

## ***Interaction of Fentanyl and Nitrous Oxide on Peripheral and Cerebral Hemodynamics in Newborn Lambs***

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**Background:** The ability of opioids to produce complete general anesthesia is controversial. Nitrous oxide (N<sub>2</sub>O) is often added to fentanyl-based anesthetics to produce unconsciousness and amnesia. The addition of N<sub>2</sub>O may adversely affect fentanyl's hemodynamic stability and safety. The purpose of this study was to determine the physiologic consequences of combining N<sub>2</sub>O with fentanyl in newborn animals.

**Methods:** The effects of 50% nitrous oxide in oxygen (O<sub>2</sub>), and 50% N<sub>2</sub>O in O<sub>2</sub> combined with 3,000 µg/kg fentanyl, on cerebral and peripheral hemodynamics were studied in seven unanesthetized newborn lambs, in whom catheters were previously inserted. After a control period, lambs were placed in a hood in which inspired gas concentrations were controlled and which minimized external stimuli. After 30 min of breathing room air, the lambs breathed 50% N<sub>2</sub>O in O<sub>2</sub> for an additional 30 min. The lambs were then given 3,000 µg/kg fentanyl by intravenous bolus and by infusion (1,000 µg · kg<sup>-1</sup> · h<sup>-1</sup>) for 60 min while continuing to breathe 50% N<sub>2</sub>O in O<sub>2</sub>.

**Results:** All animals responded to pain (tail clamp) and alerted to sound when breathing room air or when N<sub>2</sub>O was used alone. Adding fentanyl to the N<sub>2</sub>O abolished all responses to pain, but not to sound. Additionally, fentanyl produced immediate apnea necessitating tracheal intubation and mechanical ventilation. Mean arterial pressure and heart rate increased 27% and 23%, respectively, after fentanyl administration, intubation, and ventilation. It did not change over the course of the fentanyl infusion. Cerebral blood flow, O<sub>2</sub> consumption, and O<sub>2</sub> delivery did not change when N<sub>2</sub>O was administered alone or in combination with fentanyl. Splanchnic

blood flow was unaffected by treatment over time. Renal blood flow decreased by 21% after fentanyl administration, but was unaffected by N<sub>2</sub>O alone. Right and left ventricular blood flow increased (47% and 26%, respectively) after fentanyl administration, intubation, and ventilation, but not when N<sub>2</sub>O was administered alone.

**Conclusions:** Fentanyl (3,000 µg/kg) when combined with 50% N<sub>2</sub>O in O<sub>2</sub> produced a plane of general anesthesia in newborn lambs in which the behavioral responses to painful stimuli were abolished. The response to sound was never eliminated, nor was cerebral oxygen consumption decreased. The combination of 50% N<sub>2</sub>O in O<sub>2</sub>, 3,000 µg/kg fentanyl, tracheal intubation, and mechanical ventilation did not depress heart rate, blood pressure, or blood flow to any of the major organs, except the kidneys. (Key words: Anesthesia: pediatric; neonatal. Anesthetics, gases: nitrous oxide. Anesthetics, intravenous: fentanyl. Animals, lambs: neonatal. Brain: blood flow; carbon dioxide tension; metabolism; oxygen consumption. Gastrointestinal tract: blood flow; large intestine; small intestine; stomach. Heart: blood flow, myocardial. Kidney: blood flow.)

AT equipotent doses (minimum alveolar concentration [MAC] and the effective dose in 50% of subjects), halothane, enflurane, and isoflurane can produce unacceptable hypotension in human newborns undergoing emergency surgery.<sup>1,2</sup> Given such a narrow therapeutic index, in the past, many newborns underwent surgery with little, if any, anesthesia. Fentanyl and related opioids are increasingly being used as the sole or major component of newborn anesthesia because, when administered in sufficient doses, they produce anesthesia with concomitant circulatory stability.<sup>3</sup> However, does fentanyl "anesthesia" exist?<sup>4</sup> The ability of fentanyl to produce unconsciousness, amnesia, and suppression of reflex responses to noxious stimuli is controversial. Several studies in various species (dog, rat, sheep, and human) have shown that fentanyl, when administered as the sole anesthetic drug, is incapable of preventing movement or suppressing sympathetic-endocrine responses to noxious stimulation in all subjects.<sup>5-7</sup> Fentanyl's ability to produce unconsciousness and amnesia in human patients is even less clear.<sup>4,8,9</sup> Thus, to assure

