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Hormonal–Metabolic Stress Responses in Neonates Undergoing Cardiac Surgery

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Hormonal and metabolic responses were measured in 15 neonates who underwent repair of complex congenital heart defects during a standardized anesthetic protocol. Four of the 15 neonates died postoperatively in the intensive care unit. Analysis of arterial plasma samples obtained before, during, and 24 h after surgery showed that plasma epinephrine, norepinephrine, cortisol, glucagon, and beta endorphin increased in all patients ($P < 0.05$). Insulin levels increased only at the end of surgery but remained elevated for 24 h postoperatively ($P < 0.02$). Intraoperative metabolic changes were characterized by hyperglycemia and lactic acidemia that persisted postoperatively. This pattern of neonatal stress responses is distinct from and more extreme than that seen in adult cardiac surgical patients. The four neonates who died postoperatively tended to have higher stress responses intra- and postoperatively despite having been indistinguishable from survivors by the usual clinical and hemodynamic criteria. These preliminary results suggest that neonatal hormonal and metabolic responses to cardiac surgical operations in neonates are extreme and are associated with a high hospital mortality rate. (Key words: Anesthesia, pediatric: neonate. Outcome. Hormones: stress response. Surgery, cardiac: neonatal.)

RECENT COMPARATIVE CLINICAL TRIALS have shown a greater incidence of postoperative complications in adult patients with increased hormonal and metabolic responses to major operations.[1,2] Increased morbidity and mortality also have occurred in intensive care patients who have increased stress responses.[3] Previous studies have shown a comparable relationship between increased perioperative stress responses and postoperative complications in newborn infants undergoing noncardiac operations.[4,5] Thus, in both adults and newborn infants, increased hormonal and metabolic responses to major surgery may be directly related to postoperative complications. Anesthetic management can substantially attenuate such intra- and postoperative stress responses, and therapy thus targeted may improve outcome.[1,2,4,5]

Stress and postoperative outcome may be linked most closely in critically ill newborn infants. Sick neonates exist in a precarious metabolic balance, exemplified by frequent and rapid development of metabolic derangements such as hypoglycemia, hyperglycemia, metabolic acidosis, or electrolyte imbalances. The neonatal predisposition to metabolic instability occurs as a result of many factors. These include: 1) adaptation to the extrauterine environment and postnatal nutrition (*i.e.*, the need to maintain temperature, water, and electrolyte homeostasis, and to make metabolic adjustments to alternate feeding and fasting); 2) limited endogenous reserves of carbohydrates, proteins, and fats; 3) the metabolic cost of rapid neonatal growth; and 4) limited functional capabilities of immature organ systems. Catabolic stress responses have been found in neonates undergoing noncardiac operations.[4,5] These catabolic responses may be greater and particularly detrimental for critically ill neonates undergoing the more extreme stresses of cardiac surgery, cardiopulmonary bypass (CPB), and deep hypothermic circulatory arrest (DHCA).

No data in the literature describe the hormonal and metabolic responses of neonates during and after cardiac operations. We have measured hormonal and metabolic stress indicators in 45 neonates prospectively randomized to different anesthetic regimens for cardiac surgery. This study intended to define the impact of different anesthetic techniques on the magnitude and pattern of neonatal stress responses to cardiac operations. We report in this analysis the stress responses in one standardized anesthetic group (15 neonates) with a particularly high hospital mortality (4/15, 27%). This report describes stress responses to cardiac surgery in these high-risk neonates, and particularly in the nonsurvivors, for comparison with adult data.

Materials and Methods

STUDY DESIGN

Approval of our hospital's Clinical Investigation Committee and written parental consent after informed discussion were obtained to enter 45 neonates undergoing open heart surgery into a controlled clinical trial. This paper presents the data from 15 neonates randomized to the control group, which received prospectively standardized regimens for anesthesia and analgesia during and after surgery. Feedings were withheld for 6–8 h before surgery and an intravenous dextrose infusion was maintained at 4–6 $mg \cdot kg^{-1} \cdot min^{-1}$ before and after surgery. A radial or umbilical artery was cannulated before surgery. All neonates received a uniform anesthetic regimen with halothane, ketamine, morphine, pancuronium, and an oxygen–air mixture according to clinical require-

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ments (see appendix for details). Cooling procedures for hypothermia; the composition of the CPB prime and perfusion flow rates during CPB; dextrose infusion rates before CPB, after CPB, and postoperatively; and postoperative analgesic regimens were standardized for all neonates (see appendix).

All patients survived their surgical procedures, which included CPB and DHCA. Two deaths occurred without obvious precipitating cause in neonates apparently recovering well, within 24 h postoperatively in the intensive care unit. Two other neonates died in the intensive care unit after prolonged complications postoperatively. Arterial blood (2–2.5 ml) was sampled from all neonates preoperatively, just before the start of CPB (approximately 15 min after sternotomy), 5 min after the resumption of CPB after the period of DHCA, at the end of the operation, and 6, 12, and 24 h postoperatively.

Analytical Methods

Blood concentrations of glucose, lactate, and alanine were measured by specific enzymatic methods;[6] plasma insulin, glucagon, cortisol, aldosterone and beta-endorphins were measured by radioimmunoassay techniques;[7–10] and plasma norepinephrine and epinephrine were measured by a double-isotope radioenzymatic assay.[11] All samples for hormonal measurements by radioimmunoassay were included in one assay; intraassay coefficients of variation were <5%. Interassay coefficients of variation for all metabolite assays were <3% and for the radioenzymatic assay of catecholamines were <10%.

Statistical Methods

Statistical tests using data from all 15 neonates included Kruskal-Wallis analysis of variance (ANOVA), followed by Wilcoxon's signed rank test to test for differences from the preoperative baseline values. Nonparametric statistical tests were used because the data did not conform to a normal distribution. According to convention, graphic and tabular presentation of all data include mean ± standard error of the mean (SEM).

