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## HALOTHANE-MORPHINE COMPARED WITH HIGH-DOSE SUFENTANIL FOR ANESTHESIA AND POSTOPERATIVE ANALGESIA IN NEONATAL CARDIAC SURGERY

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**Abstract Background.** Extreme hormonal and metabolic responses to stress are associated with increased morbidity and mortality in sick adults. We hypothesized that administering deep opioid anesthesia to critically ill neonates undergoing cardiac surgery would blunt their responses to stress and might improve clinical outcomes.

**Methods.** In a randomized trial, 30 neonates were assigned to receive deep intraoperative anesthesia with high doses of sufentanil and postoperative infusions of opiates for 24 hours; 15 neonates were assigned to receive lighter anesthesia with halothane and morphine followed postoperatively by intermittent morphine and diazepam. Hormonal and metabolic responses to surgery were evaluated by assay of arterial blood samples obtained before, during, and after the operations.

**Results.** The neonates who received deep anesthesia (with sufentanil) had significantly reduced responses of beta-endorphin, norepinephrine, epinephrine, glucagon,

aldosterone, cortisol, and other steroid hormones; their insulin responses and ratios of insulin to glucagon were greater during the operation. The neonates who received lighter anesthesia (with halothane plus morphine) had more severe hyperglycemia and lactic acidemia during surgery and higher lactate and acetoacetate concentrations postoperatively ( $P < 0.025$ ). The group that received deep anesthesia had a decreased incidence of sepsis ( $P = 0.03$ ), metabolic acidosis ( $P < 0.01$ ), and disseminated intravascular coagulation ( $P = 0.03$ ) and fewer postoperative deaths (none of 30 given sufentanil vs. 4 of 15 given halothane plus morphine,  $P < 0.01$ ).

**Conclusions.** In neonates undergoing cardiac surgery, the physiologic responses to stress are attenuated by deep anesthesia and postoperative analgesia with high doses of opioids. Deep anesthesia continued postoperatively may reduce the vulnerability of these neonates to complications and may reduce mortality. (N Engl J Med 1992;326:1-9.)

OPIOID anesthetic agents in high doses can blunt endocrine and metabolic responses to cardiac or noncardiac operations in adults, as demonstrated by perioperative changes in the levels of cortisol,<sup>1,2</sup> catecholamines,<sup>3</sup> vasopressin,<sup>4</sup> and growth hormone.<sup>1</sup> These drugs may also reduce the mobilization of metabolic substrates that follows stimulation of glycogenolysis, gluconeogenesis, lipolysis, and protein breakdown.<sup>2,3</sup> Deeper levels of opioid anesthesia produce a dose-dependent inhibition of responses to the stress of surgery; such effects may be due to central or peripheral neuroendocrine regulatory mechanisms or may be the direct effects of opioids on endocrine glands.<sup>5</sup>

The metabolic balance of neonates is precarious, with hypoglycemia, hyperglycemia, metabolic acidosis, and electrolyte disturbances occurring frequently. This vulnerability to metabolic derangements may accentuate the detrimental effects of catabolic responses to stress triggered by major operations. It appears that the response of newborns to the stress of cardiac<sup>6</sup> and

noncardiac<sup>7,8</sup> operations is substantially greater than that of adults. A physiologic basis has been proposed<sup>9</sup> for the use of deep levels of anesthesia and postoperative analgesia to attenuate the extreme responses of newborns to perioperative pain and stress. We report the results of a test of this hypothesis in critically ill neonates undergoing severe surgical stress. We measured perioperative changes in the circulating levels of stress hormones and metabolic substrates and monitored postoperative morbidity and mortality in 45 neonates undergoing cardiac surgery, in a randomized trial of two regimens of intraoperative anesthesia and postoperative analgesia. The hypothesis to be tested proposed that the stress responses of newborns to cardiac operations are not altered by the use of opiates in high doses for intraoperative anesthesia and postoperative analgesia.

### METHODS

We obtained approval from our hospital's Clinical Investigation Committee and informed consent from the parents of 45 neonates scheduled to undergo repair of complex congenital heart defects to enroll the children in a controlled clinical trial. Feedings were withheld for six to eight hours before operation, and intravenous dextrose (4 to 6 mg per kilogram of body weight per minute) was given before and after operation. A cannula was inserted in a radial or umbilical artery of each infant before operation, and all received ventilation with an oxygen-air mixture.

In the newborns randomly assigned to the control regimen (the

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halothane group) anesthesia was induced with halothane (0.5 to 2.0 percent), ketamine (1 to 2 mg per kilogram), and repeated doses of morphine (0.1 to 0.2 mg per kilogram) and pancuronium (0.1 mg per kilogram) as required; and for 24 hours after operation, they received intermittent intravenous doses of morphine (0.1 mg per kilogram) and diazepam (0.1 mg per kilogram) for sedation and analgesia. Neonates randomly assigned to the experimental regimen (the sufentanil group) received repeated doses of sufentanil (5 to 15  $\mu$ g per kilogram) and pancuronium (0.1 mg per kilogram) as required, and for 24 hours after operation a continuous infusion of fentanyl (8 to 10  $\mu$ g per kilogram per hour) or sufentanil (2  $\mu$ g per kilogram per hour) (see Appendix). For both groups we standardized the procedures for inducing hypothermia, the composition of the perfusate used for cardiopulmonary bypass, the perfusion flow rates during bypass, and the infusion rates of dextrose given before and after bypass (see Appendix). Arterial blood samples (2 to 2.5 ml) were obtained from all neonates before operation, just before cardiopulmonary bypass, 5 minutes after termination of circulatory arrest during deep hypothermia, at the end of operation, and 6, 12, and 24 hours after operation.

