced materno–fetal exchange, maternal hyperoxygenation would improve fetal oxygenation. Direct evidence for improved fetal blood gases was provided by cordocentesis[6]. Furthermore, several studies in intrauterine growth retardation have variably demonstrated that short-term maternal hyperoxygenation is associated with increased incidence especially of fetal breathing movements and increased fetal heart rate variation[10,11].

In fetal hypoxemia there is an associated decrease in aortic V_m and carotid PI[2]. These findings have been attributed to chemoreceptor-mediated redistribution in blood flow in favor of the brain and at the expense of the viscera and musculoskeletal system[2–4]. The observed increase in fetal aortic V_m in response to maternal hyperoxygenation can be the consequence of improved fetal oxygenation and reversal of the chemoreceptor-mediated redistribution in fetal circulation. However, the increase in aortic V_m was not accompanied by increased carotid PI. Therefore, an alternative explanation for the observed Doppler changes is improved cardiac oxygenation leading to increased cardiac output and blood velocity in the descending thoracic aorta, without alteration in impedance to flow in the brain. Rizzo et al. have demonstrated that during hyperoxygenation there is a change in the distribution of cardiac output in favor of the right side and therefore in aortic V_m[12].

These findings are in contrast to those of Arduini et al. who examined 22 third-trimester small-for-gestational-age fetuses (mean gestation 32 weeks) with abnormal fetal velocity waveforms in the aorta and internal carotid artery[13]. During 20 min of maternal hyperoxygenation, impedance to flow in the aorta decreased and
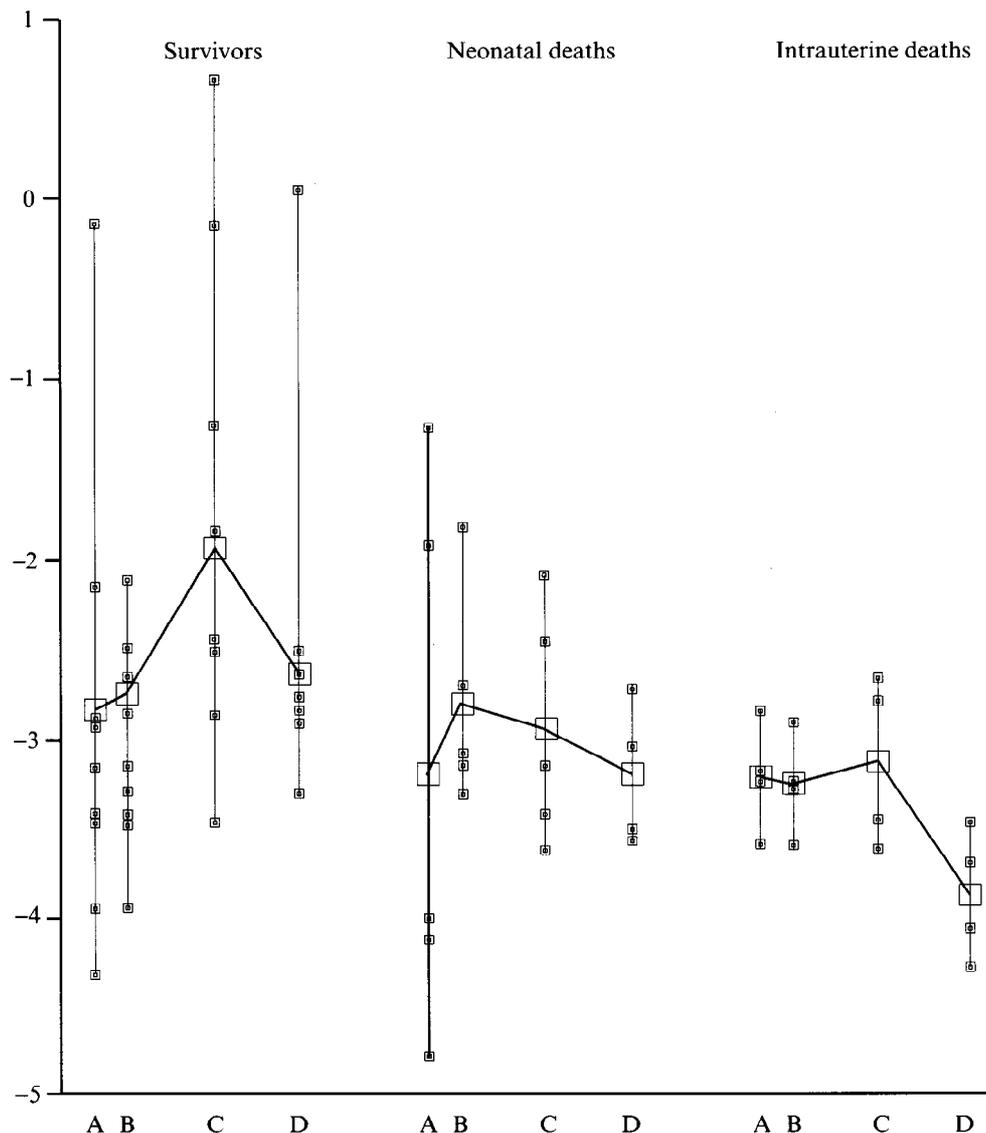
Figure 7 Changes in fetal common carotid artery pulsatility index during maternal hyperoxygenation in the three outcome groups. The mean common carotid PI did not change significantly during maternal hyperoxygenation in any of the three groups. However, in the fetuses that survived, there was a tendency for improvement and in the subgroups of neonatal and intrauterine deaths there was a non-significant trend for continuing deterioration

in the internal carotid increased to normal in 12 of the fetuses; in ten cases there was no hemodynamic response. Subsequently, the non-responders developed acute fetal distress (abnormal fetal heart rate patterns) and were delivered within 3–9 days of the test. In contrast, the responders were delivered 7–28 days (median 18 days) after the test. All infants survived.