Results

Hormonal–Metabolic Responses

The characteristics and clinical management for all 15 neonates together and for survivors and nonsurvivors separately appear in tables 1 and 2. Hormonal responses for all neonates are shown in figures 1 and 2, and metabolic responses in figure 3. The means, SEM, and ranges of the hormonal and metabolic data are shown in table 3 for all 15 neonates as well as for survivors and nonsurvivors separately. Detailed statistical comparisons between nonsurvivors and survivors are not presented because of the small numbers involved. Table 4 presents the hormonal and metabolic data for the CPB pump prime for the assessment of possible pump prime contributions to intraoperative changes.

Table 1. Patient Characteristics and Preoperative Clinical Management

	All patients (n = 15)	Nonsurvivors (n = 4)	Survivors (n = 11)
Age (days)	5.3 ± 0.8	7.7 ± 1.9	4.4 ± 0.7
Sex (M, F)	11 M, 4 F	3 M, 1 F	8 M, 3 F
Gestation (weeks)	40.2 ± 0.1	40.3 ± 0.3	40.2 ± 0.1
Weight (kg)	3.6 ± 0.1	3.7 ± 0.3	3.6 ± 0.2
Diagnoses			
HLHS	6	2	4
TGA	8	2	6
IAA	1	—	1
Preop starvation (h)	6.9 ± 0.4	8.0 ± 0.0	6.6 ± 0.5
Vasoactive infusions			
PGE_1	10/15	2/4	8/11
Dopamine	4/15	1/4	3/11
Arterial blood gases			
*p*H	7.49 ± 0.03	7.56 ± 0.09	7.47 ± 0.01
P_{O_2} (mmHg)	45 ± 4	51 ± 12	43 ± 4
P_{CO_2} (mmHg)	30 ± 2	32 ± 7	30 ± 2
Hematocrit	41.5 ± 2.0	42.3 ± 2.9	41.0 ± 2.8
Serum electrolytes			
Sodium (mEq/l)	138 ± 2	135 ± 4	139 ± 1
Potassium (mEq/l)	3.6 ± 0.1	3.8 ± 0.5	3.5 ± 0.1
Calcium (mEq/l)	1.00 ± 0.04	0.97 ± 0.10	1.02 ± 0.05
Dextrose infusion rate ($mg \cdot kg^{-1} \cdot min^{-1}$)	3.4 ± 0.6	3.3 ± 1.2	3.5 ± 0.7

All values are given as mean ± SEM.
HLHS = hypoplastic left heart syndrome; TGA = transposition of the great arteries; IAA = interrupted aortic arch.

TABLE 2. Intraoperative and Postoperative Clinical Management

	All Patients	Nonsurvivors	Survivors
Intraoperative Data:			
Dextrose infusion rate ($mg \cdot kg^{-1} \cdot min^{-1}$)	5.4 ± 0.4	5.3 ± 0.8	5.4 ± 0.5
Vasoactive infusions			
Dopamine ($\mu g \cdot kg^{-1} \cdot min^{-1}$)	12/15	3/4	9/11
	7.2 ± 1.5	8.7 ± 5.8	6.7 ± 1.1
Epinephrine ($\mu g \cdot kg^{-1} \cdot min^{-1}$)	5/15	2/4	3/11
	0.18 ± 0.05	0.25 ± 0.15	0.13 ± 0.03
Arterial blood gases:			
Before CPB;			
*p*H	7.51 ± 0.03	7.61 ± 0.10	7.47 ± 0.02
P_{CO_2} (mmHg)	29 ± 2	26 ± 5	30 ± 2
P_{O_2} (mmHg)	45 ± 5	56 ± 16	42 ± 4
After DHCA			
*p*H	7.54 ± 0.03	7.55 ± 0.03	7.54 ± 0.04
P_{CO_2} (mmHg)	26 ± 1	27 ± 1	25 ± 2
P_{O_2} (mmHg)	279 ± 51	266 ± 117	284 ± 58
Pavulon dose (mg/kg)	0.54 ± 0.07	0.67 ± 0.18	0.49 ± 0.08
Morphine dose (mg/kg)	0.35 ± 0.05	0.38 ± 0.15	0.35 ± 0.05
Ketamine dose (mg/kg)	1.5 ± 0.2	1.5 ± 0.1	1.5 ± 0.2
Duration of surgery (min)	232 ± 21	293 ± 60	210 ± 17
Duration of CPB (min)	124 ± 4	114 ± 8	127 ± 4
Duration of DHCA (min)	46 ± 6	58 ± 4	42 ± 7
Postoperative Data:			
Dextrose infusion rate ($mg \cdot kg^{-1} \cdot min^{-1}$)	4.2 ± 0.3	4.8 ± 0.6	4.1 ± 0.4
Vasoactive infusions			
Dopamine ($\mu g \cdot kg^{-1} \cdot min^{-1}$)	14/15	4/4	10/11
	6.7 ± 1.1	9.3 ± 5.8	6.2 ± 0.8
Epinephrine ($\mu g \cdot kg^{-1} \cdot min^{-1}$)	5/15	2/4	3/11
	0.13 ± 0.03	0.13 ± 0.04	0.13 ± 0.08
Arterial blood gases:			
On reaching ICU;			
*p*H	7.50 ± 0.02	7.48 ± 0.04	7.51 ± 0.02
P_{CO_2} (mmHg)	28 ± 2	25 ± 6	29 ± 2
P_{O_2} (mmHg)	95 ± 24	123 ± 84	87 ± 23
6 hours later;			
*p*H	7.53 ± 0.02	7.51 ± 0.06	7.54 ± 0.03
P_{CO_2} (mmHg)	30 ± 1	32 ± 3	30 ± 2
P_{O_2} (mmHg)	97 ± 19	79 ± 43	100 ± 22
Pancuronium dose ($mg \cdot kg^{-1} \cdot 24\ h^{-1}$)	1.23 ± 0.19	1.83 ± 0.02	1.16 ± 0.19
Morphine dose ($mg \cdot kg^{-1} \cdot 24\ h^{-1}$)	1.45 ± 0.34	1.05 ± 0.78	1.56 ± 0.40

All values are given as mean ± SEM.

