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Human fetal sympathoadrenal responsiveness

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Summary

A reference range of fetal noradrenaline levels related to gestational age was calculated from 27 normal pregnancies between 16 and 36 weeks of gestation. Growth retarded, hypoxic fetuses had significantly elevated noradrenaline levels ($P < 0.01$)

cordocentesis; catecholamines; intrauterine growth retardation; hypoxia.

Introduction

The preterm infant's sympathoadrenal system is responsive immediately prior to birth. Infants, as immature as 26 weeks gestation, delivered either with an acidotic cord pH or asphyxiated as evidenced by a low 5 min Apgar score have elevated catecholamine levels, particularly noradrenaline [3]. It has now become possible to obtain access to the fetal circulation during pregnancy and before the onset of labour by cordocentesis, ultrasound-guided puncture of the umbilical cord [1,6]. The aim of the present study was, by using this technique [6], to establish a normal range of fetal catecholamine levels with respect to gestational age. Results from growth retarded fetuses with hypoxia [7] and anaemic fetuses from red cell isoimmunised pregnancies [8] were then compared to these reference ranges to assess the responsiveness of the fetal sympathoadrenal system.

Patients and Methods

Patients

Control fetal samples were taken from 27 pregnancies at 16—36 weeks of gestation. The indications for cordocentesis were a family history of inherited disease, the

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ultrasonic detection of small fetal structural abnormalities or blood grouping of fetuses because of a high maternal haemolytic antibody titre. All the fetuses were subsequently shown to be haematologically and cytogenetically normal. In all cases the fetuses delivered at term and both their one and five minute Apgar scores were equal to or greater than 8.

Nine samples were obtained from severely growth retarded fetuses at 16—36 weeks. In all cases the fetal PO_2 was at least two standard deviations below the reference range for gestation [4]. The most severely hypoxic (Table I) fetuses were also acidotic (pH < 7.25). Six samples were obtained from anaemic fetuses suffering from rhesus isoimmunisation, immediately prior to intra-uterine transfusion at 27—36 weeks gestation; in all cases the fetal haemoglobin concentration was more than two standard deviations below the normal range for gestation [8].

Ethical permission

Ethical permission for this study was granted by the hospital's ethics committee.

Methods

Fetal blood samples were obtained by cordocentesis of the umbilical vein, which was performed without maternal sedation or fetal paralysis [6]. Blood gas measurements were made at standard temperature using a blood gas analyser. The plasma was then immediately separated for analysis of catecholamine, noradrenaline and adrenaline. This was performed by high pressure liquid chromatography and the lowest value which could be detected was 0.05 nmol/l in a plasma volume of 1 ml [3,5]. Analysis was done blind of the clinical details.

Statistical analysis

To assess the relationship between catecholamine levels and gestational age a Spearman's rank correlation coefficient was calculated from the normal data. The results of the stressed fetuses were then related to the reference range and a z-score calculated. To assess if differences in the results of the stressed and non-stressed fetuses were significant, comparison was made of the catecholamine levels between the two groups using a Wilcoxon Rank Sum test.

Results

Noradrenaline was detected in all infants studied, including the most immature. Adrenaline was detected in only 22 fetuses and only in those more mature than 23 weeks gestation.

In all fetuses, adrenaline levels were lower than noradrenaline and less than 10% of the total catecholamines. Adrenaline levels regardless of diagnosis were less than 1.0 nmol/l and did not correlate with gestational age. There was no significant difference between hypoxic and non-hypoxic fetuses and anaemic and non-anaemic fetuses.

Noradrenaline levels, however, did tend to increase with gestational age, $P <$

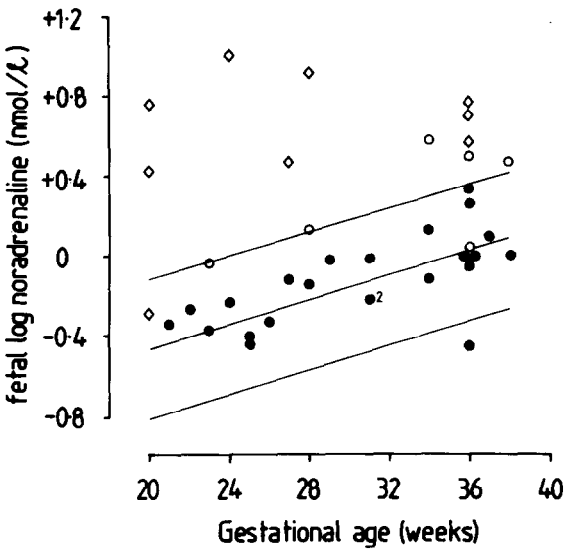

Fig. 1. Noradrenaline (NA) levels related to gestational age. Log NA = −1.28 + 0.038 gestational age, r = 0.69, $P < 0.001$. (The regression line and 95% confidence limits are shown) Individual data points are shown for: ●, non-hypoxic fetuses; □, hypoxic fetuses; ○, anaemic fetuses.

