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Pancuronium Does Not Alter the Hemodynamic Status of Piglets after Normoxia or Hypoxia[1]

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ABSTRACT. Pancuronium is a neuromuscular blocking agent commonly used to eliminate agitation in sick newborn infants requiring mechanical ventilation. Experimental data supporting this method of intervention are controversial, and hemodynamic studies in newborn infants report conflicting results. This study was designed to determine the hemodynamic effects of pancuronium administered under conditions of normoxia, hypoxia, and preexposure to hypoxia in neonatal piglets with normal lungs. After baseline hemodynamic and blood gas measurements were obtained, pancuronium was administered in two i.v. bolus injections of 0.1 mg/kg. Tidal volume and minute ventilation were maintained constant during the experimental procedure by adjusting ventilator settings. Twenty min after pancuronium, no changes from baseline values were found in arterial blood gases, heart rate, cardiac output, mean arterial pressure, systemic vascular resistance, pulmonary artery pressure, pulmonary vascular resistance, central venous pressure, or pulmonary capillary wedge pressure in any of the three conditions studied. In conclusion, pancuronium administered during normoxia, hypoxia, or after preexposure to hypoxia while controlled ventilation is maintained does not alter systemic or pulmonary hemodynamic status of the newborn piglet. (*Pediatr Res* 33: 365–372, 1993)

Abbreviations

CO, cardiac output
CVP, central venous pressure
FiO_2, fraction of inspired oxygen
HR, heart rate
MAP, mean arterial pressure
PAP, pulmonary artery pressure
PCWP, pulmonary capillary wedge pressure
PIP, peak inspiratory pressure
PaO_2, partial pressure arterial O_2
$PaCO_2$, partial pressure arterial CO_2
PVR, pulmonary vascular resistance
SVR, systemic vascular resistance
V_T, tidal volume
V_E, minute ventilation

Pancuronium is the most common neuromuscular blocking agent used in the neonatal intensive care unit (1). It is used to treat sick newborn infants requiring mechanical ventilation in an effort to eliminate agitation and permit synchronous breathing with the ventilator (2). When pancuronium is used for this purpose, some studies document improved oxygenation (3, 4), whereas others report the opposite (5, 6).

Studies of the hemodynamic effects of pancuronium administration in newborn infants are also equivocal. A spectrum of effects has been reported including increasing (7) or decreasing blood pressure (8), increasing HR (7), and no effect on HR or blood pressure (4, 9–11). Because pancuronium is currently used for treating sick infants without a consensus regarding its effects on oxygenation and hemodynamic function, its therapeutic use has remained controversial (1, 2).

Different responses to pancuronium may reflect differences in the pulmonary hemodynamic status of the newborn infant before pancuronium administration. For example, pancuronium (as well as other pharmacologic agents) may exhibit different effects depending on whether it is given during baseline normoxic conditions or when the pulmonary vasculature is sensitized to vasoconstrictive stimuli during, or even after, preexposure to hypoxia (12–14). Alternatively, if the pulmonary vasculature is already maximally vasoconstricted during hypoxia, no further vasoconstrictive action by pancuronium may be detected. In any case, the use of pancuronium in the hypoxic, sick newborn infant at risk for pulmonary hypertension may have dramatically different effects from those observed in an infant with normal pulmonary function.

Also, it is possible that rather than being direct effects of the drug, the reported hemodynamic effects of pancuronium may represent a secondary response to altered ventilation. Drug-induced muscle paralysis of infants who during mechanical ventilation are breathing spontaneously may lead to hypoventilation after the loss of spontaneous respirations (15, 16). This could stimulate the release of catecholamines, resulting in elevation of HR and blood pressure (7). Maintaining adequate ventilation by increasing PIP immediately before pancuronium administration has been shown to decrease noradrenaline levels and prevent blood pressure changes in infants (17). In other circumstances, spontaneous respirations may interfere with otherwise adequate mechanical ventilation, and pancuronium administration may improve ventilation while preventing catecholamine-mediated hemodynamic effects. This concept is supported by Crone and Favorito (4), who demonstrated improvement in PaO_2 and reduction in $PaCO_2$ without changes in HR or blood pressure after pancuronium administration.

Therefore, in this study we investigated whether different conditions of normoxia, hypoxia, or preexposure to hypoxia could be responsible for variable hemodynamic and blood gas responses to pancuronium. We hypothesized that under these conditions, pancuronium would not result in perturbations in

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[1] The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Department of the Army or the Department of Defense.