Hormonal Changes

Plasma epinephrine increased above preoperative values before CPB ($P = 0.0016$), after DHCA ($P = 0.0072$), at the end of the operation ($P = 0.0006$), and 6, 12, and 24 h postoperatively ($P = 0.033$–0.048). The nonsurvivors tended to have higher epinephrine concentrations at the end of the operation. Plasma norepinephrine increased after DHCA ($P = 0.0017$) and at the end of the operation ($P = 0.0007$). Both survivors and nonsurvivors had similar norepinephrine concentrations during and after the operation. Plasma beta-endorphins (PBEs) increased before CPB ($P = 0.0035$), after DHCA ($P = 0.0016$), and at the end of the operation ($P = 0.039$), and returned to baseline postoperatively. Survivors tended to have greater PBE concentrations prior to CPB and postoperatively.

Plasma insulin increased at the end of the operation ($P = 0.016$), and 6 h ($P = 0.0039$), 12 h ($P = 0.0117$), and 24 h ($P = 0.0117$) postoperatively; responses were similar in survivors and nonsurvivors. Plasma glucagon values increased after DHCA ($P = 0.018$) and had increased further by 24 h postoperatively ($P = 0.046$); postoperative glucagon values tended to be higher in the nonsurvivors. The insulin/glucagon molar ratio had decreased before CPB ($P = 0.036$), but reverted to preoperative baseline values at the end of the operation and postoperatively. Plasma aldosterone values were unchanged during the operation, but decreased at 6, 12, and 24 h postoperatively

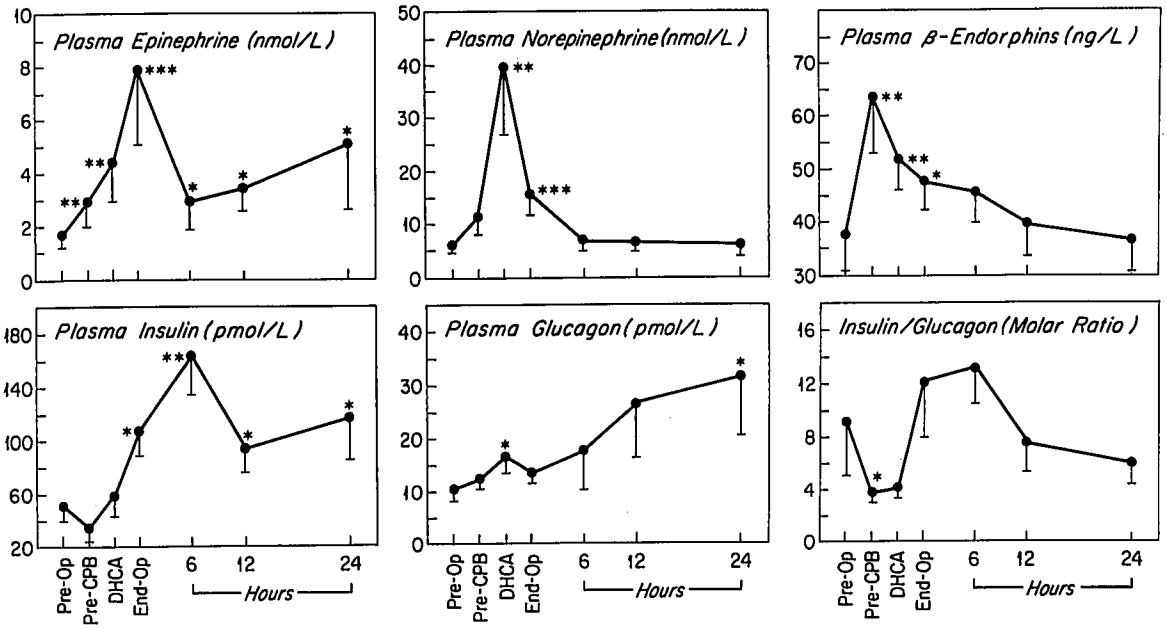

FIG. 1. Hormonal changes in all neonates: Epinephrine, norepinephrine beta-endorphins, insulin, glucagon, insulin/glucagon (molar ratio). $*P < 0.05$, $**P < 0.01$, $***P < 0.001$ compared to preop baseline.

($P = 0.036$); nonsurvivors tended to have greater aldosterone responses to surgical stimuli before CPB. Plasma cortisol increased before CPB ($P = 0.021$) and at the end of the operation ($P = 0.033$), but decreased below preoperative values by 12 h ($P = 0.046$). In the nonsurvivors, cortisol concentrations tended to be greater intraoperatively after DHCA and postoperatively.

Metabolic Changes

Blood glucose increased after sternotomy before CPB ($P = 0.0009$), after DHCA ($P = 0.0008$), and increased further at the end of the operation ($P = 0.0008$). Hyperglycemia continued at 6 h ($P = 0.018$) and 12 h ($P = 0.041$) postoperatively, but was not significantly different from preoperative values at 24 h. Nonsurvivors tended to have greater hyperglycemic responses intraoperatively. Blood lactate also increased before CPB ($P = 0.0041$), with further increases after DHCA ($P = 0.0008$) and at the end of the operation ($P = 0.0005$). At 6 h, blood lactate had increased over preoperative values ($P = 0.0016$), but this difference did not continue at 12 and 24 h. Lactate concentrations in nonsurvivors tended to be much higher at the end of the operation. Concentrations of blood alanine did not change during or after the operation, except for a small increase after DHCA ($P = 0.024$); nonsurvivors tended to have higher alanine blood concentration at the end of the operation and 6 h postoperatively.

