Stress, severity of illness, and outcome in ventilated preterm infants

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Aim—To determine physiological and hormonal stress responses in ventilated preterm infants.

Methods—Physiological and hormonal stress responses were studied in 47 ventilated preterm infants who were judged clinically to require sedation. The correlation between the stress response and severity of illness was examined, and responses were compared between infants with different clinical outcomes.

Results—Stress hormone concentrations were significantly correlated with severity of illness, assessed using the arterial:alveolar oxygen partial pressure ratio. Noradrenaline showed the strongest correlation, with an exponential pattern of increased secretion. Catecholamine concentrations before sedation were significantly higher among infants who subsequently died ($n = 15$, at a median age of 6 days) than among survivors: median noradrenaline 4.31 vs 2.16 nmol/l, median adrenaline 0.69 vs 0.31 nmol/l. The observed fall in noradrenaline with sedation was lower among those who died than survivors (median fall 2% vs 40%).

Conclusion—Preterm infants are capable of hormonal stress responses appropriate for the severity of their illness. Extreme catecholamine responses, in the sickest infants, are associated with the worst outcome.

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The ability of newborn infants to mount hormonal and metabolic stress responses to surgery was demonstrated by Anand and colleagues in the 1980s.^{1,2} Responses vary in direct proportion to the degree of surgical stress.³ Responses to other types of stress have received comparatively little attention, and it is unclear whether Anand's findings can be extrapolated to preterm infants receiving intensive care. Sources of stress for these infants include respiratory disease and recurrent invasive procedures,⁴ yet some appear unable to produce appropriate responses.⁵

Whether the stress response helps or hinders preterm infants receiving intensive care is an important question, as opiate sedation and analgesia have been advocated for ventilated infants, and are effective in lowering stress hormone concentrations.^{6,7} The aim of this study was to investigate the correlation between severity of illness and stress responses in venti-

lated preterm infants, and to compare responses between infants with different clinical outcomes.

Methods

Forty seven preterm infants (26 boys) receiving mechanical ventilation on the neonatal intensive care unit of Nottingham City Hospital were studied. They were of median gestational age 28 weeks (range 24 to 35) and median birthweight (1.14 kg, range 0.52 to 3.05). Twenty three infants were delivered vaginally and 24 by caesarean section, with 36 (77%) mothers having received dexamethasone before delivery. Respiratory distress syndrome was the predominant clinical diagnosis, with 42 (89%) infants treated postnatally with surfactant.

Infants became eligible for inclusion when a decision was made by the clinical team to start sedation, based on the level of ventilatory support required and the infants' perceived distress judged by spontaneous activity and responses to handling (none was receiving muscle relaxants). An indwelling arterial line and no previous opiate treatment were additional entry criteria. The sedation regimen consisted of an intravenous bolus of diamorphine given over 30 minutes via syringe pump, followed by a continuous diamorphine infusion. Twenty five infants were included in a concurrent study comparing physiological and hormonal responses to two different loading doses (in which no significant difference in hormonal responses between dose regimens was found).⁸ Thus 34 infants received a bolus dose of 50 mcg/kg, while 13 received a 200 mcg/kg dose. In all cases the continuous infusion was started at 15 mcg/kg/hour, but was adjusted as required by the clinical team. Physiological variables (heart rate, mean blood pressure, and blood gases), ventilator settings, and plasma cortisol and catecholamine concentrations were measured before loading, and six hours after starting treatment. Blood specimens for hormonal analysis were centrifuged and the separated plasma stored at -25°C .^{9,10}

Severity of illness was assessed using the arterial:alveolar oxygen partial pressure (a:A) ratio.¹² Statistical analysis of data was performed using the Wilcoxon signed rank test for paired data, the Mann-Whitney U test for unpaired data, Spearman's rank correlation coefficient, and the χ^2 test for categorical data. Ethical approval for the study was granted, and written parental consent was obtained for each infant.