0.001, (Fig. 1). The anaemic fetuses tended to have higher noradrenaline levels (Table I) but this did not reach statistical significance (Fig. 1). The hypoxic fetuses had significantly elevated noradrenaline levels (Table I) (5.75 nmol/l, 0.49—13.29; median and range) when compared to non-hypoxic fetuses (0.78, 0.1—3.0; median

TABLE I

Noradrenaline levels related to fetal pO_2 in the hypoxic fetuses and haemoglobin in the anaemic fetuses (individual data shown).

Hypoxic fetuses (N = 9)		Anaemic fetuses (n = 6)	
Noradrenaline (mmol/l)	Po_2 (mmHg)	Noradrenaline (mmol/l)	Haemoglobin (g/dl)
13.29	10	1.13	6.5
0.53	20	1.39	8.0
5.75	18	3.0	5.5
0.49	21	3.22	6.2
2.64	19	5.3	5.0
12.72	12	3.89	7.0
5.86	16		
8.51	14		
5.03	16		

and range), $P < 0.01$. The median z-score of the hypoxic fetuses was 8.7 (range 0.22 —21.8).

Discussion

The fetal animal adrenaline gland synthesises little or no adrenaline early in gestation and at about 24 weeks' gestation adrenaline accounts for only 14% of the total catecholamine content of the adrenal medulla, the proportion increasing with maturity of the fetus [2]. This study confirms similar findings in the human fetus.

Our results demonstrate for the first time that the human fetus prior to delivery is able to mount a response to stress by a significant increase in the level of noradrenaline. Hypoxia in this series was a more potent stress than anaemia as assessed by the degree of elevation of the noradrenaline levels. We did not measure Po_2 in the control fetuses as none were growth retarded and thus from our previous work [7] we predicted that such fetuses would have Po_2 levels within the normal range. This hypothesis was confirmed by the lack of perinatal problems found in our control group.

Only ten hypoxic infants were studied, thus we did not attempt to correlate the noradrenaline level and fetal Pao_2. Although sampling from the umbilical artery might have given a truer reflection of the exact severity of fetal hypoxia, because of the numbers of patients involved we still would not have attempted a correlation between fetal Pao_2 and noradrenaline levels. The "elevation" of noradrenaline associated with fetal hypoxia was significantly lower than the level achieved in preterm neonates, both at birth in response to asphyxia [3] and in the first few days when actively expiring against positive pressure ventilation [6]. As the fetuses included in our series were of similar gestational ages to the neonates studied [4,6] this poorer response to stress is unlikely to be due to differences in the maturation of the adrenal gland. It may, however, be a reflection that the fetal "stress" studied was of a chronic nature.

Catecholamine levels have been measured previously in preterm infants [3], but until the present study results were only available relating to samples taken during labour or immediately after delivery [3]. The present results, for the first time in the human fetus, indicate sympathoadrenal activity prior to labour. We have also demonstrated that even amongst very immature fetuses even prior to labour, antenatal stress does cause elevation of noradrenaline levels.

References

1 Daffos, F., Capella-Pavlovsky, M. and Forestier, F. (1983): Fetal blood sampling via the umbilical cord using a needle guided by ultrasound. Report of 66 cases. Prenatal Diagn., 3, 271—277.

2 Comline, R.S. and Silver, M. (1975): Development of the activity in the adrenal medulla of the fetus and newborn animal. Br. Med. Bull., 22, 16—20.

3 Greenough, A., Lagercrantz, H., Pool, J. and Dahlin, I. (1987): Plasma catecholamine levels in preterm infants. Acta Paediatr. Scand., 76, 54—59.

4 Greenough, A., Pool, J. and Lagercrantz, H. (1988): Catecholamine and blood pressure levels in paralysed preterm ventilated infants. Early Hum. Dev., 16, 19—24.

5 Hjemdahl, P., Daleskog, M. and Kahan, T., (1979): Determination of plasma catecholamines by high pressure liquid chromatography with electro-chemical detection. Comparison with radioenzymatic methods. Life Sci., 25, 131—140.
6 Nicolaides, K.H., Soothill, P.W., Rodeck, C.H. and Campbell, S. (1986): Ultrasound guided sampling of the umbilical cord and placental blood to assess fetal well being. Lancet, i, 1065—1067.
7 Nicolaides, K.H., Campbell, S. and Bradlley, R.J., (1987): Maternal oxygen therapy for intrauterine growth retardation. Lancet, i, 942—945.
8 Nicolaides, K.H., Soothill, P.W. and Clewell, C.H. (1988): Fetal haemoglobin concentration to assess the severity of red cell isoimmunisation. Lancet, i, 1073—5.