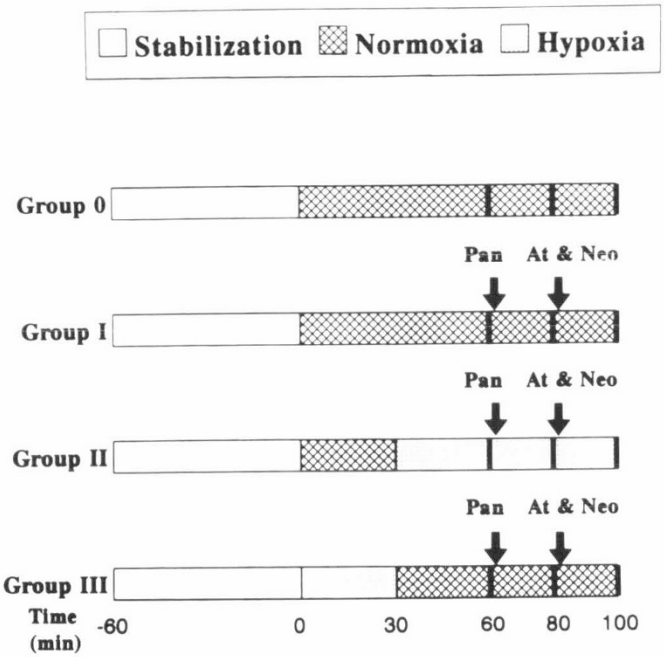

Fig. 1. Outline of study design with groups designated as 0, I, II, and III. *Arrows* are time points when drugs were administered. *Pan*, pancuronium; *At & Neo*, atropine and neostigmine. The *black vertical bars* at 60, 80, and 100 min represent measurement times; results are shown in Figures 2–6. The measurement at 60 min represents a baseline just before pancuronium administration (designated Baseline in Figs. 2–6). The 80-min measurement represents effects 20 min after pancuronium (designated Pan in Figs. 2–6). The 100-min measurement represents effects 20 min after atropine and neostigmine (designated At & Neo in Figs. 2–6).

hemodynamic function if V_T and V_E were maintained constant after drug administration.

MATERIALS AND METHODS

Animal preparation. This study was approved by the Institutional Animal Use and Care Committee of Tripler Army Medical Center and was in compliance with the Animal Welfare Act. Twenty-three newborn pigs of either sex, 6.5 ± 1 d postnatal age, weighing 2.2 ± 0.2 kg (Shimokawa Farms, Waimanalo, HI) were studied in the supine position after intraperitoneal anesthesia with pentobarbital sodium 30 mg/kg (Wyeth Laboratories, Philadelphia, PA) supplemented by 5–10 mg/kg intraarterially as needed. Piglets were intubated with a 3.0-mm cuffed endotracheal tube for mechanical ventilation with a Baby Bird pediatric ventilator (Bird Corp., Palm Springs, CA).

Initial ventilator settings were PIP 1.18–1.37 kPa (12–14 cm H_2O), positive end-expiratory pressure 0.20 kPa (2 cm H_2O), rate 35–40/min, inspiratory time 0.35 s, and FiO_2 0.21. Blood gas values were maintained at pH 7.35–7.45, $PaCO_2$ 4.67–6.00 kPa (35–45 torr), and PaO_2 8.00–10.67 kPa (60–80 torr) by appropriate ventilator adjustments. Ventilator parameters were set and monitored with a microprocessor-based ventilator monitor (model 1200, Novametrics, Wallingford, CT), on-line CO_2 was monitored with an end-tidal CO_2 monitor (model 47210A, Hewlett-Packard Co., Palo Alto, CA), and V_T (inspiratory and expiratory) and V_E were monitored with a neonatal V_T monitor (Bear Medical Systems NVM-1, Riverside, CA). The validity of this monitor, using a hot-wire anemometer to measure V_T, has recently been demonstrated (18, 19).

The femoral artery was cannulated with a 4 French double-lumen catheter (Cook Inc., Bloomington, IN) for arterial blood sampling and measuring MAP. The femoral vein was cannulated with a 0.06-mm outer diameter catheter (Norton Performance Plastics, Akron, OH) for continuous infusion of normal saline, 100 μL/kg/min. The right external jugular was cannulated with a 5 French Swan-Ganz catheter (Baxter Healthcare Corp., Irvine,