### Trial Design and Statistical Analysis

Neonates eligible for surgical repair of congenital heart defects were screened to exclude those with chromosomal abnormalities or serious neurologic, endocrine, metabolic, renal, or hepatic disorders. After the parents gave consent, the patients were randomly assigned to the two study groups in a ratio of one infant in the halothane group for every two in the sufentanil group. A schedule for balanced randomization in blocks was prepared by an independent observer and retained until completion of the trial. To calculate the sample size needed to test the stated hypothesis, five index variables were selected a priori (plasma cortisol, beta-endorphin, norepinephrine, blood glucose, and blood lactate) and the standardized differences between the groups were calculated on the basis of findings from previous studies and clinical relevance. Using these standardized differences, we calculated the sample size required to give the trial a power of 80 percent (for  $\alpha < 0.05$ ) from a nomogram.<sup>10</sup>

The "response" of each neonate was characterized by the change in the concentration of each hormonal or metabolic variable from its respective preoperative base-line value in that neonate; thus, the patients served as their own controls. This method of analysis was adopted because it made intuitive physiologic sense and because it would reduce the effect of variations in base-line data caused by varying degrees of preoperative illness in the neonates. Kruskal-Wallis analysis of variance and the Mann-Whitney U test were used for comparison of hormonal and metabolic data, and Fisher's exact test was used to compare the clinical outcomes of the two study groups. The responses of the groups (changes from base line) were compared at the six sampling points after the preoperative base-line sample; thus, each datum point was used in only one statistical comparison of the groups. Despite the power analysis described above, the level of significance was arbitrarily set at  $P < 0.025$ , to minimize the probability of a Type I ( $\alpha$ ) error. All values are presented as means  $\pm$  SE.

### Analytical Methods

Plasma concentrations of insulin, glucagon, and beta-endorphin were measured by radioimmunoassay,<sup>11-13</sup> and those of plasma norepinephrine and epinephrine by double-isotope radioenzymatic assay.<sup>14</sup> The steroid hormones cortisol, aldosterone, progesterone, 17-hydroxyprogesterone, corticosterone, 11-deoxycorticosterone, 11-deoxycortisol, and cortisone were measured simultaneously by specific radioimmunoassays after extraction and automated liquid chromatography.<sup>15</sup> Blood concentrations of glucose, lactate, pyruvate, acetoacetate, 3-hydroxybutyrate, and alanine were measured by specific enzymatic assays.<sup>16</sup> Hormone assays were usually performed in the laboratories in which the assays had originally been developed.<sup>12,14,15</sup> The intraassay coefficients of variation for all radioimmunoassays were less than 5 percent; the interassay coefficients of variation for the radioenzymatic assay of catecho-

lamines were less than 10 percent, and those for all metabolite assays were less than 3 percent.

### Collection of Outcome Data

Postoperative mortality was defined in advance as death after cardiac surgery but before discharge from the cardiac intensive care unit (ICU). Postoperative morbidity was defined in advance as the presence of complications requiring specific therapy, leading to marked clinical deterioration or death, or prolonging the patient's postoperative stay in the ICU. Hypotension was defined as a decrease in the mean arterial pressure of more than 20 percent from base line, necessitating therapy with intravenous fluids or pressor agents. Atrial or ventricular arrhythmias were considered serious if they were prolonged or caused hemodynamic instability or required specific therapy. The presence or absence of sepsis or necrotizing enterocolitis was confirmed by blood culture and clinical and radiographic evaluation. Disseminated intravascular coagulation was diagnosed if indicated by appropriate laboratory values and a need for specific therapy. Seizures were diagnosed if indicated by clinical features and electroencephalographic recordings; persistent metabolic acidosis was considered serious if therapy with bicarbonate infusion was required. Data on clinical outcome were obtained by recording events at the patient's bedside and by reviewing the medical record after the patient's discharge from the hospital. All notes of the nursing staff and physicians were examined to confirm the incidence of postoperative complications; postmortem reports were examined if available. An analysis of some data on the halothane group has been reported previously.<sup>6</sup>

### RESULTS

All patients survived the surgical procedure, which included cardiopulmonary bypass and hypothermic circulatory arrest. The characteristics and clinical care of all 45 neonates are described in Tables 1 and 2.

Table 1. Patients' Characteristics and Preoperative Clinical Care.\*

VARIABLE	HALOTHANE GROUP (N = 15)	SUFENTANIL GROUP (N = 30)
Age (days)	5.3 $\pm$ 0.8	9.4 $\pm$ 1.8
Sex (M/F)	11/4	19/11
Gestation (wk)	40.2 $\pm$ 0.1	39.6 $\pm$ 0.3
Weight (kg)	3.6 $\pm$ 0.1	3.5 $\pm$ 0.1
Diagnosis		
Hypoplastic left-heart syndrome	6 (40)	9 (30)
Transposition of great arteries	8 (53)	18 (60)
Interrupted aortic arch	1 (7)	0
Tetralogy of Fallot	0	2 (7)
Truncus arteriosus, Type II	0	1 (3)
Time feedings withheld (hr)	6.9 $\pm$ 0.4	7.3 $\pm$ 0.3
Arterial blood gases†		
pH	7.49 $\pm$ 0.03	7.47 $\pm$ 0.01
pCO <sub>2</sub> (kPa)	4.0 $\pm$ 0.3	4.3 $\pm$ 0.1
pO <sub>2</sub> (kPa)	6.0 $\pm$ 0.4	6.2 $\pm$ 0.4
Vasoactive infusions		
Prostaglandin E <sub>1</sub>	10 (67)	23 (77)
Dopamine	4 (27)	9 (30)
Hematocrit	41.5 $\pm$ 2.0	39.3 $\pm$ 0.9
Serum electrolytes (mmol/liter)		
Sodium	138 $\pm$ 2	137 $\pm$ 1
Potassium	3.6 $\pm$ 0.1	3.4 $\pm$ 0.1
Calcium	1.00 $\pm$ 0.04	1.04 $\pm$ 0.02
Dextrose infusion rate (mg/kg/min)	3.4 $\pm$ 0.6	4.9 $\pm$ 0.5

\*Plus-minus values are means  $\pm$  SE. Values in parentheses are percentages. There were no significant differences between the groups according to Fisher's exact test and the Mann-Whitney U test.

†pCO<sub>2</sub> denotes partial pressure of carbon dioxide, and pO<sub>2</sub> partial pressure of oxygen.

