Cardiorespiratory effects of epidural administration of morphine and fentanyl in dogs anesthetized with sevoflurane

Kiyokazu Naganobu, BVSc, PhD; Noriaki Maeda, DVM; Toru Miyamoto, DVM, PhD; Mitsuyoshi Hagio, DVM, PhD; Tadashi Nakamura, MD; Mayumi Takasaki

Objective—To determine the cardiorespiratory effects of epidural administration of morphine alone and in combination with fentanyl in dogs anesthetized with sevoflurane.

Design—Prospective study.

Animals—6 dogs.

Procedure—Dogs were anesthetized with sevoflurane and allowed to breathe spontaneously. After a stable plane of anesthesia was achieved, morphine (0.1 mg/kg [0.045 mg/lb]) or a combination of morphine and fentanyl (10 µg/kg [4.5 µg/lb) was administered through an epidural catheter, the tip of which was positioned at the level of L6 or L7. Cardiorespiratory variables were measured for 90 minutes.

Results—Epidural administration of morphine alone did not cause any significant changes in cardiorespiratory measurements. However, epidural administration of morphine and fentanyl induced significant decreases in diastolic and mean arterial blood pressures and total peripheral resistance. Stroke volume was unchanged, $Paco_2$ was significantly increased, and arterial pH and base excess were significantly decreased. Heart rate was significantly lower after epidural administration of morphine and fentanyl than after administration of morphine alone. None of the dogs had any evidence of urine retention, vomiting, or pruritus after recovery from anesthesia.

Conclusions and Clinical Relevance—Results suggest that epidural administration of morphine at a dose of 0.1 mg/kg in combination with fentanyl at a dose of 10 µg/kg can cause cardiorespiratory depression in dogs anesthetized with sevoflurane. (*J Am Vet Med Assoc* 2004;224:67–70)

In dogs, epidural administration of morphine can result in long-lasting analgesia, and serious complications are rare following epidural administration of morphine in dogs.[1-4] However, the onset of action of morphine following epidural administration is slow, and additional drugs are sometimes needed for adequate analgesia.[5] Fentanyl, a more potent mu-opioid receptor agonist than morphine, has also been used for epidural administration, and because the onset of action of fentanyl is rapid,[6,7] epidural administration of a combination of morphine and fentanyl could potentially shorten the onset of analgesia and enhance the analgesic effect.[1,8,9]

In general, because opioids are considered to not induce significant sympathetic blockade following epidural adminsitration,[6,7] one would expect epidural administration of a combination of morphine and fentanyl to have few clinically important cardiovascular effects. However, decreases in mean arterial blood pressure and **heart rate (HR)** and an increase in $Paco_2$ have been observed following epidural administration of fentanyl in cats anesthetized with isoflurane.[10] To our knowledge, the cardiorespiratory effects of epidural administration of a combination of morphine and fentanyl in dogs have not been reported. The purpose of the study reported here, therefore, was to determine the cardiorespiratory effects of epidural administration of morphine alone and in combination with fentanyl in dogs anesthetized with sevoflurane.

Materials and Methods

The study protocol was approved by the Committee of the Ethics on Animal Experiment in the Faculty of Agriculture, Miyazaki University. Six healthy dogs (1 female and 5 males) ranging from 1 to 6 years old (except that age of 1 dog was unknown) and weighing between 8.9 and 22.6 kg (19.6 and 49.7 lb) were used in the study. Each dog underwent 2 experimental trials. In 1 trial, the dog was anesthetized with sevoflurane, and morphine (0.1 mg/kg [0.045 mg/lb]) was administered epidurally. In the other trial, the dog was anesthetized with sevoflurane, and a combination of morphine (0.1 mg/kg) and fentanyl (10 µg/kg [4.5 µg/kg]) was administered epidurally. Experimental trials were separated by 7 to 10 days, and treatments were administered in random order.