SURVIVORS AND NONSURVIVORS

The survivors and nonsurvivors appeared similar in demographics and preoperative clinical condition (table 1). Likewise, hemodynamics were similar at times when blood samples were collected for hormonal–metabolic measurement, as were arterial blood gases measured intraoperatively, at ICU admission, and 6 h postoperatively (tables 1 and 2). Similar doses of anesthetic and vasoactive infusions were required during and after the surgical procedure in both groups, which required similar intraoperative surgical, CPB, and DHCA times (table 2). Thus, in the perioperative period (including the first 24 h postoperatively), survivors and nonsurvivors received similar treatment and were not readily distinguishable by the usual clinical criteria, and particularly by hemodynamic measures. Despite very similar clinical appearances, the hormonal and metabolic responses of the neonates who died postoperatively tended to be more extreme, as outlined above and as detailed in table 3. This tendency appeared after incision and sternotomy, even before CPB and the hemodynamic results of the surgical repair could have influenced hormonal and metabolic responses in nonsurvivors.

Discussion

Remarkably little is known about newborn hormonal and metabolic responses to severe stress such as cardiac surgery.[12] Studies during noncardiac surgery have shown

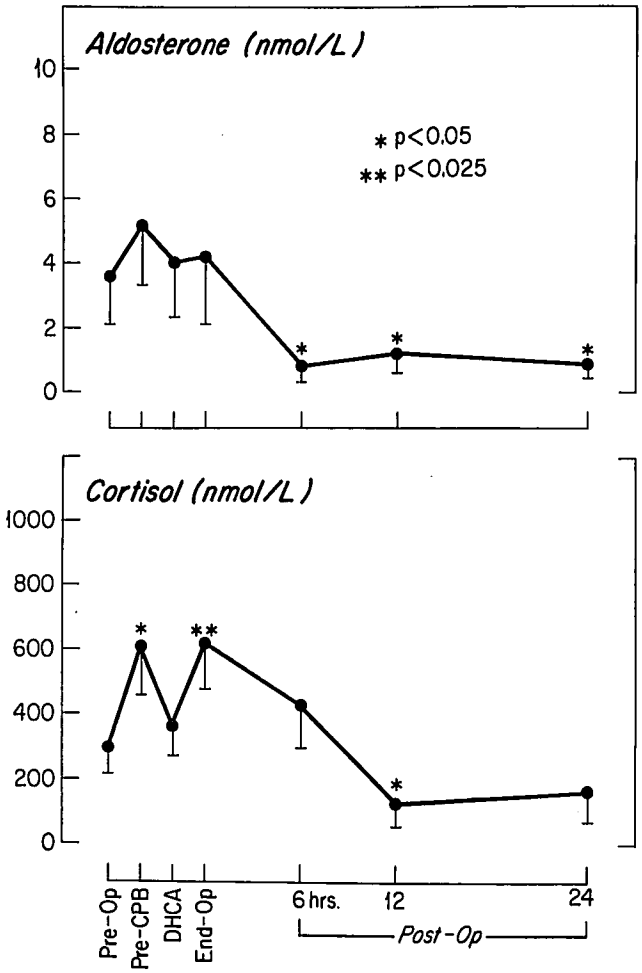

FIG. 2. Hormonal changes in all neonates: Aldosterone, cortisol. *$P < 0.05$, **$P < 0.025$ compared to preop baseline.

more extreme and prolonged stress responses in neonates than in adult patients.[4,5] Extreme hormonal and metabolic responses may become maladaptive and detrimental with respect to relative ability to cope with surgical injury. As in adults, it is unclear in neonates under what circumstances such detrimental effects of stress responses may occur and when anesthetic management should be targeted at attenuating such responses.

The most prominent hormonal responses of these newborns were the intraoperative catecholamine increases. Firmin *et al.* reported similar results in older infants (mean age 6 months) undergoing cardiac surgery, although wide variations occurred in the age, weight, cardiac diagnoses, and surgical procedures in their study.[13] Also, Firmin *et al.* used formal surface cooling to 26° C before CPB, whereas surface cooling was not used in the current study. Although both studies had similar response patterns, peak norepinephrine values in the current study were four times those reported by Firmin *et al.*[13] This extreme response is characteristic of the *neonatal* stress response, but also may reflect the more complex surgical repairs involved in the current study. Peak epinephrine responses occurred at the end of operation rather than after deep hypothermic circulatory arrest as in the study by Firmin *et al.* This pattern may be an effect of the prolonged surface cooling used by Firmin *et al.*, as others have shown.[14] Table 5 compares the peak catecholamine values in neonates in the current study and in adult patients undergoing cardiac surgery. Despite variations in catecholamine measurement methods, adult patient characteristics, and anesthetic management, catecholamine responses in neonates clearly were greater than in adults. In all neonates, peak catecholamine values oc-