In the study of Arduini et al.[13], since the reversal of redistribution was immediate, this is likely to be the consequence of a chemoreceptor-mediated effect. Our fetuses were much younger and more severely growth-retarded and, although their carotid PI was well below the normal range, it did not change significantly in response to maternal hyperoxygenation. These findings suggest that chemoreceptor control of the cardio-vascular system either occurs after 30 weeks' gestation or, if it occurs earlier in normal pregnancy, it is delayed in severe growth retardation. The low carotid PI both before and during maternal hyperoxygenation could be

a consequence of local metabolite-mediated cerebral vasodilation.

Irrespective of the underlying mechanism, the lack of significant effect of maternal hyperoxygenation on fetal carotid PI could be beneficial for the fetus. Hypoxemic growth-retarded fetuses are also hypoglycemic[14]. If the increased cerebral perfusion of hypoxemic fetuses was suppressed during maternal hyperoxygenation, the result would be a decreased supply of glucose and other essential nutrients to the brain.

Long-term maternal hyperoxygenation was associated with three patterns of change in fetal aortic V_m and this was related to outcome. In the group of fetuses that died in utero, the aortic V_m continued to decrease despite maternal hyperoxygenation, presumably because the extreme impairment of placental perfusion did not allow an increased diffusion of oxygen into the fetal circulation or, alternatively, the fetus was already so irreversibly compromised that no response to the increased pO_2 could
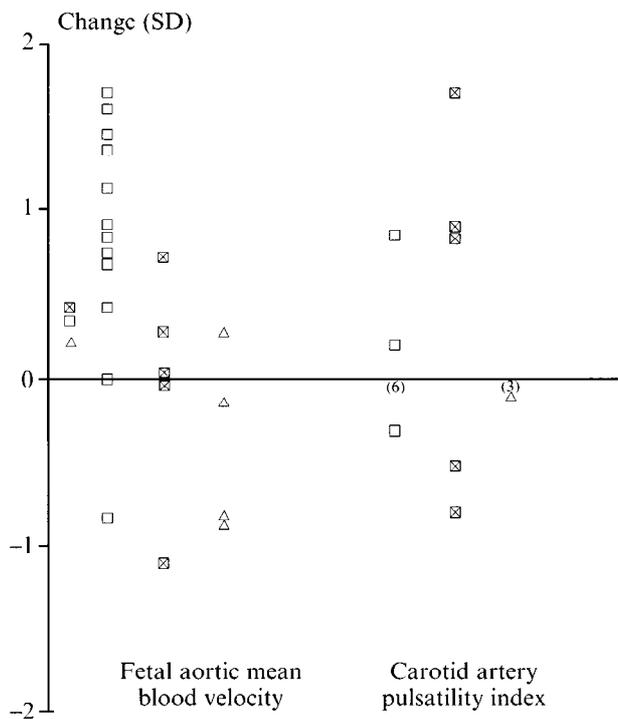
Figure 8 Changes in fetal aortic time-averaged, intensity-weighted mean blood velocity and carotid artery pulsatility index after 24–72 h of maternal hyperoxygenation. The distance of each symbol from the zero line represents the degree change from pretreatment measurements in SDs. In the group where fetal aortic mean blood velocity increased there were ten survivors (□), two neonatal deaths (⊠) and one intrauterine death (△). In contrast, in the group with no change or decrease in fetal aortic mean blood velocity, there were six deaths and only two survivors. Increase in carotid artery pulsatility index was observed in only five of the 18 cases in which it was measured; two infants survived and two died in the neonatal period

take place. Similarly in those babies that died in the neonatal period, maternal hyperoxygenation did not improve fetal oxygenation and there was no significant change in aortic V_m during therapy. Alternatively, in these fetuses a tendency for improved oxygenation was counterbalanced by a trend of worsening placental function; the fetal pO_2 was maintained and the aortic V_m did not change. In the group of fetuses that survived, there was a significant increase in aortic V_m and in some cases improvement was such that delivery could be postponed for several weeks. Indeed, in seven of these cases delivery was undertaken for maternal complications, such as antepartum hemorrhage or worsening hypertension, rather than abnormal fetal heart rate patterns. In the latter group, after an initial temporary increase in aortic V_m, the velocity decreased to pretreatment levels and this was followed by the development of abnormal fetal heart rate patterns which prompted an emergency delivery.

The value of maternal hyperoxygenation for the treatment of severe, early onset, hypoxemic growth retardation remains to be established. Nevertheless, the findings of the present study suggest that lack of improvement in aortic blood velocity within 72 h of maternal hyperoxygenation is associated with a very poor prognosis. In those fetuses that do respond, serial Doppler measurements may be useful in timing delivery.

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