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## BLOOD FLOW WITH FENTANYL AND NITROUS OXIDE

complete anesthesia, that is, amnesia, unconsciousness, and suppression of sympathetic-endocrine responses to noxious stimulation, many anesthesiologists often combine fentanyl with other agents, such as nitrous oxide (N<sub>2</sub>O), benzodiazepines, and barbiturates. Unfortunately, the addition of virtually any of these drugs to large doses of fentanyl adversely affects fentanyl's hemodynamic stability and safety.<sup>10,11</sup>

The purpose of this study was to determine the physiologic consequences of combining N<sub>2</sub>O with fentanyl in newborn animals. Specifically, we examined whether fentanyl and 50% N<sub>2</sub>O in oxygen (O<sub>2</sub>) could: (1) produce anesthesia, as determined by absence of movement in response to tail clamping and response to sound; (2) affect circulatory stability and the regional distribution of cardiac output; and (3) affect cerebral blood flow (CBF) and cerebral O<sub>2</sub> consumption (CMRO<sub>2</sub>).

## Materials and Methods

### *Subjects and Preparation*

Seven healthy lambs, 3–5 days old, weighing  $5.3 \pm 0.5$  (range, 2.8–6.6) kg, were chronically catheterized for blood flow determinations by the radiolabeled microsphere technique during halothane-N<sub>2</sub>O anesthesia, as described previously.<sup>6,12</sup> Axillary arteries, femoral arteries, and femoral veins were cannulated. A catheter was also inserted into the sagittal sinus. The catheters were filled with heparin, tunneled subcutaneously, and exteriorized in an external pouch. After surgery and anesthesia, the lambs received intramuscular antibiotics (300,000 U of procaine penicillin), recovered, and were returned to their ewes. All catheter positions were verified at autopsy. Approval for this study was obtained by the Institution's Animal Care and Use Committee.

### *Experimental Protocol*

Each animal was studied approximately 24 h after surgery. The lamb was removed from the ewe, weighed, and placed in an environmental chamber that minimized external stimulation and kept the lamb calm. The lamb was free to sit and stand, but not to turn about. Thirty milliliters of blood was collected from the femoral venous catheter for future transfusion and replaced with 100 ml of Ringer's lactated solution. The lamb was unsedated, unstimulated, and left quiet and resting for 60 min (control). The lamb was then placed in a hood in which inspired gas concentration was con-

trolled, and that also minimized external stimuli. The initial inspired gas was room air, which was changed 30 min later to 50% N<sub>2</sub>O in O<sub>2</sub>. Thirty minutes later, the lamb, while continuing to breathe 50% N<sub>2</sub>O in O<sub>2</sub>, was given 3,000  $\mu\text{g}/\text{kg}$  fentanyl by intravenous bolus. This was followed by a 1,000  $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$  fentanyl infusion for 60 min. Blood samples for blood gas, pH, O<sub>2</sub> content, and hematocrit were obtained from the subclavian artery and sagittal sinus catheters after the control period, 30 min of breathing room air in a hood, and 30 min of breathing 50% N<sub>2</sub>O in O<sub>2</sub>. They were also obtained 5 min after the fentanyl bolus, and 30 and 60 min after the fentanyl infusion. Two minutes after obtaining blood samples for analysis, radiolabeled microspheres were injected into the left ventricular catheter. Blood losses resulting from sampling were replaced with autologous blood after each microsphere reference sample was collected. After the microsphere injection, anesthesia was assessed by noting the animal's level of consciousness in response to foot or tail clamping, or both, with a 10-inch hemostat clamped to the first ratchet for 30 s.<sup>5,6,12,13</sup> Consciousness was inferred if the lamb's eyes were open, if the lamb vocalized ("baaed") when breathing spontaneously, and if it would alert to sound (clanging bell). Responses to foot and tail clamping included purposeful withdrawal of the stimulated foot (or nonwithdrawal); gross purposeful muscular movement, usually of the head (jerking or twisting); and increased (or no change in) systolic arterial blood pressure. All animals initially breathed spontaneously. When apnea or respiratory depression occurred, that is, an increase in arterial carbon dioxide tension (PaCO<sub>2</sub>) of 20% or greater above baseline, or a decrease in arterial O<sub>2</sub> content of 20% or greater from baseline, the lamb's trachea was orally intubated and the lungs were ventilated with a Harvard small animal ventilator to return to baseline levels of PaCO<sub>2</sub> and arterial O<sub>2</sub> content. Fifty percent N<sub>2</sub>O in O<sub>2</sub> was added to the inspiratory limb of the ventilator.