Table 1. *Ventilatory parameters and hemodynamic values for group 0 vs group I**

	Group 0 (n = 5)			Group I (n = 6)		
	60 min	80 min	100 min	60 min (baseline)	80 min (Pan)	100 min (At & Neo)
V_T (mL/kg)	9.3 ± 0.5	9.2 ± 0.5	9.1 ± 0.5	10.6 ± 1.0	10.9 ± 1.0	10.5 ± 0.9
V_E (L/min)	0.87 ± 0.1	0.86 ± 0.1	0.85 ± 0.1	1.02 ± 0.25	1.03 ± 0.25	0.99 ± 0.23
pH	7.46 ± 0.01	7.46 ± 0.01	7.46 ± 0.01	7.43 ± 0.01	7.42 ± 0.012	7.41 ± 0.009
$PaCO_2$ (kPa)	5.12 ± 0.11	5.15 ± 0.11	5.17 ± 0.09	5.23 ± 0.08	5.19 ± 0.15	5.41 ± 0.15
$PaCO_2$ (torr)	38.4 ± 0.8	38.64 ± 0.8	38.8 ± 0.7	39.2 ± 0.6	38.9 ± 1.1	40.6 ± 1.1
PaO_2 (kPa)	9.62 ± 0.12	9.53 ± 0.15	9.52 ± 0.12	10.2 ± 0.39	10.21 ± 0.43	9.70 ± 0.27
PaO_2 (torr)	72.2 ± 0.9	71.5 ± 1.1	71.4 ± 0.9	76.5 ± 2.9	76.6 ± 3.2	72.8 ± 2.0
Systemic						
HR (beats/min)	201 ± 8	207 ± 10	204 ± 13†	226 ± 12	235 ± 11	245 ± 8
CO (mL/min/kg)	225 ± 26	225 ± 23	241 ± 23	209 ± 12	209 ± 9	218 ± 25
MAP (kPa)	10 ± 0.4†	10 ± 0.4†	9.6 ± 0.4	8.13 ± 0.53	8.13 ± 0.4	8.4 ± 0.4
MAP (mm Hg)	75 ± 3†	75 ± 3†	72 ± 3	61 ± 4	61 ± 3	63 ± 3
SVR kPa/(mL/min/kg)	0.04 ± 0.005	0.04 ± 0.004	0.04 ± 0.005	0.04 ± 0.004	0.04 ± 0.003	0.04 ± 0.004
SVR mm Hg/(mL/min/kg)	0.35 ± 0.04	0.34 ± 0.03	0.33 ± 0.04	0.29 ± 0.03	0.29 ± 0.02	0.29 ± 0.03
Pulmonary						
PAP (kPa)	1.87 ± 0.13	1.87 ± 0.13	1.87 ± 0.13	2.4 ± 0.13	2.4 ± 0.13	2.27 ± 0.13
PAP (mm Hg)	14 ± 1	14 ± 1	14 ± 1	18 ± 1	18 ± 1	17 ± 1
PVR kPa (mL/min/kg)	0.007 ± 0.001	0.006 ± 0.001	0.006 ± 0.001	0.008 ± 0.001	0.008 ± 0	0.007 ± 0
PVR mmHg (mL/min/kg)	0.05 ± 0.01	0.05 ± 0.01	0.05 ± 0.01	0.06 ± 0.01	0.06 ± 0	0.06 ± 0
CVP (kPa)	0.21 ± 0.02	0.19 ± 0.02	0.19 ± 0.02	0.24 ± 0.02	0.27 ± 0.02	0.27 ± 0.02
CVP (mm Hg)	1.6 ± 0.14	1.4 ± 0.14	1.4 ± 0.14	1.8 ± 0.13	2 ± 0.13	2 ± 0.13
PCWP (kPa)	0.37 ± 0.05	0.43 ± 0.05	0.4 ± 0.05	0.71 ± 0.04	0.78 ± 0.04	0.64 ± 0.04
PCWP (mm Hg)	2.8 ± 0.35	3.2 ± 0.35	3 ± 0.35	5.33 ± 0.32	5.83 ± 0.32	4.83 ± 0.32

* Values are mean ± SEM. Pan, after paralysis with pancuronium; At & Neo, after treatment with atropine and neostigmine.
† Group 0 different from group I; $p < 0.05$.