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Table 1 Physiological and hormonal data

	Baseline median (range)	6 hours median (range)	Change 0 to 6 hours median (range)	Significance
Mean blood pressure (mm Hg)	35 (23-57)	32 (18-53)	-4 (-15 to +9)	P = 0.0001
Heart rate (bpm)	149 (114-195)	143 (109-197)	-3 (-34 to 70)	P > 0.05
Arterial pH	7.29 (6.86-7.56)	7.29 (7.11-7.51)	-0.01 (-0.15 to +0.42)	P > 0.05
pO ₂ (kPa)	7.9 (3.5-20.0)	7.9 (4.0-15.8)	-0.10 (-10.9 to +7.9)	P > 0.05
pCO ₂ (kPa)	5.4 (2.9-12.8)	5.3 (2.9-8.5)	+0.18 (-7.8 to +2.6)	P > 0.05
Noradrenaline (nmol/l)	2.40 (0.87-14.13)	1.51 (0.63-14.7)	-0.71 (-7.2 to +1.3)	P < 0.0005
Adrenaline (nmol/l)	0.33 (0.11-2.83)	0.19 (0.04-2.91)	-0.11 (-1.5 to +1.8)	P < 0.005
Cortisol (nmol/l)	364 (47-8041)	162 (26-7799)	-96 (-1712 to +2278)	P = 0.005

Results

Sedation was started at a median age of 15 hours (range 3 to 64). Baseline and 6 hour physiological and hormonal data are summarised in table 1. No significant changes in heart rate or blood gases occurred, but a small, significant fall in mean blood pressure was observed. Stress hormone values also showed a significant fall over the six hour period (Wilcoxon signed rank test).

Figure 1 shows the correlation between stress hormone and a:A ratio values, with combined data from baseline and 6 hours displayed for each infant. Data analysis using Spearman's rank correlation coefficient was performed separately on baseline and 6 hour data, yielding a significant negative correlation for noradrenaline at both times: rho = -0.57 and -0.52, (P<0.0005 and <0.005) for 0 and six hours, respectively. For adrenaline the corresponding values were: rho = -0.30 and -0.42 (P=0.05 and <0.01), and for cortisol rho =

-0.33 and -0.30 (P<0.05 and P=0.05). Fifteen infants died, at a median age of 6 days. Contributory factors included intraventricular haemorrhage (grade 3 or worse) in seven, pneumothorax in five, septicaemia in three, patent ductus arteriosus treated with indomethacin in four, and pulmonary haemorrhage in one. Among the survivors the median duration of ventilation was five days. Fifteen infants (47%) developed bronchopulmonary dysplasia (defined as a requirement for supplemental oxygen at 36 weeks postconceptional age), of whom five were subsequently discharged on home oxygen treatment. Two infants developed intraventricular haemorrhage (grade 3 or worse), seven had a pneumothorax, and eight (25%) received treatment with indomethacin for a patent ductus arteriosus.

Birth details and physiological variables before starting treatment with diamorphine were compared between fatalities and survivors

Figure 1 Stress hormone response compared with severity of illness

Figure 2 Baseline stress hormone values and outcome

Table 2 Comparison of infant characteristics: death vs survivors

	Deaths (n=15) median (range)	Survivors (n=32) median (range)	Significance
Gestation (weeks)	26 (24-30)	29 (25-35)	P = 0.0001
Birth weight (kg)	0.84 (0.68-1.72)	1.31 (0.52-3.04)	P < 0.001
Vaginal delivery	10 (67%)	13 (41%)	P > 0.05
Apgar score			
1 minutes	2 (1-9)	5 (1-9)	P < 0.005
5 minutes	6 (1-9)	8 (4-10)	P < 0.005
Age at starting sedation (hours)	15 (3-60)	18 (4-64)	P > 0.05
FIO ₂	0.79 (0.46-1.00)	0.68 (0.22-1.00)	P < 0.05
Arterial pH	7.26 (7.11-7.37)	7.31 (6.86-7.56)	P > 0.05
pO ₂ (kPa)	7.8 (4.4-13.8)	7.95 (3.5-20)	P > 0.05
pCO ₂ (kPa)	5.6 (4.7-8.9)	5.3 (2.9-12.78)	P > 0.05
Heart rate (bpm)	155 (130-195)	142 (114-173)	P < 0.05
Mean blood pressure (mm Hg)	30 (23-40)	37 (27-57)	P = 0.001

(table 2). Infants who died were of significantly lower gestational age and birthweight, with significantly lower Apgar scores and mean blood pressures. Baseline heart rate and inspired oxygen requirements were significantly higher. However, the age at which diamorphine was started and baseline arterial blood gas variables did not differ significantly between groups.

Figure 2 shows baseline stress hormone values for infants who died and survived. Complete data were obtained from 41 infants (87%), with at least one hormone measured in the remaining six infants (three fatalities and three survivors). Plasma catecholamine values were significantly higher among infants who died (median noradrenaline 4.31 *vs* 2.16 nmol/l, $P < 0.05$; median adrenaline 0.69 *vs* 0.31 nmol/l, $P < 0.005$). Plasma cortisol values did not differ significantly between groups (median cortisol 443 *vs* 352 nmol/l, $P = 0.08$, Mann-Whitney U test).