### *Measurements*

Regional blood flow measurements were made with radiolabeled microspheres ( $16 \pm 0.5$   $\mu\text{m}$  diameter) (DuPont, NEN Products, Boston, MA) using the reference sample technique.<sup>14</sup> Approximately  $1-1.5 \times 10^6$  microspheres of each isotope (<sup>153</sup>Gd, <sup>114</sup>In, <sup>113</sup>Sn, <sup>103</sup>Ru, <sup>95</sup>Nb, and <sup>46</sup>Sc) were injected into the left ventricle over a 30-s period, followed by a 10-ml saline flush over 15 s. The reference withdrawal blood samples were collected simultaneously from both the subcla-

vian artery and abdominal aorta at 2.5 ml/min, beginning 15 s before the injection and lasting for 3 min. This injection technique does not alter aortic blood pressure, blood gases, heart rate, or pH, and has been used previously in our laboratory.<sup>6,12</sup>

At the conclusion of the experiment, the animal was killed by an overdose of sodium pentobarbital followed by potassium chloride, and the brain and internal organs were removed. The brain was dissected into the following regions: medulla, pons, midbrain, diencephalon, caudate nucleus, white matter, and cerebral hemispheres. Multiple samples of heart, kidney, stomach, small intestine, and large intestine were obtained to average spatial inhomogeneities and to ensure that calculations were based on the presence of at least 1,000 microspheres for each organ. Samples were counted in a Packard Multichannel Autogamma Scintillation Spectrometer (model 9042, United Technology, Downers Grove, IL), and backscatter from higher-energy isotopes into windows of lower-energy emission was subtracted for a corrected count value with the use of differential spectroscopy by the simultaneous equation method. Tissue blood flow ( $\dot{Q}_t$ ) was calculated as the product of this corrected tissue count ( $C_t$ ) and the counts in the reference withdrawal rate ( $Q_r$ ) divided by the counts in the reference sample ( $C_r$ ) and by the weight of the tissue ( $W$ ); that is,

$$\dot{Q}_t = (C_t \cdot Q_r) / (C_r \cdot W).$$

Blood flow to cephalic tissues was calculated using the subclavian arterial reference sample. Blood flow to the abdominal and lower body tissues was calculated using the abdominal aortic reference sample.

Aortic blood pressure was continuously monitored with a Satham pressure transducer (Gould, Oxnard, CA) referenced to the level of the right atrium. Arterial and sagittal sinus  $P_{O_2}$ ,  $P_{CO_2}$ , and pH were measured with Radiometer BMS3 electrodes and analyzer (Copenhagen, Denmark), and  $O_2$  content was calculated by the formula:

$$O_2 \text{ content} = (1.35) (O_2 \text{ saturation}) (\text{hemoglobin}) + (0.003 \times P_{O_2})$$

where fractional  $O_2$  saturation and hemoglobin concentration (g/dl) were measured with a Radiometer Hemoximeter (OSM2), and  $P_{O_2}$  is in mmHg.  $CMRO_2$  was calculated as the product of hemispheric blood flow and the arterial-sagittal sinus  $O_2$  content difference. Cerebral fractional  $O_2$  extraction was calculated as the arteriovenous  $O_2$  content difference divided by arterial  $O_2$  content. Cerebral  $O_2$  transport was calcu-

lated as the product of arterial  $O_2$  content and hemispheric blood flow.

#### Statistical Analysis

The effect of 50%  $N_2O$  in  $O_2$  administered alone and in combination with a 3,000  $\mu\text{g}/\text{kg}$  bolus and a 60-min infusion ( $1,000 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ ) of fentanyl on each measured variable was examined by one-way ANOVA with repeated measurements. Multiple comparisons of mean values were made by the Duncan Multiple Range Test. Brain regional blood flow was analyzed using two-way ANOVA in which brain region was one factor and time was the second. Probability values of less than 0.05 were considered significant. All results are presented as mean  $\pm$  SEM.

## Results

### Behavioral Effects

In the baseline condition, the lambs stood or lay down, rolled their heads, spontaneously vocalized, alerted to sound, spontaneously closed and opened their eyes, and moved when lightly touched. Additionally, they responded to painful stimuli (tail clamping) by brisk, purposeful withdrawal and with increased blood pressure. In all animals, when 50%  $N_2O$  in  $O_2$  was administered alone, behavioral responses were unchanged from baseline conditions. The addition of fentanyl to  $N_2O$  terminated all spontaneous activity. The lambs laid on their sides with extension of their limbs, they no longer vocalized, and their eyes were closed (absent lid reflex). Furthermore, all behavioral responses to pain were abolished. However, all animals continued to alert to sound, that is, they lifted their heads, ears, or both in the direction of a loud noise, even when the response to tail clamp was abolished.