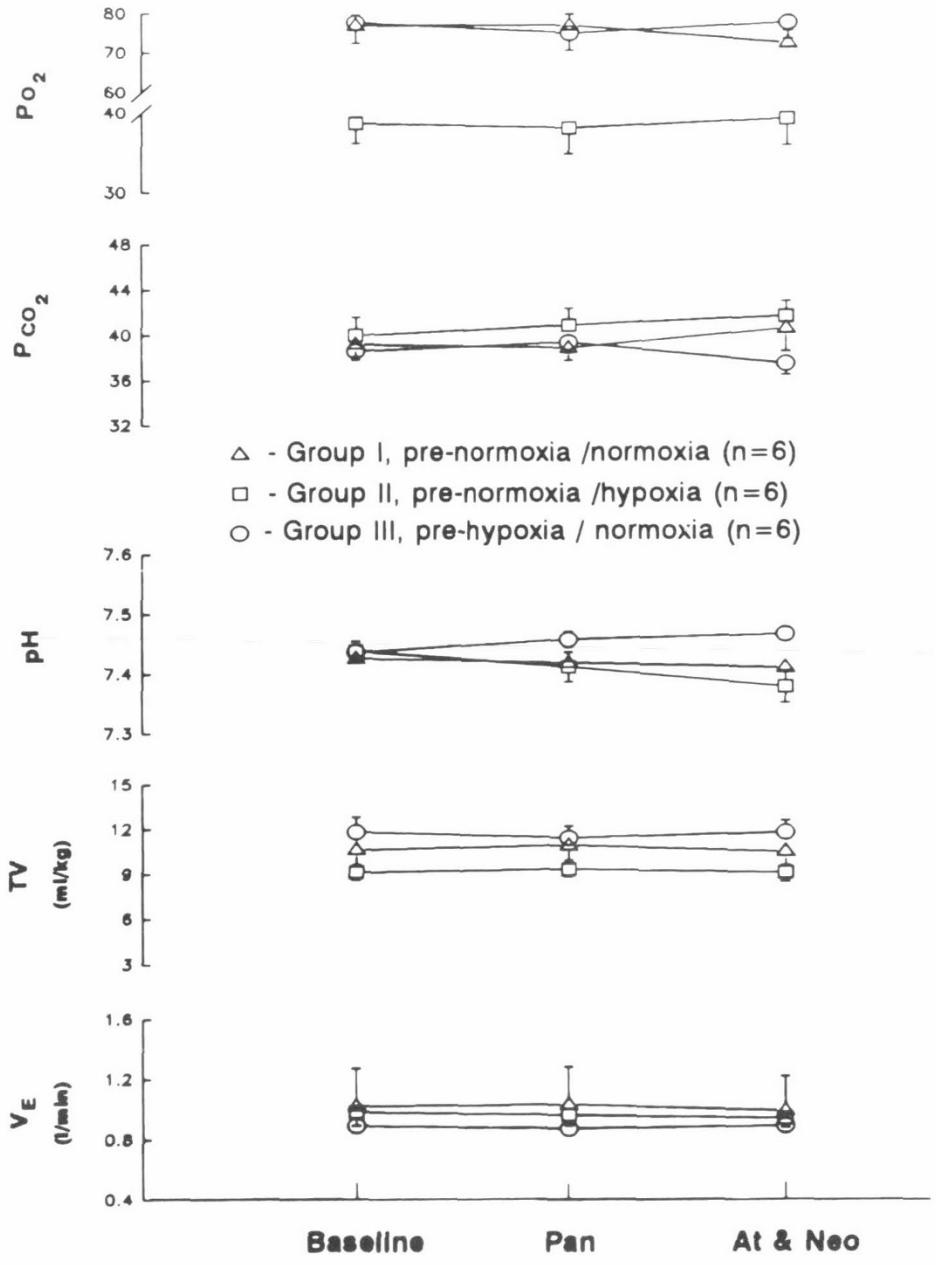

Fig. 2. Pa_{O_2}, Pa_{CO_2}, pH, V_T (*TV*), and V_E in group I *vs* II *vs* III. *Baseline*, before pancuronium; *Pan*, 20 min after pancuronium; *At & Neo*, 20 min after atropine and neostigmine. Pa_{O_2} and Pa_{CO_2} units are torr; Pa_{O_2} or Pa_{CO_2} in kPa = value × 0.1333. Values are mean ± SEM.

CA), after which the tip was advanced to the pulmonary artery for measurement of PAP, PCWP, and CO. Confirmation of catheter placement was made by identifying the characteristic wave forms and at autopsy. A 4 French polyurethane catheter (Arrow International Inc., Reading, PA) was inserted into the right atrium via the left external jugular vein for measurement of CVP and administration of cold dextrose (5% in water) for CO determination by thermodilution (Hewlett-Packard model 66#M1176A6). Femoral artery, right atrial, and Swan-Ganz catheters were connected to pressure transducers (Hewlett-Packard model 1290A for CVP, model 1290C for PAP and MAP), zeroed at the midcardiac level, and signals were recorded and displayed with a monitor (Hewlett-Packard model 66#M1176A6). Body temperature was monitored continuously with a rectal probe connected to the Hewlett-Packard monitor and was maintained between 38° and 39°C by use of a heating pad. Arterial blood was drawn at preset intervals for measurement of blood gases (model 168 pH/blood gas analyzer, Corning Medical, Medfield, MA), osmolality, hematocrit, and electrolytes.

Experimental design. After instrumentation and 60 min of stabilization, piglets were randomly assigned to one of four groups and studied as outlined in Figure 1. Groups I, II, and III were all treated with pancuronium (Astra Pharmaceutical Products, Westborough, MA; 0.1 mg/kg i.v., two rapid bolus injections administered 5 min apart) after baseline values were obtained. Twenty min after pancuronium administration, atropine (Elkins-Sinn Inc., Cherry Hill, NJ; 0.02 mg/kg i.v.) and neostigmine (Squibb-Marsam, Princeton, NJ; 0.08 mg/kg i.v.) were given to reverse any pancuronium effects. Another group of piglets was studied as a normoxia control group (group 0) not exposed to pancuronium to verify the stability of the animal preparation and document that there were no hemodynamic changes over time in piglets not exposed to pancuronium.

Group I piglets were subjected to normoxia (FiO_2 = 0.21) throughout the experiment. Group II piglets were subjected to 30 min of normoxia, followed by 70 min of hypoxia (FiO_2 = 0.15); drugs were administered during hypoxia. Group III piglets