For each experimental trial, anesthesia was induced by mask administration of 5% sevoflurane in oxygen delivered via a circle breathing system. Dogs were intubated with a cuffed endotracheal tube, and anesthesia was maintained with sevoflurane in oxygen. Dogs were placed in sternal recumbency and allowed to breathe spontaneously. An 18-gauge Tuohy needle[a] was inserted into the lumbosacral epidural space. Correct positioning of the needle was confirmed by a lack of resistance to injection of saline solution and the absence of any aspirate from the needle. Spontaneous sucking of a drop of saline solution from the hub was also used as a sign of correct positioning of the needle in some dogs. After correct positioning of the Tuohy needle was confirmed, a 20-gauge epidural catheter[a] was introduced through the needle, and the Tuohy needle was removed. The epidural catheter was sutured to the skin, and the dog was then placed in left lateral recumbency. The tip of the epidural catheter was confirmed to be positioned at the level of L6 or L7 by means of radiography.

From the Veterinary Teaching Hospital, Faculty of Agriculture, Miyazaki University, Miyazaki 889-2192, Japan (Naganobu, Maeda, Miyamoto, Hagio); and the Department of Anesthesiology, Miyazaki Medical College, Kiyotake, Miyazaki 889-1692, Japan (Nakamura, Takasaki).

Address correspondence to Dr. Naganobu.

Following epidural catheterization, a thermodilution catheter (5 or 7 Fr) was inserted into the right jugular vein through an introducer and advanced to the pulmonary artery under fluoroscopic guidance. In each dog, thermodilution catheters used during the 2 experimental trials were the same size. **Cardiac output**[b] **(CO)** and pulmonary arterial blood pressure[c] were measured with the thermodilution catheter. For measurement of CO, 5 mL of iced 5% dextrose solution was rapidly injected during the expiration phase of respiration. At least 3 measurements were performed, and 3 consecutive measurements that had < 10% variation were averaged to obtain the CO for that time point. **Stroke volume (SV)**, **cardiac index (CI)**, and **total peripheral resistance (TPR)** were calculated with standard equations.[11]

The femoral artery was catheterized percutaneously with a 20-gauge, over-the-needle catheter for continuous measurement of systemic arterial blood pressure, which was displayed on an amplifier[d] and recorded with an oscillograph,[e] and also for collection of blood samples for blood gas analysis.[f] Blood gas analyses were performed immediately after blood sample collection, and results were compensated for body temperature. A lead II ECG[c] was displayed and monitored continuously. Inspired and expired sevoflurane concentration, inspired and end-tidal carbon dioxide partial pressure, and respiratory frequency were monitored with a calibrated anesthetic gas monitor.[g] Respiratory frequency was also confirmed by counting movements of the breathing bag or thorax. Rectal temperature was maintained between 36.3° and 38.6°C (97.3° and 101.5°F) with an electric heating pad and blanket.

After instrumentation, dogs were stabilized for 30 minutes at an expired sevoflurane concentration between 2.3% and 2.5%. Baseline data were collected, and morphine (0.1 mg/kg) or a combination of morphine (0.1 mg/kg) and fentanyl (10 µg/kg) was administered through the epidural catheter over 2.5 minutes. For this injection, preservative-free morphine hydrochloride (10 mg/mL)[h] was diluted with normal saline (0.9% NaCl) solution so that the total volume injected was 0.25 mL/kg (0.11 mL/lb). The fentanyl citrate solution[i] (50 µg/mL) that was used had a low osmolarity;

Table 1—Cardiorespiratory variables in dogs (n = 6) anesthetized with sevoflurane and given morphine (0.1 mg/kg [0.045 mg/lb]) or a combination of morphine (0.1 mg/kg) and fentanyl (10 µg/kg [4.5 µg/kg]) epidurally