Perioperative levels of arterial blood gases were similar in the two groups except for a slightly greater degree of alkalosis after surgery in the sufentanil group (pH 7.56 vs. 7.50,  $P = 0.0182$ ). There were no significant differences between the groups in the preoperative values of the hormonal and metabolic variables measured (Table 3) or in the composition of the

Table 2. Intraoperative and Postoperative Clinical Care of the Two Groups of Neonates.\*

VARIABLE	HALOTHANE GROUP (N = 15)	SUFENTANIL GROUP (N = 30)
<b>Intraoperative data</b>		
Dextrose infusion rate (mg/kg/min)	5.4±0.4	5.1±0.4
Vasoactive infusions		
Dopamine		
No. of patients (%)	12 (80)	24 (80)
Rate (μg/kg/min)	7.2±1.5	6.4±0.5
Epinephrine		
No. of patients (%)	5 (33)	2 (7)
Rate (μg/kg/min)	0.18±0.05	0.10±0.00
Arterial blood gases		
Before bypass		
pH	7.51±0.03	7.56±0.02
pCO <sub>2</sub> (kPa)	3.8±0.3	3.7±0.2
pO <sub>2</sub> (kPa)	6.1±0.7	8.3±0.9
After circulatory arrest		
pH	7.54±0.03	7.53±0.02
pCO <sub>2</sub> (kPa)	3.4±0.2	3.5±0.1
pO <sub>2</sub> (kPa)	37.2±6.8	23.5±3.6
Anesthetic agents		
Pancuronium (mg/kg)	0.54±0.07	0.50±0.03
Morphine (mg/kg)	0.35±0.05	—
Sufentanil (μg/kg)	—	37±2
Ketamine (mg/kg)	1.5±0.2	—
Thiopental (mg/kg)	—	6.4±0.6
Duration of procedures (min)		
Surgery	232±21	240±9
Bypass	124±4	128±5
Circulatory arrest	46±6	54±4
<b>Postoperative data</b>		
Dextrose infusion rate (mg/kg/min)	4.2±0.3	4.5±0.3
Vasoactive infusions		
Dopamine		
No. of patients (%)	11 (73)	25 (83)
Rate (μg/kg/min)	6.7±1.1	5.7±0.6
Epinephrine		
No. of patients (%)	5 (33)	4 (13)
Rate (μg/kg/min)	0.13±0.03	0.06±0.01
Arterial blood gases		
On reaching ICU		
pH	7.50±0.02	7.56±0.02†
pCO <sub>2</sub> (kPa)	3.8±0.3	3.5±0.2
pO <sub>2</sub> (kPa)	12.6±3.2	19.2±2.9
Six hr later		
pH	7.53±0.02	7.55±0.01
pCO <sub>2</sub> (kPa)	4.1±0.2	4.3±0.2
pO <sub>2</sub> (kPa)	12.9±2.6	12.0±1.2
Analgesic agents		
Pancuronium (mg/kg/24 hr)	1.23±0.19	1.05±0.13
Morphine (mg/kg/24 hr)	1.45±0.34	—
Sufentanil (μg/kg/24 hr)	—	49.3±1.3‡
Fentanyl (μg/kg/24 hr)	—	178±25‡

\*Plus-minus values are means ±SE. Values in parentheses are percentages. pCO<sub>2</sub> denotes partial pressure of carbon dioxide, and pO<sub>2</sub> partial pressure of oxygen.

† $P = 0.0182$  by the Mann-Whitney U test for the comparison between the study groups. There were no other significant differences between the groups according to the Mann-Whitney U test and Fisher's exact test.

‡Only 15 patients received the drug.

Table 3. Preoperative Hormonal and Metabolic Values in the Two Groups of Neonates.

VARIABLE	HALOTHANE GROUP (N = 15)	SUFENTANIL GROUP (N = 30)	P VALUE*
Beta-endorphin (pg/ml)	38±7	54±6	0.08
Norepinephrine (nmol/liter)	6.2±1.3	7.9±1.4	0.26
Epinephrine (nmol/liter)	1.7±0.5	2.1±0.6	0.47
Glucagon (pmol/liter)	10.4±2.1	16.8±3.5	0.11
Insulin (pmol/liter)	50±13	44±9	0.39
Insulin:glucagon molar ratio	8.9±4.0	4.5±1.1	0.08
Progesterone (nmol/liter)	0.9±0.2	1.2±0.2	0.06
17-Hydroxyprogesterone (nmol/liter)	0.8±0.2	0.5±0.1	0.05
11-Deoxycortisol (nmol/liter)	0.4±0.2	0.8±0.5	0.42
Cortisol (nmol/liter)	293±83	212±40	0.11
Cortisone (nmol/liter)	109±63	54±13	0.41
Deoxycorticosterone (nmol/liter)	0.39±0.17	0.29±0.08	0.24
Corticosterone (nmol/liter)	5.6±1.2	8.3±1.8	0.38
Aldosterone (nmol/liter)	2.8±0.9	3.6±0.8	0.11
Glucose (mmol/liter)	5.1±0.6	7.5±1.5	0.26
Lactate (mmol/liter)	2.1±0.3	2.7±0.3	0.09
Pyruvate (mmol/liter)	0.11±0.02	0.13±0.02	0.28
Alanine (mmol/liter)	0.28±0.05	0.35±0.04	0.16
Acetoacetate (mmol/liter)	0.07±0.02	0.09±0.02	0.18
3-Hydroxybutyrate (mmol/liter)	0.10±0.03	0.07±0.02	0.39

\*By the Mann-Whitney U test.

cardiopulmonary-bypass perfusate (presented elsewhere\*). Significant differences were found in the hormonal and metabolic responses to surgery (Fig. 1 to 4). Values for all variables are presented elsewhere\*; data on clinical outcome are shown in Table 4 and Figure 5.