### Respiratory Effects

Table 1 shows arterial blood gases, pH, hematocrit, and arterial and cerebral venous  $O_2$  content data. There was no significant effect on arterial  $P_{CO_2}$  when 50%  $N_2O$  in  $O_2$  was given alone. After fentanyl administration, all animals immediately became apneic and required prompt tracheal intubation and mechanical ventilation. Thus, the blood gases obtained after fentanyl administration (table 1) represent the effects of mechanical ventilation. The lambs did not resist or struggle during tracheal intubation or ventilation.

## BLOOD FLOW WITH FENTANYL AND NITROUS OXIDE

Table 1. Blood Gasses, Hemoglobin, and Hemodynamics with Fentanyl and Nitrous Oxide

	Control Room Air	Hood		Fentanyl		
		Room Air	50% N <sub>2</sub> O + 50% O <sub>2</sub>	3,000 μg · kg <sup>-1</sup> 50% N <sub>2</sub> O + 50% O <sub>2</sub> 5 min	1,000 μg · kg <sup>-1</sup> · h <sup>-1</sup> 50% N <sub>2</sub> O + 50% O <sub>2</sub> 30 min	1,000 μg · kg <sup>-1</sup> · h <sup>-1</sup> 50% N <sub>2</sub> O + 50% O <sub>2</sub> 60 min
				Room Air	50% N <sub>2</sub> O + 50% O <sub>2</sub>	3,000 μg · kg <sup>-1</sup> 50% N <sub>2</sub> O + 50% O <sub>2</sub> 5 min
pH	7.40 ± 0.04	7.39 ± 0.04	7.38 ± 0.06	7.38 ± 0.04	7.34 ± 0.06	7.33 ± 0.04
Pa <sub>O<sub>2</sub></sub> (mmHg)	97 ± 10	94 ± 9	237 ± 22*	225 ± 31*	202 ± 34*	205 ± 45*
Pa <sub>CO<sub>2</sub></sub> (mmHg)	38 ± 5	38 ± 3	39 ± 5	35 ± 5	37 ± 6	38 ± 2
Hemoglobin (g/dl)	10.1 ± 1.4	9.8 ± 1.4	9.9 ± 1.3	9.2 ± 1.3	8.9 ± 1.1	8.8 ± 1.4
Ca <sub>O<sub>2</sub></sub> (ml/dl)	13.4 ± 1.7	13.1 ± 2.0	14.1 ± 1.8	13.2 ± 1.8	12.8 ± 1.6	12.6 ± 1.9
Cv <sub>O<sub>2</sub></sub> (ml/dl)	7.4 ± 1.8	7.1 ± 1.6	8.0 ± 1.7	6.9 ± 1.9	6.7 ± 2.2	6.4 ± 1.7
Heart rate (beats · min <sup>-1</sup> )	174 ± 37	186 ± 44	159 ± 25	216 ± 26*	217 ± 40*	223 ± 45*
Mean aortic pressure (mmHg)	73 ± 7	76 ± 11	76 ± 12	93 ± 21*	86 ± 19*	93 ± 10*

Each value represents the mean ± SE for seven animals.

In each animal, the trachea was intubated and the lungs mechanically ventilated after administration of 3,000 μg · kg<sup>-1</sup> fentanyl.

Pa<sub>CO<sub>2</sub></sub> = arterial CO<sub>2</sub> tension; Pa<sub>O<sub>2</sub></sub> = arterial O<sub>2</sub> tension; Ca<sub>O<sub>2</sub></sub> = arterial O<sub>2</sub> content; Cv<sub>O<sub>2</sub></sub> = sagittal sinus O<sub>2</sub> content.

\* *P* < 0.05 compared with control.

### Cardiovascular Effects

Mean arterial pressure and heart rate did not change when 50% N<sub>2</sub>O in O<sub>2</sub> was administered alone. Heart rate and blood pressure significantly increased, by 27% and 23%, respectively, after the administration of fentanyl, tracheal intubation, and mechanical ventilation (table 1). The increase in heart rate and blood pressure did not change further over the course of the fentanyl infusion. Right- and left-ventricular blood flow increased (47% and 26%, respectively) after the administration of fentanyl, tracheal intubation, and mechanical ventilation, but not when N<sub>2</sub>O was administered alone (fig. 1). Blood flow to the stomach, small intestine, and large intestine was unaffected by 50% N<sub>2</sub>O in O<sub>2</sub>, 3,000 μg/kg fentanyl, tracheal intubation, mechanical ventilation, and a 1-h fentanyl infusion (fig. 1). However, renal blood flow decreased by 21% when fentanyl was added to the N<sub>2</sub>O, but not when N<sub>2</sub>O was administered alone (fig. 1).