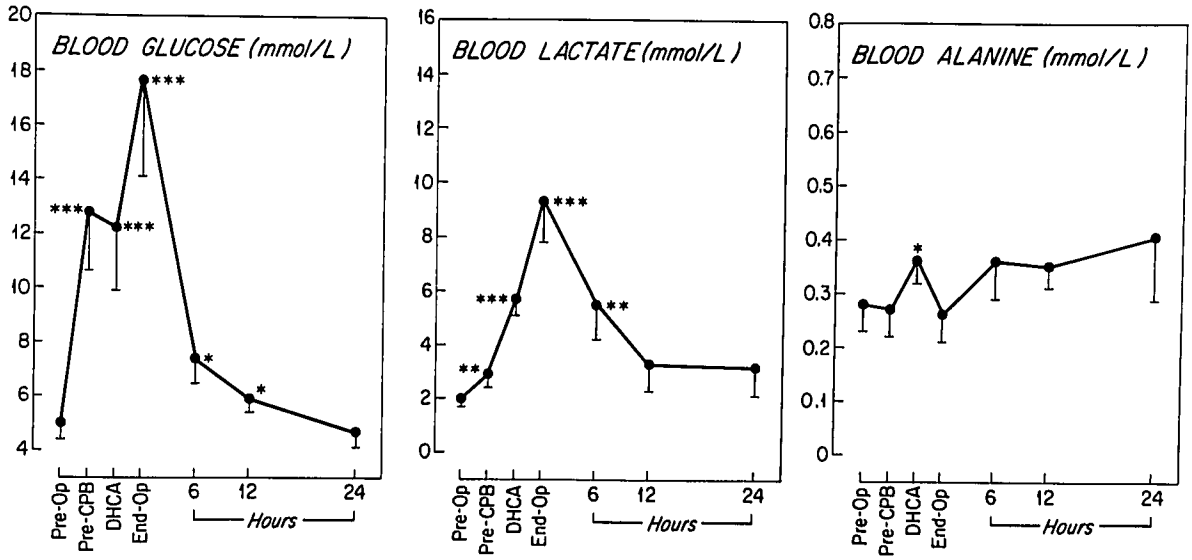

FIG. 3. Metabolic changes in all neonates: Glucose, lactate, alanine. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$ compared to preop baseline.

TABLE 3A. Epinephrine, Norepinephrine, and Beta-endorphin Data

Variable	All Neonates		Survivors		Nonsurvivors	
	Mean ± SEM	Range	Mean ± SEM	Range	Mean ± SEM	Range
Epinephrine (nM)						
Preop	1.7 ± 0.5	0.1–6.3	1.9 ± 0.6	0.1–6.3	1.1 ± 0.5	0.1–2.3
Pre-CPB	2.9 ± 0.8	0.4–11.6	3.5 ± 1.1	0.4–11.6	1.2 ± 0.4	0.5–2.3
DHCA	4.4 ± 1.5	0.3–18.9	4.6 ± 2.1	0.3–18.9	4.2 ± 1.5	0.7–7.8
End-op	7.9 ± 2.9	0.2–36.2	5.9 ± 2.7	0.2–31.0	13.2 ± 8.0	0.6–36.2
6 h	2.9 ± 1.2	0.1–14.5	3.4 ± 1.3	0.1–14.5	0.5 ± 0.3	0.1–0.8
12 h	3.4 ± 0.8	0.1–7.5	3.1 ± 0.8	0.1–7.2	4.5 ± 3.0	1.5–7.5
24 h	5.1 ± 2.5	0.1–29.2	5.7 ± 3.0	0.1–29.2	2.4 ± 1.1	1.3–3.5
Norepinephrine (nM)						
Preop	6.2 ± 1.3	0–16.5	5.8 ± 1.4	0–16.5	7.5 ± 3.1	1.3–16.2
Pre-CPB	11.3 ± 2.9	0.2–39.9	11.5 ± 3.7	0.2–39.9	10.8 ± 5.2	2.3–25.3
DHCA	39.8 ± 12	1.6–162	35.3 ± 16.1	1.6–162	50.9 ± 16.3	2.3–72
End-op	15.7 ± 3.5	0.1–44	13.4 ± 4.0	0.1–44	22.0 ± 7.6	10.3–44
6 h	7.0 ± 2.1	0.4–24.6	7.7 ± 2.4	0.4–24.6	2.9 ± 1.1	1.8–4.0
12 h	6.3 ± 1.5	0.8–16.7	6.7 ± 1.9	0.8–16.7	5.0 ± 0.1	4.9–5.0
24 h	6.2 ± 2.0	0.4–23.1	7.0 ± 2.4	0.4–23.1	2.7 ± 1.2	1.5–4.0
Endorphins (pg/ml)						
Preop	38 ± 6.9	3–68	43 ± 8	3–68	25 ± 12	4–52
Pre-CPB	64 ± 11.1	4–158	76 ± 13	4–158	36 ± 11	8–59
DHCA	52 ± 5.8	9–75	55 ± 8	9–74	45 ± 8	24–62
End-op	48 ± 5.6	3–74	52 ± 7	3–74	35 ± 9	14–58
6 h	46 ± 6.1	1–73	46 ± 7	1–73	47 ± 11	36–59
12 h	40 ± 6.1	11–59	45 ± 6	11–59	23 ± 12	11–34
24 h	37 ± 6.0	1–66	40 ± 7	1–66	27 ± 16	12–43

See figures and text for significant differences.

curred *before* any epinephrine infusions were started so that epinephrine infusions did not influence the peak epinephrine concentrations reported.

The preoperative PBE values were greater than normal for newborns, but the PBE values increased significantly intraoperatively, and peaked before CPB. Similarly high PBE values have been reported in neonates with acute clinical illness,[15] although even higher values have been found at birth,[16] especially with drug-addicted mothers.[17] There are no published data on neonatal endorphin responses to operation. Similar peak PBE responses occurred in adult cardiac surgery patients, but at the end of operation.[18]

In the newborns studied for the current report, plasma aldosterone values were greater than normal before operation, remained high intraoperatively, and decreased significantly to more normal levels during the postoperative period. These findings may reflect the fluid and electrolyte status of neonates stressed preoperatively and relative normalization of homeostasis postoperatively. There are no published data on aldosterone for comparison in term neonates undergoing other surgical procedures. Plasma cortisol concentrations were higher than normal during operation, and were increased before CPB and at the end of operation, similar to those seen in neonates undergoing noncardiac surgery.[4,5,19] The decrease in plasma cortisol after DHCA may be associated with decreased adrenocortical perfusion, dilution during CPB, or decreased cortisol responses secondary to steroids added to the pump prime. A similar pattern of cortisol responses in older infants (mean age 13 months) undergoing cardiac surgery was reported by Milne *et al.*[20] In their study, peak responses occurred 1 h postoperatively and were greater than peak neonatal responses in the current study, reflecting maturational changes in the adrenal cortex during early infancy.