### Hormonal Responses

The halothane group had significantly higher responses with respect to the following variables than did the sufentanil group: beta-endorphin responses after sternotomy ( $P < 0.0001$ ) and after hypothermic circulatory arrest ( $P = 0.0001$ ), epinephrine responses after sternotomy ( $P = 0.0001$ ) and at the end of operation ( $P = 0.0241$ ), and norepinephrine responses after sternotomy ( $P = 0.0012$ ) and at the end of operation ( $P = 0.0087$ ) (Fig. 1). The halothane group also had significantly higher glucagon responses after sternotomy ( $P = 0.0049$ ), after hypothermic circulatory arrest ( $P = 0.001$ ), and at the end of operation ( $P = 0.0027$ ), but significantly decreased insulin responses after sternotomy ( $P = 0.0099$ ) and insulin:glucagon molar ratios after sternotomy ( $P = 0.001$ ) and after circulatory arrest ( $P = 0.0032$ ) (Fig. 2). The halothane group had higher values than the sufentanil group for cortisol responses after sternotomy ( $P < 0.0001$ ), after hypothermic circulatory arrest ( $P = 0.001$ ), and at the end of

\*See NAPS document no. 04918 for seven pages of supplementary material. Order from NAPS c/o Microfiche Publications, P.O. Box 3513, Grand Central Station, New York, NY 10163-3513. Remit in advance (in U.S. funds only) \$7.75 for photocopies or \$5 for microfiche. Outside the U.S. and Canada add postage of \$4.50 (\$1.75 for microfiche postage). There is a \$15 invoicing charge on all orders filled before payment.

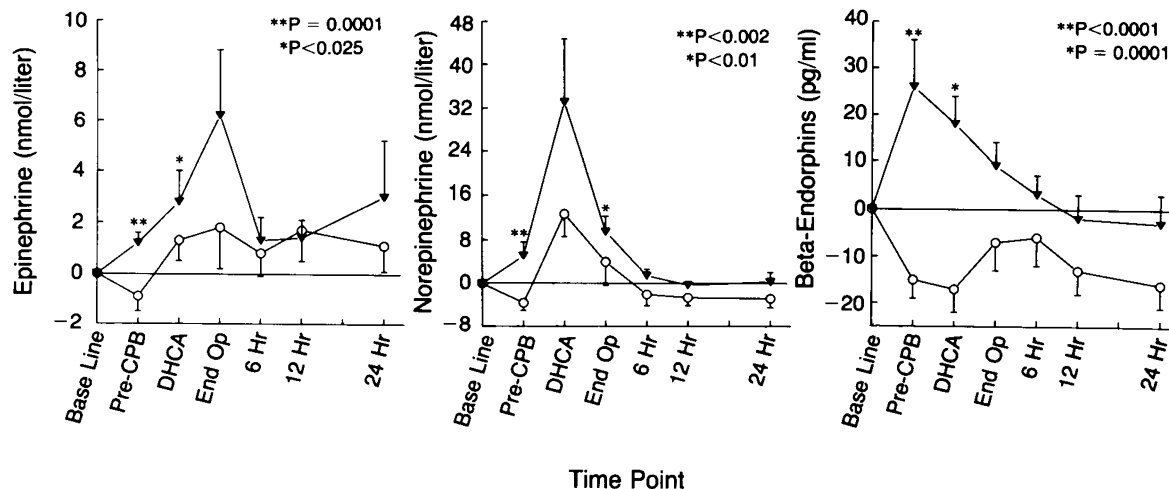


Figure 1. Perioperative Changes in Plasma Epinephrine and Norepinephrine Concentrations and Plasma Beta-Endorphin Immunoreactivity in the Halothane Group (▼, N = 15) and the Sufentanil Group (○, N = 30).

The rounded P values shown were determined with the Mann-Whitney U test. Pre-CPB denotes measurement before cardiopulmonary bypass, DHCA measurement after deep hypothermic circulatory arrest, and End Op measurement at end of operation.

operation ( $P = 0.0076$ ) and for 11-deoxycortisol responses after sternotomy ( $P = 0.0059$ ) (Fig. 3A); this group also had higher values for progesterone responses after circulatory arrest ( $P = 0.0027$ ) and 24 hours after operation ( $P = 0.0104$ ), corticosterone responses after sternotomy ( $P = 0.0001$ ) and after circulatory arrest ( $P = 0.0003$ ), and aldosterone responses after sternotomy ( $P = 0.0096$ ) and after circulatory arrest ( $P = 0.0087$ ) (Fig. 3B). The two study groups did not differ significantly in their cortisone, 17-hydroxyprogesterone, or 11-deoxycorticosterone responses.

### Metabolic Responses

The increases in blood glucose and lactate concentrations in the halothane group were twice those

of the sufentanil group at the end of operation ( $P = 0.017$  and  $P = 0.0248$ , respectively); the changes in lactate and acetoacetate concentrations in the halothane group were greater 6 hours after operation ( $P = 0.0248$  and  $P = 0.0223$ , respectively) and 24 hours after operation ( $P = 0.0088$  and  $P = 0.0168$ , respectively) (Fig. 4). The groups did not differ with respect to perioperative changes in blood levels of pyruvate, alanine, or 3-hydroxybutyrate.

### Clinical Outcome

Data on clinical outcome were not taken into account in our hypothesis or in the power analysis described above; differences for which the P value was less than 0.05 were considered significant in this small series of patients. The halothane group had an in-