### Cerebral Effects

Cerebral blood flow, CMRO<sub>2</sub>, cerebral O<sub>2</sub> delivery, and the ratio of cerebral O<sub>2</sub> delivery and consumption, the fractional extraction of O<sub>2</sub>, were unaffected by treatment over time (fig. 2). Two-way ANOVA indicated no effect of repeated measures over time, and no interaction of brain region with time (fig. 3).

### Discussion

When combined with 50% N<sub>2</sub>O in O<sub>2</sub>, fentanyl (3,000 μg/kg) abolished both spontaneous and pur-

poseful movement in response to a painful stimulus in 100% of all newborn lambs studied. Additionally, fentanyl administration produced apnea in all study animals, necessitating immediate tracheal intubation and mechanical ventilation. It is interesting that the response to sound was never abolished after fentanyl administration, nor was CMRO<sub>2</sub> decreased. The combination of 50% N<sub>2</sub>O in O<sub>2</sub>, 3,000 μg/kg fentanyl, tracheal intubation, and mechanical ventilation did not depress heart rate, blood pressure, or blood flow to any of the major organs, except the kidneys. However, when administered alone, 50% N<sub>2</sub>O in O<sub>2</sub> did not produce unconsciousness, and it did not affect the behavioral or blood pressure responses to pain or the blood flow to any of the major organs, including the brain.

The loss of spontaneous and purposeful movement in response to tail clamp with retention of the ability to alert to sound raises important questions about how we define general anesthesia. Movement in response to a supramaximal pain stimulus, such as surgical incision or tail clamping, is the standard method of assessing anesthesia, and has been so since the concept of MAC was introduced more than 20 yr ago.<sup>5,15</sup> Originally defined for inhalational agents as the alveolar concentration at which one half of patients or animals move in response to a surgical stimulus, MAC has subsequently been extended to intravenous anesthetic agents, such as barbiturates, benzodiazepines, opioids, and phenol derivatives, as well. However, intravenous anesthetic agents produce effects that are both clinically and neuropharmacologically different than the inhalational