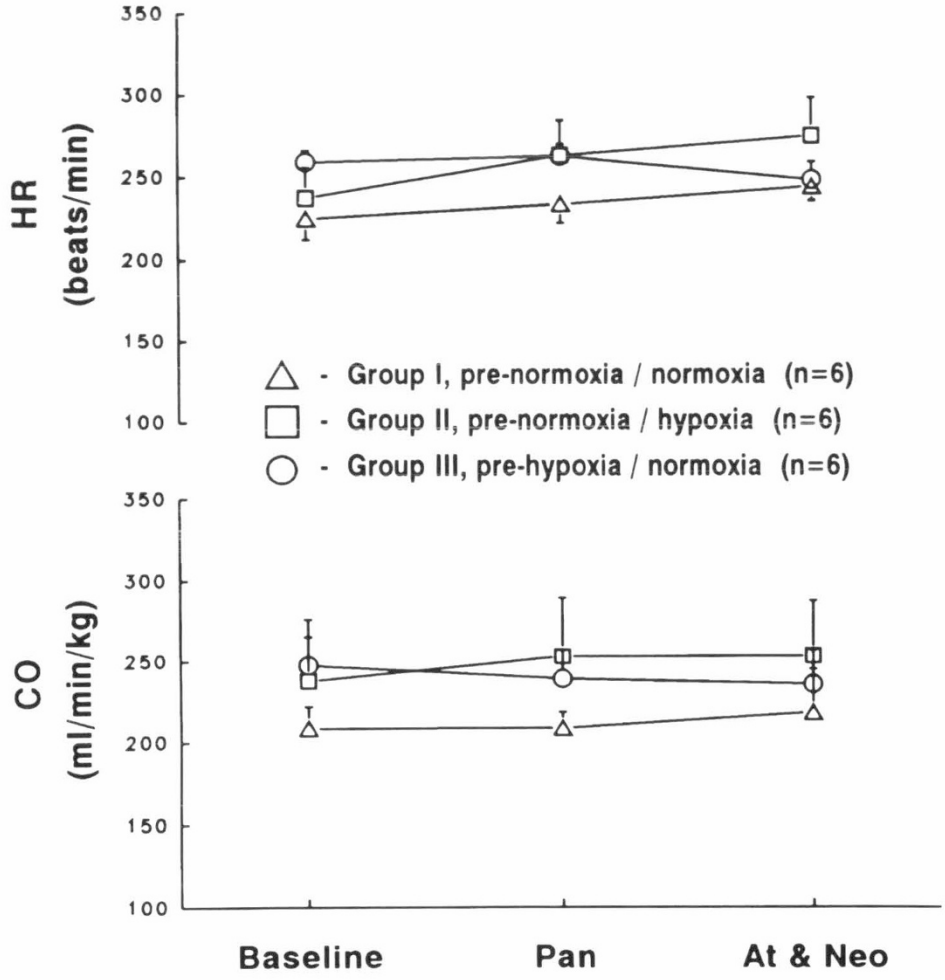

Fig. 3. HR and CO in group I *vs* II *vs* III. Values are mean ± SEM.

were subjected to 30 min of hypoxia followed by 70 min of normoxia; drugs were administered during normoxia (Fig. 1). Hypoxia ($FiO_2 = 0.15$) was achieved with a mixture of nitrogen in air.

Hemodynamic measurements (MAP, HR, CO, PAP, PCWP, and CVP) were recorded and blood was sampled just before pancuronium, 20 min after pancuronium, and 20 min after reversal of pancuronium action with atropine and neostigmine. Although these values represent spot measurements, hemodynamic and pulmonary function parameters were continuously observed before, during, and after drug administration; the 20-min values were representative of the entire preceding 20-min period. Arterial blood (0.3 mL) was drawn for measurement of blood gases. An additional blood sample (1.0 mL) was drawn and plasma was separated for osmolality (micro-osmometer model 3MO, Advanced Instruments, Needham Heights, MA), hematocrit, and sodium and potassium (ASTRA-4, Beckman Instruments, Brea, CA) analyses. The remaining red blood cells were reinfused after reconstitution in normal saline within 10 min of blood sampling.

End-tidal CO_2, V_T, and V_E were continuously monitored. When necessary during pancuronium administration, the ventilator was immediately adjusted to maintain a constant V_T and V_E. PIP was adjusted [−0.29 to +0.49 kPa (−3 to +5 cm H_2O)] to maintain V_T; rate was adjusted no more than three breaths per min to maintain V_E. The importance of immediate ventilatory changes to avoid decreases in V_T and V_E was demonstrated in two preliminary experiments. When V_T and V_E were not controlled, pancuronium administration resulted in an immediate elevation in PAP (increasing 35% and 100%, respectively) associated with a decrease in V_E, presumably as a result of respiratory acidosis and/or hypercarbia (20). PVR and SVR were calculated by standard formulas as follows:

$$PVR = (PAP - PCWP)/(CO/KG)$$

$$SVR = (MAP - CVP)/(CO/KG)$$

At the conclusion of each experiment, an autopsy was performed to examine cardiac anatomy, confirm catheter placement, and evaluate the status of the ductus arteriosus.

Data analysis. The results were analyzed by two-way analysis of variance for repeated measures. When significance ($p < 0.05$) was achieved, the Duncan's multiple range posthoc test was used for multiple comparisons between and within groups. All data are expressed as mean ± SEM.

RESULTS

Hematocrit, serum sodium, potassium, and osmolality were unchanged at 60, 80, and 100 min in all study groups, verifying the stability of fluid and electrolyte balance in this animal model.

Effect of pancuronium on stability of systemic and pulmonary hemodynamics during normoxia: group 0 versus group I. Table 1 summarizes the results of group 0 and group I piglets. There were no differences in the measurements over time in the group 0 control group. Also, there were no significant differences when comparing measurements taken at baseline with those after paralysis with pancuronium or after treatment with atropine and neostigmine in group I.