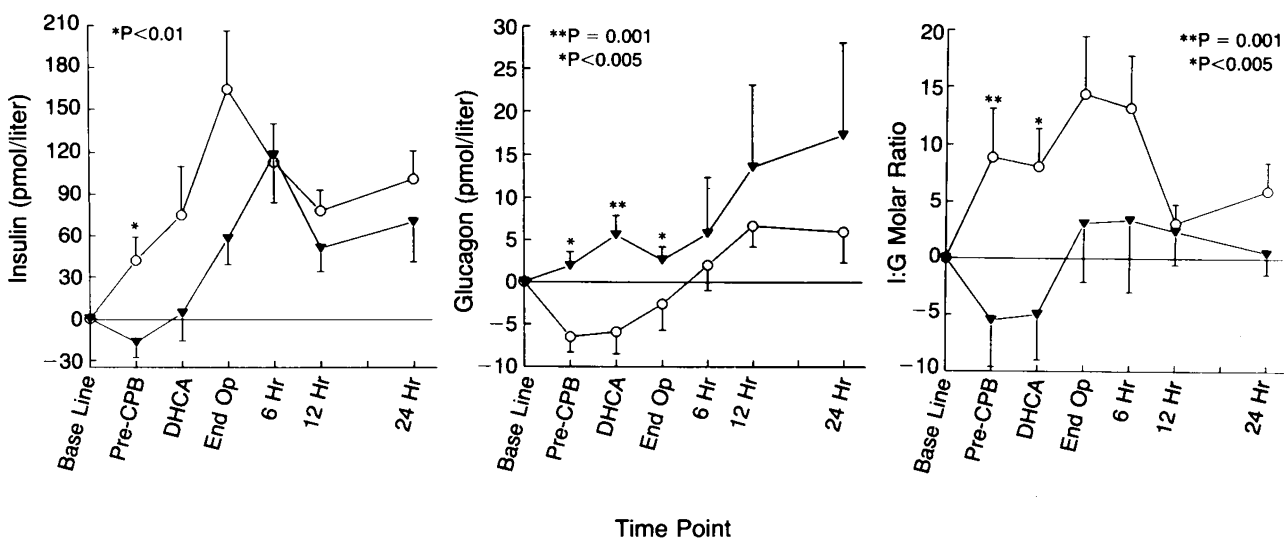


Figure 2. Perioperative Changes in Plasma Insulin and Glucagon Concentrations and the Insulin:Glucagon (I:G) Molar Ratio in the Halothane Group (▼, N = 15) and the Sufentanil Group (○, N = 30).

P values were determined with the Mann-Whitney U test. For an explanation of the abbreviations, see the legend of Figure 1.

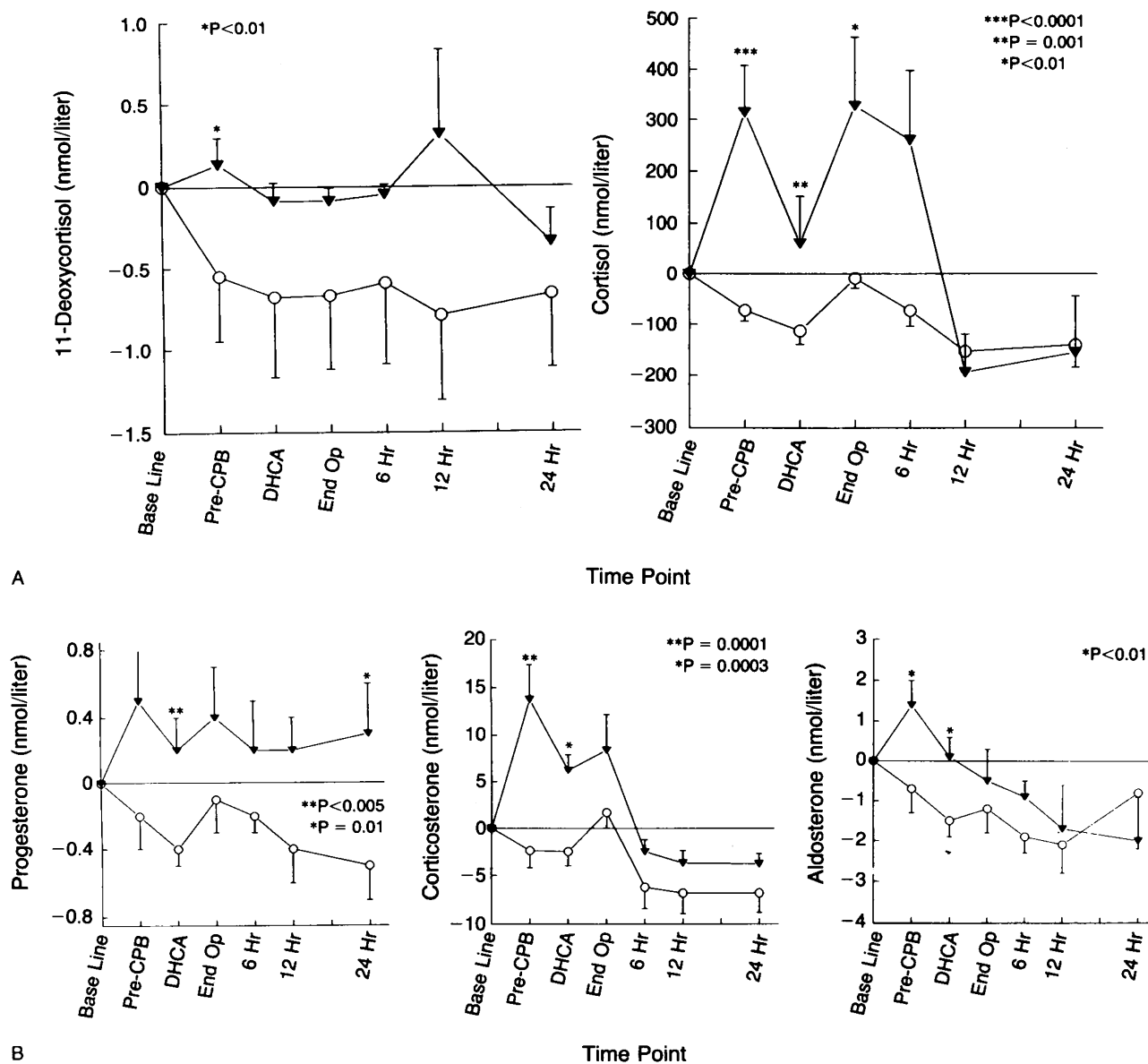


Figure 3. Perioperative Changes in Plasma 11-Deoxycortisol and Cortisol Concentrations (Panel A) and Plasma Progesterone, Corticosterone, and Aldosterone Concentrations (Panel B) in the Halothane Group (▼, N = 15) and the Sufentanil Group (○, N = 30). P values were determined with the Mann-Whitney U test. For an explanation of the abbreviations, see the legend of Figure 1.