Figure 3 shows changes in noradrenaline concentrations between 0 and 6 hours for

infants in whom paired samples were available for analysis. There was a median fall of 2% among infants who died, compared with a 40% fall among survivors ($P = 0.06$, Mann-Whitney U test). For adrenaline and cortisol the median change (fall) observed was similar for those who died and survivors (adrenaline 22% *vs* 23%, cortisol 35% *vs* 46%).

Discussion

Stress may be defined as an antagonistic state resulting from factors threatening the homeostasis or wellbeing of an organism, and the resistance offered. Although stress responses are generally considered beneficial, stress tolerance can be exceeded, leading to distress.¹² Fetal stress responses to invasive procedures occur from as early as 23 weeks of gestation,¹³ and the existence of a "fetal stress syndrome" has been postulated, with adverse effects on development and brain growth.¹⁴ Supportive evidence comes from animal studies in which glucocorticoids were found to exacerbate hypoxic-ischaemic neuronal damage, with high values associated with damage to the hippocampus.^{15,16} Hormonal stress responses to surgical procedures in neonates are well documented. There is some evidence from such studies that extreme postnatal stress may also be pathological, increasing postoperative morbidity and mortality.¹² Potential sources of stress for the sick preterm infant include respiratory disease, recurrent handling and procedures, and high ambient levels of noise and light.¹⁷ Stress responses in these circumstances are poorly defined and difficult to equate with those associated with, for example, thoracotomy. However, Hughes *et al* reported that unsedated sick preterm infants achieve cortisol values on the fourth to fifth day of life which exceed those seen in response to surgery.¹⁸ Opiates attenuate cortisol and catecholamine responses,^{6,7} but whether this produces therapeutic benefit is currently uncertain.¹⁹

Indications for starting opiate treatment vary between units, but from those stated here it is reasonable to assume that infants in this study were substantially stressed. The a:A ratio was chosen to represent severity of illness because respiratory disease was likely to have been the predominant stress factor at this time. Thirty nine infants (83%) had a:A ratios below 0.22, indicating illness of at least moderate severity,²⁰ and many were extremely unwell (shown by the high rate of complications among survivors). Most infants received surfactant before sedation was begun. Surfactant administration has little immediate effect on catecholamine concentrations.²¹

The ability of some extremely preterm infants to mount stress hormone responses has been questioned.^{5,22} Cortisol and β -endorphin have been studied in the most detail, with infants often simply categorised as well or unwell.²³ The pattern of catecholamine response seen here, with the most extreme responses in the sickest, most premature infants, has not been reported before, as far as we are aware. Noradrenaline correlated most

Figure 3 Noradrenaline response to sedation

strongly with severity of illness. This supports the concept of noradrenaline being a marker of persistent stress, or pain, as proposed by Quinn *et al.*²⁴

The infants who died were of significantly lower gestational age and birthweight. Increased oxygen requirements before sedation suggests that their clinical condition was worse, and this is consistent with the significant increases in heart rate and catecholamine values observed in these infants. Catecholamine secretion can be influenced by mode of delivery, postnatal age, and inotropes.²⁵⁻²⁷ A greater proportion of deaths (although not significant) followed vaginal delivery, which is associated with higher initial catecholamine values, but these fall rapidly after birth.²⁸ Postnatal age was very similar between groups, and the number of infants receiving dopamine was small (two in each group at the time of starting sedation). Cortisol is known to behave in a similar manner to catecholamines in relation to mode of delivery and postnatal age.^{29,30} Reynolds found significantly increased cortisol values among infants with fatal hyaline membrane disease compared with infants with "benign" respiratory distress not requiring ventilation.³¹ In the present study cortisol values were not significantly higher among those who died, perhaps because all infants were ventilated, reducing the clinical difference between groups.

When changes in stress hormone concentrations between 0 and 6 hours were considered, a different pattern was observed between noradrenaline and the other hormones, with a reduced noradrenaline response to sedation among infants who died. This failed to achieve significance, but a striking lack of response was seen in some infants with very high values (fig 3). Persistently high noradrenaline values may therefore be of some prognostic importance.

The question remains as to whether increased stress hormones merely reflect severe underlying illness or whether they are clinically important in the aetiology of adverse outcome. Theoretical grounds exist for believing that extreme stress responses may be harmful.³² Our observations do not resolve, but they do support, this argument. We believe that the careful use of opiate sedation and analgesia in ventilated preterm infants is justified on humanitarian grounds, and the possibility exists that it may also improve outcome.

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