		Time (min) after epidural administration					
Variable	**Baseline**	**5**	**10**	**15**	**30**	**60**	**90**
HR (beats/min)							
M	112 ± 14	114 ± 9	112 ± 6	109 ± 8	109 ± 10	105 ± 10	102 ± 12
M and F	105 ± 13	91 ± 20†	89 ± 20†	92 ± 20	93 ± 23	106 ± 27	107 ± 25
SAP (mm Hg)							
M	109 ± 16	112 ± 16	110 ± 17	109 ± 18	112 ± 17	111 ± 16	112 ± 21
M and F	101 ± 12	104 ± 16	102 ± 13	102 ± 15	103 ± 12	115 ± 22	116 ± 20
DAP (mm Hg)							
M	67 ± 15	68 ± 12	66 ± 13	63 ± 14	68 ± 11	70 ± 18	66 ± 14
M and F	64 ± 12	49 ± 7*†	45 ± 3*†	44 ± 5*†	48 ± 5*†	55 ± 11	56 ± 10
MAP (mm Hg)							
M	81 ± 15	83 ± 13	81 ± 14	79 ± 15	83 ± 13	83 ± 17	81 ± 16
M and F	77 ± 11	63 ± 8*†	61 ± 5*†	60 ± 6*†	64 ± 6*†	71 ± 12	73 ± 12
CO (L/min)							
M	2.2 ± 0.4	2.2 ± 0.4	2.2 ± 0.3	2.2 ± 0.4	2.3 ± 0.5	2.2 ± 0.5	2.2 ± 0.6
M and F	2 ± 0.4	1.8 ± 0.5	1.9 ± 0.5	2 ± 0.4	2.1 ± 0.6	2.3 ± 0.7	2.4 ± 0.6
SV (mL)							
M	19.5 ± 3.1	18.6 ± 2.8	19.9 ± 3.1	20 ± 2.9	20.3 ± 3.3	21 ± 4.5	20.9 ± 4.5
M and F	19.3 ± 4.3	19.7 ± 2.7	21.8 ± 1.7	22.3 ± 1.8	22 ± 2.8	21.8 ± 3.5	22.1 ± 2.9
CI (mL/min/kg)							
M	171 ± 50	169 ± 48	177 ± 59	175 ± 50	182 ± 67	177 ± 61	167 ± 55
M and F	156 ± 48	144 ± 68	156 ± 65	165 ± 70	162 ± 71	187 ± 93	189 ± 84
TPR (dynes•sec•cm^{-5})							
M	3,046 ± 753	3,164 ± 791	2,938 ± 631	2,888 ± 584	2,994 ± 779	3,122 ± 844	3,195 ± 1,101
M and F	3,223 ± 933	3,028 ± 926	2,638 ± 647	2,429 ± 567*	2,742 ± 982	2,709 ± 1,049	2,654 ± 927
PAP (mm Hg)							
M	12.2 ± 2.7	12.8 ± 2.5	12.5 ± 2.2	12.2 ± 2.9	12.8 ± 2.7	13.5 ± 0.8	12.2 ± 2.1
M and F	11.7 ± 2.9	11.3 ± 2.7	12.5 ± 3.1	13 ± 3.1	13 ± 2.8	13.3 ± 2.6	12.5 ± 3
RR (breaths/min)							
M	24 ± 10	18 ± 7	21 ± 8	19 ± 9	19 ± 9	20 ± 7	20 ± 7
M and F	23 ± 8	16 ± 10	17 ± 11	19 ± 13	23 ± 13	20 ± 11	26 ± 19
Arterial pH							
M	7.34 ± 0	7.33 ± 0.048	7.32 ± 0.042	7.32 ± 0.046	7.31 ± 0.038	7.32 ± 0.033	7.32 ± 0.04
M and F	7.33 ± 0	7.25 ± 0.05*†	7.24 ± 0.05*†	7.23 ± 0.04*†	7.25 ± 0.03*†	7.27 ± 0.04*†	7.28 ± 0.04
$Paco_2$ (mm Hg)							
M	39 ± 5	41 ± 5	41 ± 4	42 ± 5	43 ± 6	42 ± 5	42 ± 5
M and F	41 ± 4	48 ± 10*	51 ± 10*	52 ± 10*	50 ± 7*	47 ± 8	47 ± 7
Pao_2 (mm Hg)							
M	487 ± 23	490 ± 23	494 ± 16	496 ± 14	493 ± 34	486 ± 34	485 ± 36
M and F	523 ± 33	490 ± 37*	493 ± 31	497 ± 38	496 ± 48	481 ± 42*	488 ± 38*
Bicarbonate (mmol/L)							
M	21 ± 1.5	21.1 ± 1.8	20.9 ± 1.4	21.1 ± 1.7	21.2 ± 2.2	21.2 ± 2	21.7 ± 1.6
M and F	21.3 ± 1.5	21 ± 2	21.2 ± 1.9	21.2 ± 2.2	21.6 ± 1.5	21.3 ± 1.9	21.6 ± 1.7
BE (mmol/L)							
M	–4.1 ± 1.5	–4.3 ± 1.9	–4.6 ± 1.7	–4.5 ± 1.7	–4.7 ± 1.9	–4.4 ± 1.8	–3.8 ± 1.7
M and F	–3.9 ± 1.4	–5.9 ± 1*	–6.1 ± 0.5*	–6.6 ± 1*†	–5.5 ± 0.8	–5.5 ± 0.8	–4.9 ± 0.9