creased incidence of sepsis ( $P = 0.03$ ), disseminated intravascular coagulation ( $P = 0.03$ ), and persistent metabolic acidosis ( $P = 0.0092$ ). Four of the 15 neonates in the halothane group died postoperatively before discharge from the ICU, whereas none of the 30 in the sufentanil group died ( $P = 0.0092$ ). Figure 5 shows study mortality (as defined in the Methods section) and hospital mortality among neonates who underwent cardiac surgery with bypass and hypothermic circulatory arrest at our institution during and after the study period. Mortality in the sufentanil group was significantly lower than hospital mortality in other neonates undergoing cardiac surgery with bypass and circulatory arrest during the study period ( $P = 0.0067$ ), whereas mortality in the halothane group was not significantly different from hospital

mortality in these other neonates ( $P = 0.39$ ). Among the surviving neonates, the two study groups did not differ significantly with respect to the duration of postoperative ventilation, the stay in the ICU, or the total hospital stay (Table 4).

## DISCUSSION

Few attempts have been made to modify the extreme responses of neonates to perioperative pain and stress. Techniques of neonatal anesthesia have been based on the assumption that responses to pain and surgical stress are not clinically important in neonates and that the use of lighter levels of anesthesia in critically ill neonates may prevent respiratory or circulatory complications in the perioperative period. The effects of anesthesia on hormonal and metabolic re-

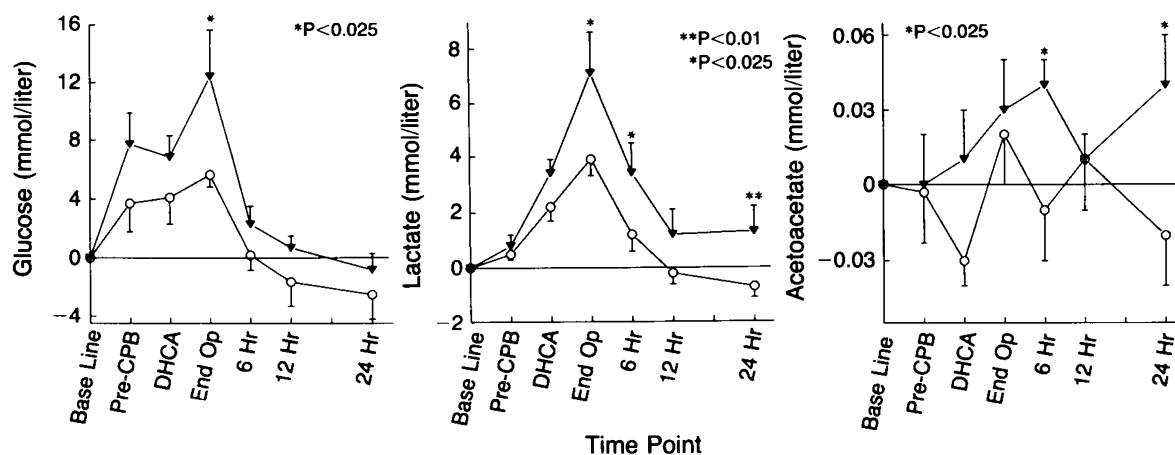


Figure 4. Perioperative Changes in Blood Glucose, Lactate, and Acetoacetate Concentrations in the Halothane Group (▼, N = 15) and the Sufentanil Group (○, N = 30).

P values were determined with the Mann-Whitney U test. For an explanation of the abbreviations, see the legend of Figure 1.

sponses of neonates undergoing cardiac surgery<sup>17</sup> and the relation of these responses to clinical outcome have not previously been evaluated in a prospective, randomized trial. Whether the reduction in the responses of neonates or adults to stress achieved with specific anesthetic techniques improves postoperative outcome has not been established, regardless of the mechanisms underlying such effects.<sup>18</sup>

The design of the present trial included randomization in a ratio of 2:1 (i.e., 2 neonates assigned to the sufentanil group for every 1 neonate assigned to the halothane group) to increase the power of the trial.<sup>19</sup> Sufentanil was used because of its receptor specificity, its efficacy and safety,<sup>20</sup> and its known pharmacokinetics in newborns.<sup>21</sup> One group received deep levels of anesthesia with sufentanil and deep analgesia and

sedation with continuous postoperative infusions of opioids. In contrast, the other group was treated with a widely used technique of light anesthesia with halothane and morphine, with conventional postoperative analgesia and sedation. This trial thus compared two levels of intraoperative anesthesia and postoperative analgesia that were as disparate as possible, so that the stated hypothesis could be tested unambiguously.<sup>19</sup>

The neonates in the two groups had similar characteristics, surgical diagnoses, and perioperative care (Tables 1 and 2). The median age in both groups was 5 days, although mean age in the sufentanil group was somewhat skewed because four neonates were more than 20 days old; this difference was not significant ( $P = 0.2681$ ). The preoperative condition of the patients and the base-line values for all variables measured were similar in the two groups (Table 3). Nonsignificant differences between the groups in base-line values would not have affected the significance of subsequent responses, because all patients served as their own controls and only their responses (i.e., changes from the preoperative base-line sample) were compared. Even the differences in base-line variables that approached significance (e.g., the differences in plasma levels of beta-endorphin, aldosterone, progesterone, glucagon, and lactate and the insulin:glucagon molar ratio) suggested that the sufentanil group had a greater degree of stress before operation, a suggestion that further emphasizes that the differences in responses to stress are due to the anesthetic regimens in the two groups.