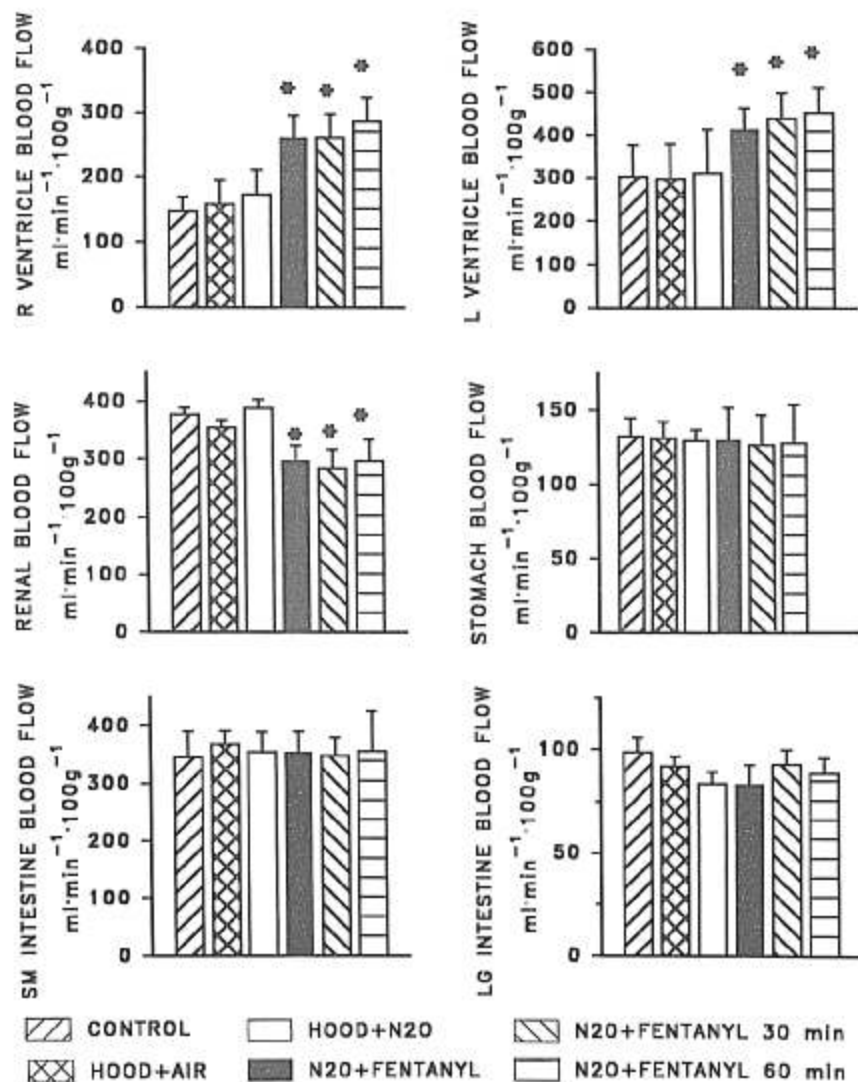


Fig. 1. Organ blood flow ( $\text{ml} \cdot \text{min}^{-1} \cdot 100 \text{g}^{-1}$ ) at control; while spontaneously breathing room air in a hood; while spontaneously breathing 50%  $\text{N}_2\text{O}$  plus 50%  $\text{O}_2$  in a hood; after receiving a bolus of  $3,000 \mu\text{g}/\text{kg}$  fentanyl, tracheal intubation, and mechanical ventilation with 50%  $\text{N}_2\text{O}$  plus 50%  $\text{O}_2$ ; and during a continuous infusion of  $1,000 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$  fentanyl at 30 and 60 min is depicted. The mean for all animals ( $n = 7$ ) is depicted. Bars represent mean  $\pm$  SEM. \* $P < 0.05$  compared with control.

agents. Unlike inhalational anesthetics, an intravenous anesthetic agent can produce immobility but have no effect on consciousness or on the relief of pain. For example, Shingu *et al.*, using rats, achieved anesthesia, as defined by lack of movement in response to tail clamping, with fentanyl.<sup>7</sup> However, by the authors' description, the rats appeared "conscious" throughout the experimental procedure. Kissin *et al.*, in several studies, demonstrated that the interactions of various intravenous anesthetic agents can be different for the different components of anesthesia.<sup>15-17</sup> For example, Kissin *et al.* used both the righting reflex and the purposeful movement response to tail clamp to demonstrate that the analgesic properties of opioids may not

adequately reflect their anesthetic potencies. They demonstrated that fentanyl augments the ability of thiopental to abolish the righting reflex (a sign of unconsciousness), but thiopental antagonizes the ability of fentanyl to block withdrawal to noxious stimuli.<sup>15</sup>

In clinical practice, general anesthesia is a state of unconsciousness (amnesia and hypnosis), during which the patient does not experience pain, is immobile, and is in as safe a physiologic state as possible.<sup>18,19</sup> Additionally, many now believe that a general anesthetic must suppress the reflex responses (heart rate, blood pressure, and neuroendocrine) to noxious stimuli, as well.<sup>20,21</sup> Neither fentanyl nor any opioid should be expected to produce and maintain complete anesthesia

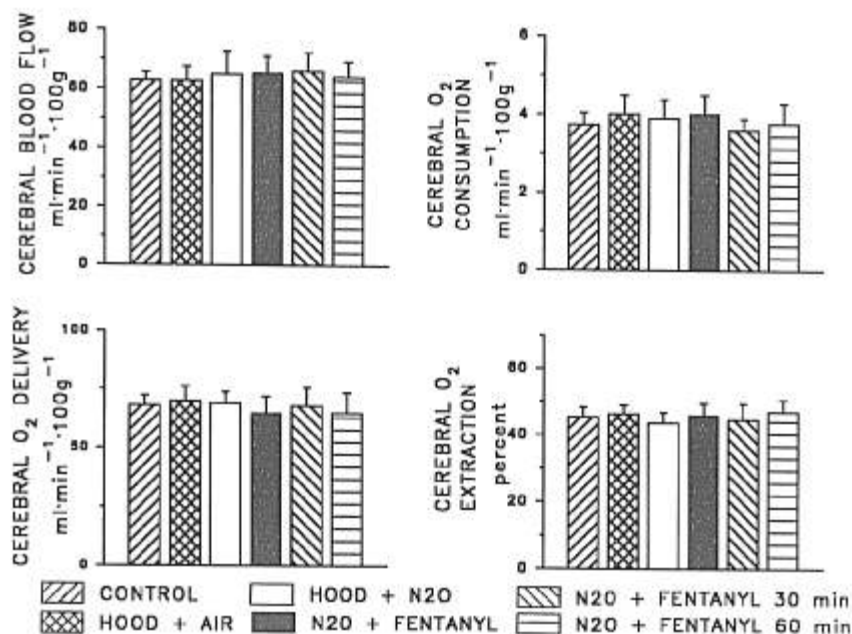
## BLOOD FLOW WITH FENTANYL AND NITROUS OXIDE