Data are given as mean ± SD. *Significantly ($P < 0.05$) different from baseline value. †Significantly ($P < 0.05$) different from value obtained with epidural administration of morphine alone. M = Morphine. F = Fentanyl. HR = Heart rate. SAP = Systolic arterial blood pressure. DAP = Diastolic arterial blood pressure. MAP = Mean arterial blood pressure. CO = Cardiac output. SV = Stroke volume. CI = Cardiac index. TPR = Total peripheral resistance. PAP = Pulmonary arterial blood pressure. RR = Respiration rate. BE = Base excess.

therefore, hypertonic NaCl solution (1 mol/L) was added to the fentanyl citrate solution to make a solution containing 143 mmol of NaCl/L. Morphine hydrochloride was then added to the solution so that the total volume injected was again 0.25 mL/kg.

Data were recorded 5, 10, 15, 30, 60, and 90 minutes after epidural administration of morphine or morphine and fentanyl. The epidural catheter was then removed, and dogs were allowed to recover from anesthesia. Dogs were observed for vomiting, pruritus, and urine retention. Neurologic examinations, including examination of proprioceptive positioning, the hopping reaction, and the flexor reflex, were performed by a single individual (NM) before and the day after each experimental trial. Study observers were aware of which treatment had been administered.

Data are expressed as the mean ± SD. Within each treatment, values for cardiorespiratory data were compared over time by means of repeated-measures ANOVA followed by the Scheffe multiple comparison test. Values were compared between treatments by means of 1-way ANOVA followed by the Scheffe multiple comparison test. Values of $P < 0.05$ were considered significant.

Results

There were no significant differences in baseline measurements between treatments (**Table 1**). When morphine was administered alone, there were no significant changes in cardiorespiratory measurements over time. However, when morphine and fentanyl were administered, diastolic and mean arterial blood pressures and TPR decreased significantly, although SV did not change significantly. Also, following epidural administration of morphine and fentanyl, $Paco_2$ was significantly increased and arterial pH, Pao_2, and base excess were significantly decreased. Although there was no significant change in HR over time following administration of morphine and fentanyl, HR after epidural administration of the combination was significantly lower than HR after epidural administration of morphine alone. No abnormalities were detected during neurologic examinations. None of the dogs had evidence of urine retention, vomiting, or pruritus at any time.

Discussion

The main finding in the present study was that concomitant epidural administration of morphine (0.1 mg/kg) and fentanyl (10 µg/kg) can cause cardiorespiratory depression in dogs anesthetized with sevoflurane. Recommended dosages for epidural administration of morphine and fentanyl in dogs range from 0.05 to 0.2 mg/kg (0.02 to 0.09 mg/lb) and from 1 to 20 µg/kg (0.45 to 9.1 µg/lb), respectively.[6,7,9] The dosages we used for combined epidural administration of morphine and fentanyl have also been used for clinical situations.[1]

In dogs, fentanyl, when administered epidurally, seems to be used more frequently as an adjunct to other drugs, such as morphine or bupivacaine, rather than being used alone.[1,9,12] We therefore determined the cardiorespiratory effects of epidural administration of a combination of morphine and fentanyl, rather than fentanyl alone. Because systemic drug redistribution occurs after epidural administration of morphine and fentanyl in dogs and humans,[13-16] cardiorespiratory effects can be induced by both spinal and systemic actions.