### Hormonal Responses

Intraoperative hormonal responses to stress in neonates given halothane anesthesia were substantially greater than those in neonates given sufentanil anesthesia. The halothane group responded to surgical stress with increases in beta-endorphin levels similar to those documented in adult surgical patients<sup>22</sup>; the inhibition of such increases in the sufentanil

Table 4. Postoperative Complications and Outcome in the Two Groups of Neonates.\*

FINDING	HALOTHANE GROUP (N = 15)	SUFENTANIL GROUP (N = 30)	P VALUE†
Hypotension	11 (73)	13 (43)	0.055
Arrhythmias	7 (47)	6 (20)	0.154
Sepsis or necrotizing enterocolitis	3 (20)	0	0.032
Disseminated intravascular coagulation	3 (20)	0	0.032
Seizures	4 (27)	3 (10)	0.154
Metabolic acidosis	4 (27)	0	0.009
Death	4 (27)	0	0.009
Postoperative ventilation (hr)	125 ± 45‡	127 ± 21	0.086§
Postoperative ICU stay (days)	9.0 ± 2.0‡	8.6 ± 0.9	0.413§
Postoperative hospital stay (days)	16.1 ± 3.6‡	16.9 ± 2.3	0.214§

\*Plus-minus values are means ± SE. Values in parentheses are percentages.

†By Fisher's exact test except as noted.

‡Data on the 11 surviving infants are given.

§By the Mann-Whitney U test.

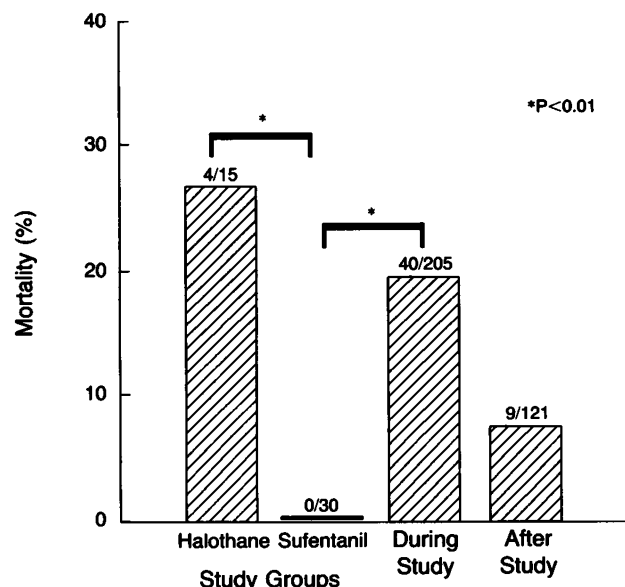


Figure 5. Mortality in the Study Groups and Hospital Mortality in All Neonates Undergoing Cardiopulmonary Bypass and Hypothermic Circulatory Arrest during the Study Period (July 1985 to December 1987) and afterward (July 1990 to June 1991).

group may have resulted from the effects of sufentanil on the hypothalamic–pituitary axis. Intraoperative responses of catecholamines were also significantly decreased by sufentanil, as in studies of adult patients,<sup>3</sup> but the differences in the present study were much greater because of the relatively higher responses of catecholamines in neonates.<sup>6</sup> The importance of glucagon as a hormone reflecting catabolic stress has been reported in adults<sup>3</sup> and infants<sup>23</sup> undergoing cardiac surgery. In our halothane group, intraoperative responses of glucagon were significantly higher and the insulin responses significantly lower than in the sufentanil group, probably owing to differences in the response of catecholamines. The low insulin:glucagon molar ratios in the halothane group during and after operation could promote a catabolic state, marked by stimulation of glycogenolysis, gluconeogenesis, and protein breakdown. The involuting fetal adrenal cortex of neonates may secrete precursor steroid hormones in response to stress.<sup>24</sup> Differences in the responses of cortisol and aldosterone and their immediate precursors (11-deoxycortisol and corticosterone, respectively) indicated the relative maturity of the adrenal cortex in the neonates studied.<sup>24</sup>

### Metabolic Responses

Few prospective clinical trials have examined the effects of opioid anesthesia on stress-induced metabolic alterations in neonates<sup>7</sup> or older children.<sup>25</sup> Hyperglycemic responses during cardiac operations, with or without lactic acidemia, have been observed in older infants, but data pertaining to neonates are sparse.<sup>17,23</sup> Hyperglycemia and lactic acidemia during cardiac operations in older children were related to the glucose

and lactate content of the cardiopulmonary-bypass perfusate.<sup>26</sup> In the present study, the composition of the bypass perfusate and the perioperative dextrose infusion rates were standardized (Tables 1 and 2). Hyperglycemic responses were decreased by anesthesia with high doses of sufentanil (Fig. 4), probably because of decreased stimulation of glycogenolysis and gluconeogenesis induced by catecholamines, glucagon, and glucocorticoids. In neonates in whom cerebral ischemia is induced during hypothermic circulatory arrest, even mild hyperglycemia can promote increased intracellular lactic acidosis and aggravate neuronal injury.<sup>27</sup> In the halothane group, the persistence of lactic acidemia after surgery may be explained by a higher lactate load at the end of surgery (Fig. 4), diminished hepatic clearance related to decreased insulin:glucagon ratios and hepatic blood flow, or lactate production due to decreased tissue perfusion.

In summary, this trial has demonstrated that the extreme stress responses to cardiac operations in neonates given light anesthesia and analgesia were attenuated in neonates given deep opiate anesthesia and analgesia.

### Clinical Outcome

In adult patients, extreme responses to stress have been associated with an increased incidence of complications after major operations,<sup>28-30</sup> trauma,<sup>31</sup> or congestive heart failure.<sup>32</sup> Randomized trials in neonates have also correlated surgical stress responses with an increased incidence of postoperative complications.<sup>7,8</sup> The present trial was originally designed to investigate the attenuation of neonatal stress responses by different depths of anesthesia and postoperative analgesia, but the observed differences in postoperative outcome also merit consideration. These differences in outcome occurred despite the similarity of the two groups with respect to patient characteristics, preoperative condition, surgical diagnoses, and surgical procedures.