Increased plasma insulin concentrations at the end of operation and postoperatively are clearly a response to perioperative hyperglycemia. Failure of insulin concentrations to increase earlier intraoperatively in response to the severe intraoperative hyperglycemia may be caused directly by hypothermia[21,22] or by decreased splanchnic circulation during hypothermic CPB. The magnitude and pattern of changes in plasma insulin values were similar to those in older infants, children, and adults undergoing cardiac surgery.[21,23,24] Older infants[20] and adults[25] undergoing cardiac operations showed CPB-related and postoperative increases in plasma glucagon similar to those seen in our neonates. Other published glucagon data in neonates undergoing cardiac surgery are not currently available for comparison. The decreased insulin/glucagon molar ratio seen after sternotomy may have resulted in a

TABLE 3B. Insulin, Glucagon, Aldosterone, and Cortisol Data

Variable	All Neonates		Survivors		Nonsurvivors	
	Mean ± SEM	Range	Mean ± SEM	Range	Mean ± SEM	Range
Insulin (pM)						
Preop	50 ± 13	7–179	45 ± 16	7–179	64 ± 24	13–109
Pre-CPB	33 ± 10	7–148	23 ± 7	7–83	62 ± 30	12–148
DHCA	58 ± 16	7–197	54 ± 16	7–163	66 ± 44	9–197
End-op	107 ± 20	7–274	99 ± 19	7–194	131 ± 59	8–274
6 h	164 ± 31	37–427	157 ± 36	37–427	202 ± 19	182–221
12 h	93 ± 18	20–188	98 ± 22	20–188	79 ± 34	37–148
24 h	116 ± 30	28–302	124 ± 36	28–302	81 ± 34	47–114
Glucagon (pM)						
Preop	10 ± 2	3–27.3	10 ± 3	3–27	10 ± 3	4–15
Pre-CPB	12 ± 2	3–23.8	11 ± 2	3–24	14 ± 5	6–24
DHCA	16 ± 4	3–41.1	15 ± 4	3–41	19 ± 7	10–40
End-op	13 ± 2	3–23.6	13 ± 2	3–24	14 ± 3	7–14
6 h	17 ± 7	4–69.5	10 ± 2	4–25	42 ± 27	15–70
12 h	26 ± 10	6–86.5	18 ± 6	6–42	50 ± 36	14–87
24 h	31 ± 11	7–75.9	31 ± 14	7–76	31 ± 19	12–49
Aldosterone (nM)						
Preop	2.8 ± 0.9	0–9.6	1.7 ± 0.7	0.3–5.4	4.7 ± 2.1	0–9.6
Pre-CPB	4.1 ± 1.4	0.1–13.4	2.7 ± 1.5	0.1–11.2	6.7 ± 2.5	2.8–13.4
DHCA	2.8 ± 1.2	0–11.5	1.8 ± 1.1	0.1–7.1	4.2 ± 2.5	0–11.5
End-op	2.2 ± 0.9	0–10.1	2.4 ± 1.3	0.1–10.1	2.0 ± 0.7	0–3.5
6 h	0.8 ± 0.5	0–4.1	1.0 ± 0.7	0–4.1	0.2 ± 0.2	0–0.4
12 h	1.2 ± 0.6	0–4.8	1.3 ± 0.8	0–4.8	0.9 ± 0.3	0.6–1.2
24 h	0.9 ± 0.4	0–2.8	1.1 ± 0.5	0–2.8	0.6 ± 0.1	0.5–0.7
Cortisol (nM)						
Preop	294 ± 83	19–970	255 ± 71	72–655	361 ± 209	19–970
Pre-CPB	608 ± 149	125–1971	435 ± 80	125–762	910 ± 366	369–1971
DHCA	363 ± 93	106–958	213 ± 35	106–357	590 ± 184	226–958
End-op	621 ± 145	133–1359	540 ± 170	133–1150	763 ± 284	179–1359
6 h	429 ± 129	67–829	450 ± 157	80–829	364 ± 297	67–661
12 h	129 ± 67	1–587	56 ± 19	1–128	350 ± 238	112–587
24 h	168 ± 88	1–606	126 ± 97	1–606	294 ± 235	59–529

See figures and text for significant differences.