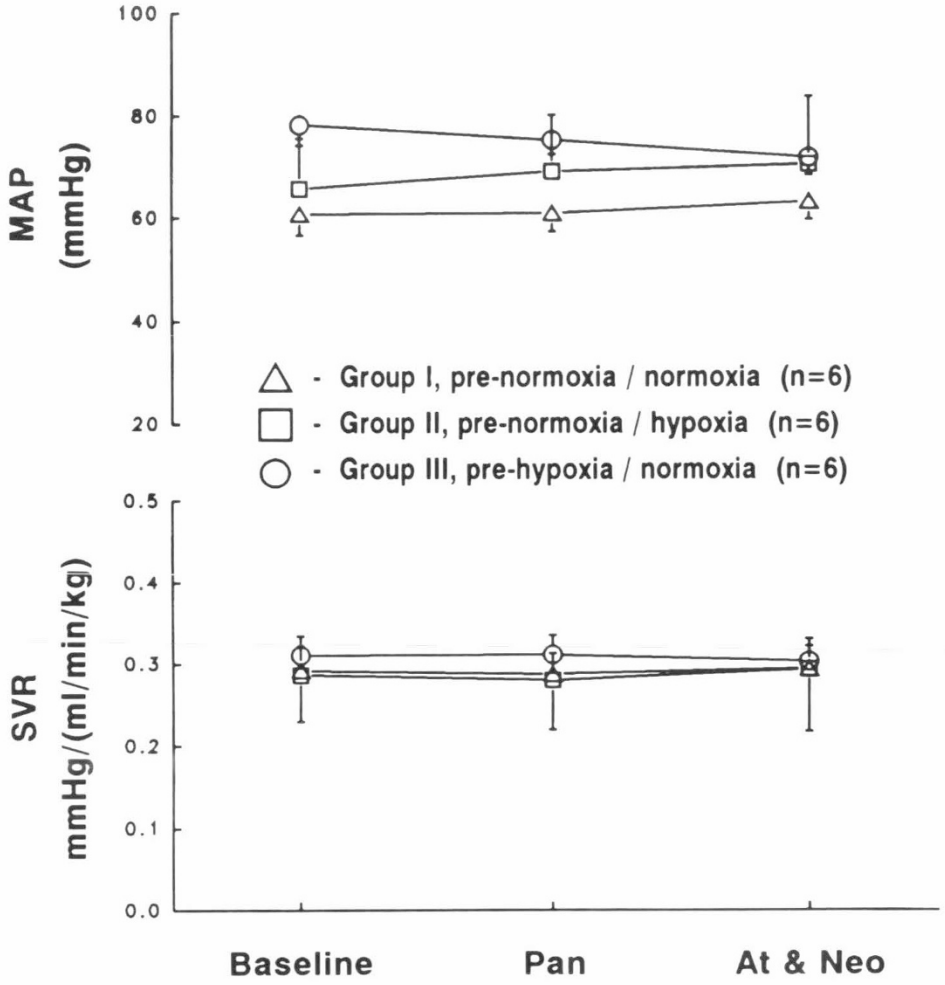

Fig. 4. MAP and SVR in group I *vs* II *vs* III. MAP or SVR in kPa = value × 0.1333. Values are mean ± SEM.

Effect of hypoxia before or during pancuronium administration on systemic and pulmonary hemodynamics: group I versus group II versus group III. Pa_{O_2}, Pa_{CO_2}, pH, V_T, and V_E remained stable before and after pancuronium administration in all groups (Fig. 2).

There were no differences in starting systemic hemodynamic values between groups I, II, and III. Within each group, HR and CO (Fig. 3), and MAP and SVR (Fig. 4), remained stable with no significant differences before and throughout the 20-min period after pancuronium administration. Similarly, blockade of any pancuronium effects with atropine and neostigmine caused no changes in systemic hemodynamic parameters up to 20 min after administration.

Reflecting the pulmonary hemodynamic response to hypoxia, starting PAP and PVR values were significantly higher in group II as compared with groups I and III (Fig. 5). Nevertheless, PAP and PVR (Fig. 5), and CVP and PCWP (Fig. 6), remained stable with no significant differences before and throughout the 20-min period after pancuronium administration in all three groups studied. Blockade of pancuronium action with atropine and neostigmine did not change pulmonary hemodynamic parameters. Thus, hypoxia or preexposure to hypoxia did not alter the apparent lack of effect of pancuronium on hemodynamic function.

At autopsy, although we did not definitively rule out ductal shunting, we were able to find only small probe-patent ductal orifices. This is consistent with the developmental and anatomical descriptions of Haworth and Hislop (21) and Evans *et al.* (22) for pigs at this age. It is also in agreement with previous studies showing a lack of ductal shunting found with hypoxia (12), bacterial infusion (23–25), or graded increases in PAP (26) to induce pulmonary hypertension.

Because these results showed no change in any of the hemodynamic parameters in all conditions studied, we analyzed the potential for false-negative results introduced by possible type II errors in each group studied (27). With a sample size of six piglets in groups I through III, after pancuronium administration, up to a 35% change in most of the hemodynamic parameters would have been detected with 85 to 100% confidence.

DISCUSSION

Our results demonstrate that pancuronium administration under conditions of normoxia, hypoxia, or preexposure to hypoxia had no significant effects on measured hemodynamics in the anesthetized newborn piglet with normal lungs for up to 20 min after administration. We believe that, by controlling ventilation through adjustments in V_T and ventilator rate, changes in Pa_{CO_2} and the increase in PAP typically associated with hypercarbia were prevented. An increase in PAP was demonstrated in preliminary studies (see Materials and Methods) when V_T and V_E were not adjusted after pancuronium, with cessation of spontaneous respirations. This supported our hypothesis that it is important to maintain ventilation after drug administration so as not to confuse effects due to hypoventilation after muscle paralysis with any direct hemodynamic effects of pancuronium.