The persistence of metabolic acidosis in the halothane group, partly as a result of the metabolic stress response, may have contributed to the poor outcome in this group. The myocardium of the newborn is more susceptible to intracellular lactate production during hypothermic circulatory arrest than that of the infant<sup>33</sup> or adult.<sup>34</sup> Myocardial hypertrophy and congestive heart failure in patients with congenital heart disease may further increase myocardial susceptibility to lactate production and ischemic injury, resulting in low-cardiac-output states, hypotension, arrhythmias, and further metabolic acidosis (Table 4). The increased incidence of sepsis in the halothane group may have been related to postoperative changes in immune function<sup>35</sup>; such changes have been correlated with hormonal stress responses in adult patients.<sup>36</sup> Beta-endorphins, glucocorticoids, catecholamines, and prolactin are important regulators of immune responses; such interactions may be integrated by the hypothalamus.<sup>37-39</sup>

A previous analysis of data on the halothane group<sup>6</sup>

indicated that the neonates who survived cardiac surgery had less extreme hormonal and metabolic responses than the neonates who died postoperatively.

This clinical trial is too small to allow firm conclusions about the associations among anesthetic techniques, increased stress responses, and poor outcome in neonates. However, the striking differences between the two study groups suggest that deeper levels of anesthesia and postoperative analgesia may improve postoperative outcome in critically ill neonates.

*Note added in proof:* The increased incidence of disseminated intravascular coagulation in the halothane group may have resulted from inappropriate activation of the coagulation cascade, as reported recently in adult patients treated with anesthetic regimens that did not minimize intraoperative as well as postoperative stress.<sup>40</sup>

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## APPENDIX

### Halothane Group

#### Details of Anesthetic Technique

##### Induction of anesthesia

Morphine, 0.1–0.2 mg/kg intravenously (repeated as required)  
Ketamine, 1–2 mg/kg intravenously  
Pancuronium, 0.1 mg/kg intravenously (repeated as required)  
Halothane, 0.5–2.0%  
Oxygen, 100% (supplemented with air if necessary)

##### Insertion of catheters, monitoring leads, and so on

##### Drugs before cardiopulmonary bypass

Heparin, 2 mg/kg intravenously  
Other drugs, as indicated by clinical condition

##### Induction of hypothermia for circulatory arrest

Passive cooling by exposure to room air  
Bypass cooling to 15–20°C (rectal)

##### Cardiopulmonary-bypass procedure

##### Composition of perfusate\*

Normosol R, 300–500 ml  
CPD blood, 500 ml

##### Drugs added

Heparin, 1–2 mg/kg  
Sodium 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 g/kg  
Calcium gluconate, 0.5–1 g  
Phentolamine, 0.1 mg/kg

##### Anesthetic management after bypass

Morphine, 0.1–0.2 mg/kg (repeated as required)  
Halothane, 0.5–1.0%  
Pancuronium, 0.1 mg/kg (repeated as required)  
Other drugs (given if clinically indicated)

Calcium gluconate  
Potassium chloride

Protamine  
Cefazolin  
Dopamine  
Isoproterenol  
Epinephrine  
Norepinephrine

##### Intravenous fluids before and after bypass

5% Dextrose, 4.8–7.2 ml/kg/hr *or*  
10% Dextrose, 2.4–3.6 ml/kg/hr *or*  
15% Dextrose, 1.6–2.4 ml/kg/hr (each infusion to provide 4–6 mg of glucose/kg/min)

##### Fluids given in unrestricted quantities as required

Normal saline  
Heparin-treated saline  
5% Albumin  
Fresh-frozen plasma  
Whole blood or blood products

### Postoperative Analgesia

Morphine, 0.1–0.2 mg/kg intravenously  
Diazepam, 0.1–0.2 mg/kg intravenously  
(Both drugs were given every 1 or 2 hr as required)

### Sufentanil Group

#### Details of Anesthetic Technique

##### Induction of anesthesia

Sufentanil, 5–10 µg/kg intravenously  
Pancuronium, 0.1 mg/kg intravenously (repeated as required)  
Oxygen, 100% (supplemented with air if necessary)

##### Insertion of catheters, monitoring leads, and so on

Sufentanil, 10 µg/kg intravenously (*before* surgical incision)

##### Drugs before cardiopulmonary bypass

Heparin, 2 mg/kg intravenously  
Other drugs, as indicated by clinical condition

##### Induction of hypothermia for circulatory arrest

Passive cooling by exposure to room air  
Bypass cooling to 15–20°C (rectal)

##### Cardiopulmonary bypass procedure

##### Composition of perfusate\*

Normosol R, 300–500 ml  
CPD blood, 500 ml

##### Drugs added

Heparin, 1–2 mg/kg  
Sodium 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

Sufentanil, 10 µg/kg  
Mannitol, 0.5 g/kg  
Calcium gluconate, 0.5–1 g  
Phentolamine, 0.1 mg/kg

##### Anesthetic management after bypass

Sufentanil, 5 µg/kg intravenously (to be repeated if surgery lasts >1 hr)

Pancuronium, 0.1 mg/kg (repeated as required)

##### Other drugs (given if clinically required)

Calcium gluconate  
Potassium chloride  
Protamine  
Cefazolin  
Dopamine  
Isoproterenol  
Epinephrine  
Norepinephrine

\*Normosol R denotes an isotonic solution containing plasma electrolytes, and CPD blood, blood treated with the anticoagulant solution citrate-phosphate-dextrose.



## Intravenous fluids before and after bypass

- 5% Dextrose, 4.8–7.2 ml/kg/hr *or*
- 10% Dextrose, 2.4–3.6 ml/kg/hr *or*
- 15% Dextrose, 1.6–2.4 ml/kg/hr (each infusion to provide 4–6 mg of glucose/kg/min)

## Fluids given in unrestricted quantities, as required clinically

- Normal saline
- Heparin-treated saline
- 5% Albumin
- Fresh-frozen plasma
- Whole blood or blood products

## Postoperative Analgesia

Sufentanil infusion, 2–4  $\mu\text{g/kg/hr}$  intravenously (for 15 neonates)  
 Fentanyl infusion, 8–15  $\mu\text{g/kg/hr}$  intravenously (for 15 neonates)  
 (Additional boluses of these drugs were given every 2 to 4 hr as required)

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