TABLE 3C. Glucose, Lactate, and Alanine Data

Variable	All Neonates		Survivors		Nonsurvivors	
	Mean ± SEM	Range	Mean ± SEM	Range	Mean ± SEM	Range
Glucose (mM)						
Preop	5 ± 0.6	1.7–10.4	5.1 ± 0.7	1.7–10.4	4.6 ± 0.9	3.1–7.1
Pre-CPB	12.8 ± 2.2	4.0–36.4	10.6 ± 1.6	4.0–20.6	18.9 ± 7.0	5.0–36.4
DHCA	12.2 ± 1.3	5.1–19.3	10.5 ± 1.0	5.1–14.0	16.2 ± 2.8	7.9–19.3
End-op	17.7 ± 3.6	4.6–59.5	17.1 ± 4.6	4.6–59.5	19.9 ± 3.5	13.5–25.4
6 h	7.4 ± 0.9	3.9–13.3	7.8 ± 0.9	4.0–13.3	3.9 ± 0.2	3.3–4.5
12 h	5.9 ± 0.5	3.8–8.6	5.7 ± 0.6	3.8–8.6	6.5 ± 1.1	5.4–7.5
24 h	4.7 ± 0.6	2.3–8.8	4.6 ± 0.8	2.3–8.8	5.0 ± 1.2	3.8–6.1
Lactate (mM)						
Preop	2.0 ± 0.3	0.7–3.7	2.0 ± 0.3	0.7–3.7	2.0 ± 0.5	1.0–3.1
Pre-CPB	2.9 ± 0.5	0.9–8.9	2.9 ± 0.7	0.9–8.9	3.2 ± 1.1	0.9–6.0
DHCA	5.7 ± 0.6	2.8–8.7	5.4 ± 0.7	2.8–8.7	6.3 ± 0.8	3.9–7.7
End-op	9.3 ± 1.6	2.3–24.6	7.6 ± 1.4	2.3–16.6	15.5 ± 4.5	10.7–24.6
6 h	5.5 ± 1.3	1.4–14.3	5.6 ± 1.4	1.4–14.3	4.7 ± 0.2	4.4–4.9
12 h	3.3 ± 1.0	0.8–10.6	3.5 ± 1.3	0.8–10.6	2.6 ± 0.7	1.9–3.3
24 h	3.2 ± 1.1	1.1–13.9	3.4 ± 1.	1.1–13.9	2.5 ± 1.1	1.4–3.6
Alanine (mM)						
Preop	0.28 ± .04	0.04–.60	.25 ± .04	0.05–.57	0.36 ± .12	0.04–.60
Pre-CPB	0.27 ± .05	0.01–.71	.25 ± .06	0.01–.71	0.34 ± .11	0.09–.59
DHCA	0.36 ± .04	0.19–.68	.35 ± .05	0.19–.68	0.38 ± .07	0.19–.51
End-op	0.26 ± .05	0.02–.75	.24 ± .06	0.02–.75	0.33 ± .05	0.27–.42
6 h	0.36 ± .07	0.01–.87	.35 ± .08	0.01–.87	0.45 ± .02	0.43–.48
12 h	0.35 ± .04	0.13–.54	.34 ± .05	0.13–.54	0.40 ± .02	0.37–.42
24 h	0.41 ± .12	0.05–1.52	.42 ± .15	0.05–1.52	0.36 ± .10	0.26–.46

See figures and text for significant differences.

TABLE 4. Hormone and Metabolite Concentrations in CPB Pump Prime

Epinephrine (nM)	1.0 ± 0.6	0.03–7.3	2.1
Norepinephrine (nM)	5.9 ± 3.8	0.16–50.2	13.9
Endorphins (ng/l)	37.7 ± 5.9	0.9–69.8	22.2
Insulin (pM)	100 ± 18	7–254	72
Glucagon (pM)	9.7 ± 1.1	4.1–14.5	3.3
Insulin/glucagon (molar ratio)	10.9 ± 2.5		
Aldosterone (nM)	0.4 ± 0.3	0.02–4.0	2.58
Cortisol (nM)	183 ± 80	22–903	277
Glucose (mM)	10.7 ± 0.9	5.2–17.8	3.6
Lactate (mM)	4.4 ± 0.3	2.7–6.0	1.05
Alanine (mM)	0.24 ± 0.02	0.09–0.36	0.08

Mean ± SEM for pump prime in all 15 cases studied.

catabolic drive leading to the intraoperative hyperglycemia and lactic acidosis noted in the current study. Changes in this ratio have greater metabolic significance than changes in the individual hormones.

Hyperglycemic responses, with or without lactic acidosis, also occurred in several previous studies of older infants undergoing cardiac surgery, although data from neonates are sparse.[21,22,26] In infants 6–25 months old, Milne *et al.*[20] reported much larger increases in blood glucose and lactate during CPB and DHCA. These differences are largely explained by the glucose and lactate in pump prime (50.8 ± 3.0 and 3.6 ± 0.2 mM, respectively, in the study by Milne *et al.*, and 10.7 ± 0.9 and 4.4 ± 0.3 mM, respectively, in our study). Hyperglycemic responses of patients in both studies were similar before CPB; thereafter, increases in blood glucose to a peak of >30 mM during CPB in the previous study[20] were mainly attributable to the glucose load in the pump prime. Although neonates in the current study received a similar lactate load in the pump prime, their last intraoperative blood lactate values were significantly higher than those in the study by Milne *et al.*[20] Greater accumulation of blood lactate in neonates may result from greater lactate production with extreme catecholamine responses or decreased utilization of lactate by immature hepatic gluconeogenic enzymes. The latter mechanism also may explain the increased blood alanine values seen after circulatory arrest.

The four postoperative deaths in neonates with a prospectively standardized anesthetic regimen provided an opportunity to relate stress responses to postoperative mortality. Conventional intraoperative and postoperative criteria of clinical condition did not differentiate survivors and nonsurvivors. Nevertheless, nonsurvivors tended to have greater stress responses than did survivors. The small numbers of nonsurvivors and survivors did not permit valid statistical comparison, so these data must be considered as only suggestive. Increased hormonal and metabolic stress responses tended to occur in nonsurvivors even before the start of CPB and DHCA, the most stressful part of the procedure, as well as during and after CPB. This suggests that postoperative mortality may be related to extreme stress responses. This tendency also appeared before problems with decreased cardiac output due to inadequate cardiac repairs could have affected stress responses.