Our failure to demonstrate any direct hemodynamic actions of pancuronium in the neonatal piglet are in agreement with Wolfson and Shaffer (28) and in partial agreement with Cameron *et al.* (13); both groups showed no change in baseline HR or

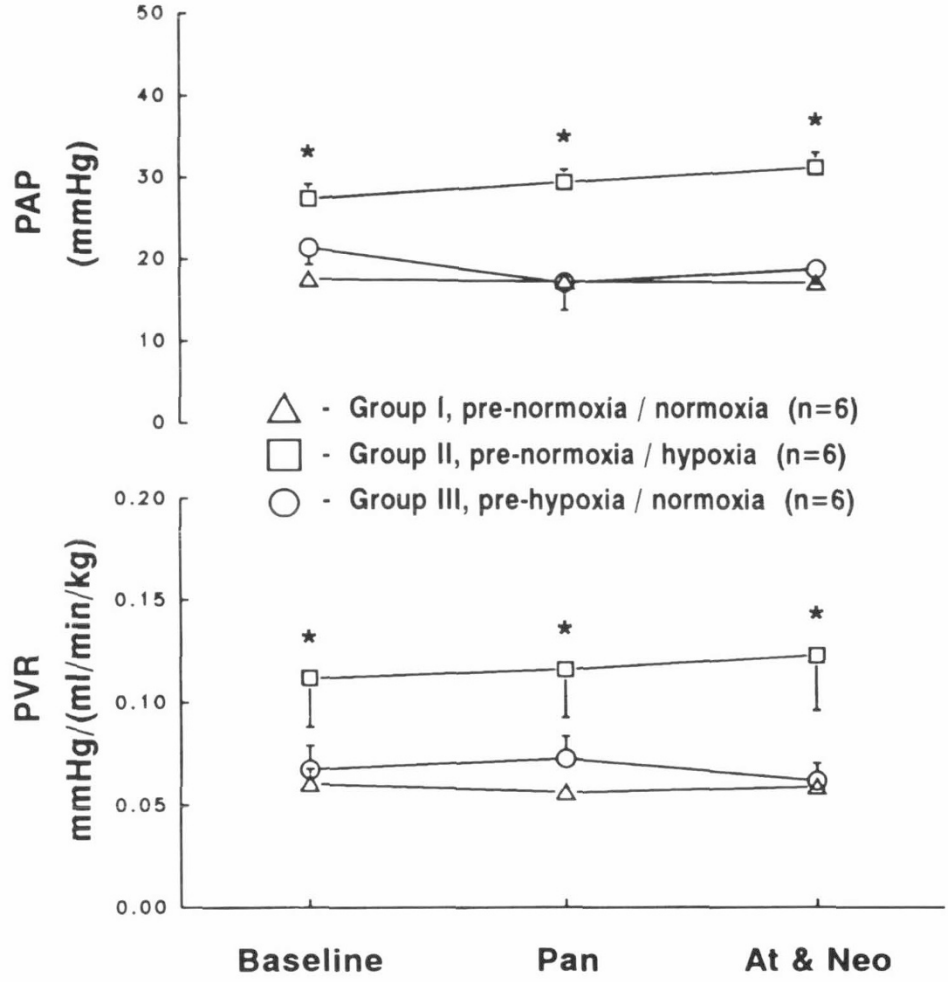

Fig. 5. PAP and PVR in group I *vs* II *vs* III. PAP or PVR in kPa = value × 0.1333. Values are mean ± SEM. *, group II is significantly different from groups I and III ($p < 0.05$).

MAP after pancuronium administration in anesthetized and nonanesthetized newborn lambs, respectively. However, although Cameron *et al.* showed no effect on CO or SVR as in the present study, they reported significant increases in PAP and PVR after administration of pancuronium during hypoxia and mechanical ventilation as compared with the same animals previously observed while spontaneously breathing during hypoxia (13). Their observed increases in PAP and PVR during hypoxia could not be duplicated in the nonhypoxic pancuronium-treated animal. The difference between their results and ours may have been due to their study design. $Paco_2$ levels during hypoxia were lower when the lambs were spontaneously breathing than when they were mechanically ventilated after pancuronium administration. We believe that, although these $Paco_2$ differences were not statistically significant, they were nevertheless of sufficient magnitude to account for differences in PAP and PVR between groups. Indeed, in our study, in which the ventilation of animals was controlled throughout hypoxia before and after pancuronium administration, no change in $Paco_2$ was allowed, and no changes in pulmonary hemodynamics resulted.

The effects of pancuronium in our study were observed during pentobarbital anesthesia. Although the pentobarbital may have attenuated any potential effects of pancuronium, despite this anesthesia, these piglets maintained the capacity to respond to vasoconstrictor stimuli such as hypoxemia or hypercapnia (as evidenced in preliminary experiments and in hypoxia-exposed animals) with increased PAP. This is in keeping with observations of Unger *et al.* (14), who showed that even large doses of pentobarbital did not blunt the pulmonary vasoconstrictor response to hypoxia in dogs. Furthermore, the lack of pancuronium effect on HR or MAP in our study was similar to results of previous studies using neonatal animals (13, 28), one of which used an unanesthetized preparation (13).