when administered alone.<sup>4,9,22</sup> Opioids do not reliably produce amnesia or unconsciousness. Furthermore, they do not reliably prevent movement in response to a supramaximal painful stimulus. We have previously demonstrated our inability to produce anesthesia, as defined as lack of movement in response to tail clamping, with fentanyl in doses as high as 4,000  $\mu\text{g}/\text{kg}$  in the newborn lamb.<sup>6,12</sup> Other investigators have reported similar findings in untrained dogs.<sup>5</sup> In analogous studies, Hug *et al.* showed that fentanyl and sufentanil can not produce complete, or a MAC level of, anesthesia. In those studies, fentanyl and sufentanil could reduce the somatic responses to painful stimuli, but could not produce 100% depression of MAC for either halothane or isoflurane.<sup>23,24</sup> In the current study, we used both response to a supramaximal painful stimulus (movement, heart rate, and blood pressure) and behavior (eyes open, vocalization, and response to sound) as indexes of anesthesia.<sup>5</sup> The combination of fentanyl and  $\text{N}_2\text{O}$  abolished spontaneous vocalization, eye opening, and movement, as well as purposeful movement in response to pain. Despite this, the lambs lifted their heads or ears and turned to the direction of a loud noise. It has long been known that some patients anesthetized with a balanced technique (opioid,  $\text{N}_2\text{O}$ ,  $\text{O}_2$ , and muscle relaxant) recall intraoperative conversations.<sup>8,25</sup> Our studies confirm that fentanyl and nitrous oxide do not completely block auditory input or abolish responses to noise.

We found no changes in global or regional brain blood flow,  $\text{CMRO}_2$ , cerebral  $\text{O}_2$  transport, and cerebral  $\text{O}_2$  extraction when 50%  $\text{N}_2\text{O}$  in  $\text{O}_2$  was administered alone or in combination with fentanyl. A number of studies have variously reported that exposure to 60–70%  $\text{N}_2\text{O}$  is associated with an increase in CBF and  $\text{CMRO}_2$ .<sup>26,27</sup> Conversely, others have found only minimal influences of  $\text{N}_2\text{O}$  on these variables.<sup>28</sup> This lack of agreement among studies may be caused, in part, by differences in experimental preparations that have included, either together or separately, paralysis, artificial ventilation, stress-inducing mechanical restraint, additional anesthetics, different  $\text{N}_2\text{O}$  concentrations, and extensive acute animal preparation. Differences in species and maturational age of the subjects studied may also be important.

Interestingly, CBF and  $\text{CMRO}_2$  did not decrease during the combination of fentanyl and  $\text{N}_2\text{O}$ . In our previous studies, when consciousness was lost by the combination of fentanyl and pentobarbital, CBF and  $\text{CMRO}_2$  decreased by equivalent percentages.<sup>12</sup> Similarly, when barbiturates alone produce a loss of consciousness, CBF and  $\text{CMRO}_2$  are reduced, as well.<sup>29,30</sup> When anesthetic doses of pentobarbital are given to dogs (30  $\mu\text{g}/\text{kg}$ ), further administration of fentanyl produces no deepening of the anesthetic state and no further reductions in CBF and  $\text{CMRO}_2$ .<sup>31</sup> Furthermore, inhalational anesthetics generally reduce  $\text{CMRO}_2$  when consciousness is lost, as well. Therefore, the combi-

Fig. 2. Hemispheric cerebral blood flow, cerebral oxygen consumption, cerebral oxygen transport, and cerebral oxygen extraction at control; while spontaneously breathing room air in a hood; while spontaneously breathing 50%  $\text{N}_2\text{O}$  plus 50%  $\text{O}_2$  in a hood; after receiving a bolus of 3,000  $\mu\text{g}/\text{kg}$  fentanyl, tracheal intubation, and mechanical ventilation with 50%  $\text{N}_2\text{O}$  plus 50%  $\text{O}_2$ ; and during a continuous infusion of 1,000  $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$  fentanyl at 30 and 60 min is depicted. The mean for all animals ( $n = 7$ ) is depicted. Bars represent mean  $\pm$  SEM. \* $P < 0.05$  compared with control.