In adult patients, preliminary results suggest that greater catecholamine responses may be associated with postoperative complications such as congestive heart failure or renal insufficiency.[2] Nonsurvivors in the current study also tended to have greater epinephrine concentrations. Further studies will be required to identify whether sympathoadrenal responses in neonates undergoing cardiac surgery can serve as indicators of postoperative outcome. Similarly, aldosterone and cortisol responses during operation and cortisol responses after operation tended to be greater in the nonsurvivors. This suggests that the nonsurvivors were more stressed intraoperatively or had abnormal fluid/electrolyte status preoperatively that was not reflected in conventional clinical measures. In contrast, PBE values tended to be higher in survivors. The reasons for these differences are unclear; it is possible that increased PBE responses may somehow protect against postoperative complications and death after cardiac surgery. This protective effect may occur as a result of decreased oxygen consumption in peripheral tissues and the myocardium, or as a result of prevention of arrhythmias, similar to the effects of exogenous opioids in high doses.[2,27]

The more extreme hormonal stress responses in nonsurvivors were accompanied by metabolic responses that tended to be more extreme, including hyperglycemia, much higher lactate concentrations, and high blood alanine concentrations intraoperatively. Milne *et al.*[20] and

TABLE 5. Peak Catecholamine Values in Neonates and Adults Undergoing Cardiac Surgery

Study	Norepinephrine	Epinephrine
Neonates	39.8 ± 12.2	7.9 ± 2.9
Adults		
Roberts *et al.*, 1977[a]	6.6 ± 1.5	4.7 ± 2.2
Landymore *et al.*, 1979[b]	~7.7	~4.9
Hoar *et al.*, 1980[c]	10.4 ± 1.7	2.8 ± 0.4
Stanley *et al.*, 1980[d]	3.9 ± 0.3	1.1 ± 0.2
Philbin *et al.*, 1981[e]	4.8 ± 0.6	5.2 ± 0.9
Tomicheck *et al.*, 1983[f]	~3.5	~2.2
Bovill *et al.*, 1983[g]	11.5 ± 2.3	5.7 ± 1.8
Scheinin *et al.*, 1987[h]	5.7 ± 1.4	1.4 ± 0.3

All values are millimolar concentrations.
[a] J Thorac Cardiovasc Surg 80:242–248, 1977.
[b] Ann Thorac Surg 28:261–268, 1979.
[c] J Thorac Cardiovasc Surg 80:242–248, 1980.
[d] ANESTHESIOLOGY 53:250–253, 1980.
[e] Circulation 64:808–812, 1981.
[f] Anesthe Analg 62:881–884, 1983.
[g] Anesth Analg 62:391–397, 1983.
[h] Acta Anaesthesiol Scand 31:762–767, 1987.

Baum *et al.*[22] also found markedly increased intraoperative blood lactate values in older infants who subsequently died.[20]

These results demonstrate a major catabolic state, mediated by extreme hormonal responses, in newborn babies who had a high mortality after cardiac operations. This catabolic state was evident even before the start of CPB; was fully expressed by the end of operation; and continued postoperatively. Whether such hormonal–metabolic responses are a cause or an effect of poor outcome when surgical repair itself appears adequate remains open to question. In this study the early tendency of the nonsurvivors to have greater hormonal and metabolic stress responses suggests that extreme stress responses may have some causal relationship to poor outcome. Many more patients need to be studied before components of the stress response affecting outcome, together with the subtle mechanisms that may mediate such effects, may be identified. Until more studies are done the current results may serve as preliminary evidence of such interactions.

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Appendix

Details of Anesthetic Technique

1) Anesthetic induction
   - Morphine 0.1–0.2 mg/kg iv (repeated as required)
   - Ketamine 1–2 mg/kg iv
   - Pancuronium 0.1 mg/kg iv (repeated as required)
   - Halothane 0.5–2.0 %
   - Oxygen 100% (supplemented with air, if necessary)
2) Insertion of catheters monitoring leads, *etc.*
3) Drugs before CPB
   - Heparin 2 mg/kg iv
   - Other drugs may be given, as *per* clinical condition
4) Cooling procedure
   - Passive cooling by exposure to room air
   - Bypass cooling to 15–20° C (rectal).
5) Cardiopulmonary bypass procedure

Composition of pump prime:	Normosol R	300–500 ml
	CPD fresh blood	500 ml
Drugs added to pump prime:	Heparin	1–2 mg/kg
	Na bicarbonate	20–25 mEq
	Furosemide	0.1 mg/kg
	Phentolamine	0.1 mg/kg
	Methylprednisolone	30 mg/kg
	Cefazolin	25 mg/kg
Perfusion rate:	100–150 ml/kg/min	
Drugs added on rewarming:	Mannitol	0.5 gm/kg
	Ca gluconate	0.5–1 gm
	Phentolamine	0.1 mg/kg

6) Anesthetic management after CPB
   - Morphine 0.1–0.2 mg/kg (repeated as required)
   - Halothane 0.5–1.0 %
   - Pancuronium 0.1 mg/kg (repeated as required)
7) Other drugs (given if clinically indicated)

Calcium gluconate	Dopamine
Potassium chloride	Isoprenaline
Protamine	Epinephrine
Cefazolin	Norepinephrine

8) Intravenous fluids before and after CPB

5% Dextrose = 4.8–7.2 ml/kg/h
10% Dextrose = 2.4–3.6 ml/kg/h
15% Dextrose = 1.6–2.4 ml/kg/h
} to provide glucose at 4–6 $mg \cdot kg^{-1} \cdot min^{-1}$

Fluids given in unrestricted quantities as required were:
a) Normal saline; b) heparinized saline; c) 5% albumin; d) fresh frozen plasma; e) whole blood or blood products.

Postoperative Analgesia

Morphine 0.1–0.2 mg/kg, iv
Diazepam 0.1–0.2 mg/kg, iv
(Repeated Q1–2 hourly as required.)