The rationale for hypothesizing that pancuronium may have had some immediate or delayed hemodynamic actions is that although the primary action of pancuronium is competitive inhibition of acetylcholine at the neuromuscular postjunctional membrane there are other reported direct effects. Pancuronium is believed to block muscarinic receptors (29), and a vagolytic effect is thought to be the mechanism responsible for increased HR and blood pressure after pancuronium administration documented in human studies (30). Increased norepinephrine release (31) and inhibition of norepinephrine reuptake at the sympathetic nerve terminal (32) after pancuronium has been demonstrated. Pancuronium has also been shown to cause the release of histamine, as well as to cause ganglionic blockade by competing for acetylcholine at the autonomic ganglia (33).

Despite the potential direct effects of pancuronium, other studies suggest that certain effects of pancuronium are indirect and occur as a consequence of muscular paralysis (34–37). In regard to this, our study is consistent with the hypothesis that many of the observed hemodynamic effects of pancuronium may be secondary to altered ventilation after muscle paralysis and associated changes in $Paco_2$.

In conclusion, pancuronium administration during normoxia, during hypoxia, and after preexposure to hypoxia does not alter the hemodynamic status of the newborn pig under conditions of controlled ventilation. These data suggest that the safe use of

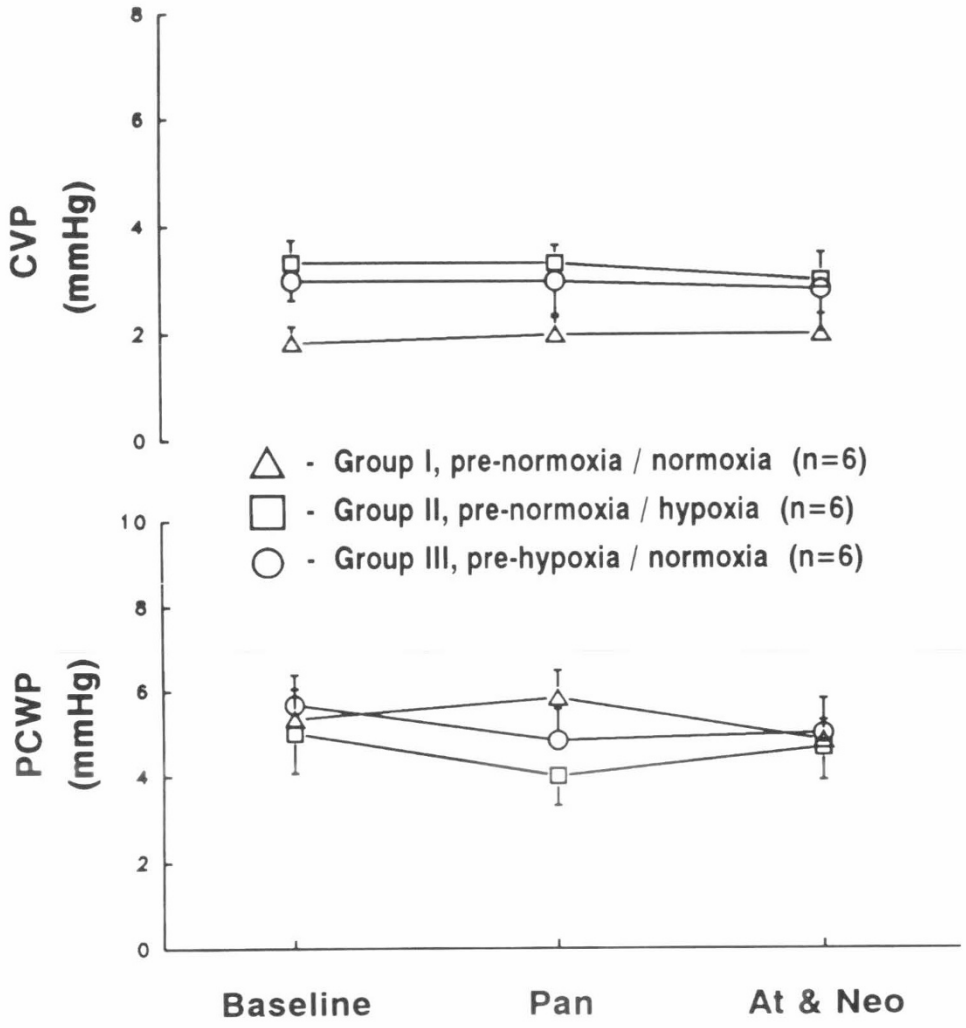

Fig. 6. CVP and PCWP in group I *vs* II *vs* III. CVP or PCWP in kPa = value × 0.1333. Values are mean ± SEM.

pancuronium clinically requires careful bedside monitoring of respiratory parameters to keep V_T and V_E constant after spontaneous respirations are eliminated.

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Announcement

1993 Annual Meetings

The American Pediatric Society, The Society for Pediatric Research, and The Ambulatory Pediatric Association will hold their annual meetings May 3–6, 1993 at the Sheraton Washington Hotel, Washington, DC. *For further information, contact*: APS/SPR Association Headquarters, 141 Northwest Point Blvd., P.O. Box 675, Elk Grove Village, IL 60009-0675, (708) 427-0205, FAX (708) 427-1305 *or* Ambulatory Pediatric Association, 6728 Old McLean Village, McLean, VA 22101, (703) 556-9222, FAX (703) 556-8729.