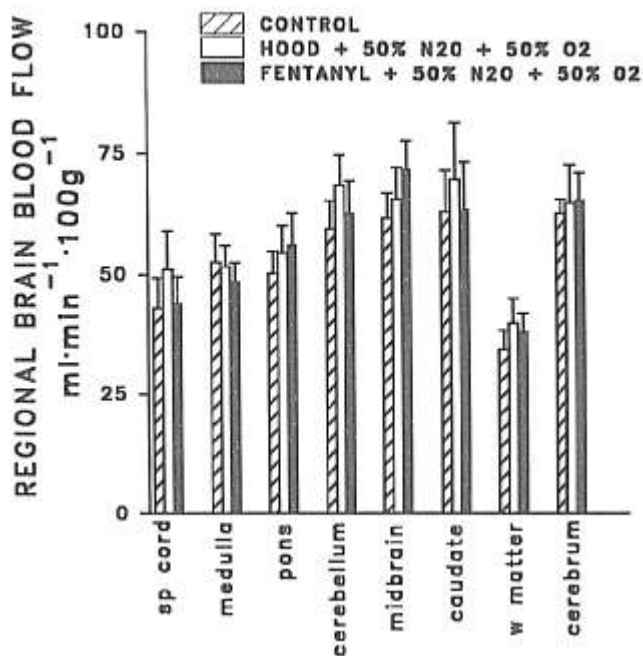


Fig. 3. Regional brain blood flow ( $\text{ml} \cdot \text{min}^{-1} \cdot 100 \text{g}^{-1}$ ) at control, after spontaneous ventilation (hood) with 50%  $\text{N}_2\text{O}$  plus 50%  $\text{O}_2$ , and after a bolus of  $3,000 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$  fentanyl, tracheal intubation, and mechanical ventilation with 50%  $\text{N}_2\text{O}$  plus 50%  $\text{O}_2$  are shown. The mean for all animals ( $n = 7$ ) is depicted. Bars represent mean  $\pm$  SEM. \* $P < 0.05$  compared with control. Other time points were omitted for clarity.

nation of 50%  $\text{N}_2\text{O}$  and high-dose fentanyl is rather unique in producing anesthesia without reducing  $\text{CMRO}_2$ .

The addition of fentanyl to 50%  $\text{N}_2\text{O}$  in  $\text{O}_2$  produced apnea and a significant decrease in renal blood flow. Similar results were obtained in our previous studies with  $3,000 \mu\text{g}/\text{kg}$  fentanyl when it was administered to newborn lambs, either alone or when combined with pentobarbital.<sup>6,12</sup> In those studies,  $3,000 \mu\text{g}/\text{kg}$  fentanyl did not reliably produce anesthesia, but did cause profound respiratory depression without any evidence of chest wall rigidity, whether it was administered alone or in combination with pentobarbital. In all studies using fentanyl alone or in combination with other agents in lambs, renal blood flow decreases, despite the maintenance of normal or elevated mean aortic blood pressure. This decrease in renal blood flow is also consistent with the work of others using various anesthetic techniques.<sup>32,33</sup>

We previously reported that the combination of high-dose fentanyl, pentobarbital, and tracheal intubation decreased blood pressure and gastrointestinal blood

flow in newborn lambs.<sup>12</sup> In contrast, our current results show that gastrointestinal blood flow is better maintained, and is not accompanied by hypotension, when fentanyl is combined with 50%  $\text{N}_2\text{O}$  in  $\text{O}_2$ , and indicates that this anesthetic technique may be a better alternative than the combination of fentanyl and a barbiturate, particularly in situations in which gastrointestinal blood flow may be compromised in the neonate.

In summary, we conclude that  $3,000 \mu\text{g}/\text{kg}$  fentanyl, when combined with 50%  $\text{N}_2\text{O}$  in  $\text{O}_2$ , produced a plane of general anesthesia in newborn lambs in which the behavioral responses to painful stimuli were abolished. The response to sound was never eliminated, nor was  $\text{CMRO}_2$  decreased. The combination of 50%  $\text{N}_2\text{O}$  in  $\text{O}_2$ ,  $3,000 \mu\text{g}/\text{kg}$  fentanyl, tracheal intubation, and mechanical ventilation did not depress heart rate, blood pressure, or blood flow to any of the major organs, except the kidneys. Intestinal and cerebral blood flow are better maintained in newborn lambs with this technique than when fentanyl is combined with a barbiturate.

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## BLOOD FLOW WITH FENTANYL AND NITROUS OXIDE

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