In humans, epidural administration of morphine or fentanyl can cause respiratory depression. In the present study, $Paco_2$ increased significantly, indicating respiratory depression, when dogs were given both morphine and fentanyl but did not increase when dogs were given morphine alone. Thus, fentanyl or the interaction between fentanyl and morphine was considered to be the cause of the respiratory depression. Following epidural administration, fentanyl may induce respiratory depression through systemic actions. On the other hand, in a study[16] involving humans, epidural administration of fentanyl induced respiratory depression, but administration of the same dose of fentanyl IM did not induce significant changes in respiration despite a significantly higher plasma fentanyl concentration. The authors of that study suggested that rostral spread of the fentanyl via the CSF or a perimedullary vascular channel was the cause of the respiratory depression. To determine the mechanism of respiratory depression in dogs given fentanyl epidurally, a comparison of the effects following epidural versus systemic administration of fentanyl would be needed.

Epidural administration of morphine did not cause any significant changes in cardiorespiratory measurements in the present study. Previous studies[17,18] have also shown that epidural administration of morphine at a dosage of 0.1 mg/kg does not induce significant hemodynamic changes in dogs anesthetized with halothane or isoflurane in which ventilation was controlled. In contrast, decreases in diastolic and mean arterial blood pressures and TPR were observed in the present study following epidural administration of morphine and fentanyl, although SV did not change. In addition, HR was significantly lower after epidural administration of morphine and fentanyl than after administration of morphine alone. Peripheral vasodilation and the lower HR could help explain the decreases in arterial blood pressure following epidural administration of morphine and fentanyl.

The mechanism of bradycardia induced by opioids is not fully understood. However, stimulation of the central vagal nucleus and blockade of sympathetic chronotropic action seem to be involved.[19] Opioid-related bradycardia is usually prevented or treated with anticholinergics. A potential cause of the decrease in TPR after epidural administration of morphine and fentanyl in the present study is the sympatholytic effect of opioids. A high concentration of some opioids may have a weak local anesthetic-type action on peripheral nerves,[20] and hypotension and peripheral vasodilation possibly resulting from the sympatholytic effect of intrathecal administration of large doses of morphine and sufentanil have been demonstrated in humans.[21] Alternatively, hypercapnia could have played a role in the vasodilation. A previous study[22] showed that an increase in $Paco_2$ from 39 to 72 mm Hg induced a decrease in TPR in anesthetized dogs. Finally, it is possible that fentanyl had a direct action on the peripheral vasculature. In a study[23] involving isolated canine hind limbs, administration of fentanyl at a dosage of 50 µg/kg of limb weight (22.7 µg/lb) induced a signif-

icant decrease in vascular resistance, whereas administration at a dosage of 5 or 30 µg/kg (2.3 and 13.6 µg/lb) caused no significant change. Because neither naloxone nor denervation affected the response, vasodilation through a direct action of fentanyl on peripheral vascular smooth muscle was suggested. It is unclear whether epidural administration of fentanyl at the dosage used in this study could induce a decrease in TPR through systemic actions alone, and the cause of the decrease in TPR among dogs in the present study remains unknown. However, if we consider the possible mechanisms for the lower HR and TPR, then administration of anticholinergics, fluids, or vasopressors and maintenance of an adequate Pa_{CO_2} would likely be useful in treating or preventing the decrease in arterial blood pressure induced by epidural administration of morphine and fentanyl.

Urine retention has been associated with epidural opioid administration. In the present study, the lack of IV fluid infusion during experimental trials and the fact that the urinary bladder was not expressed prior to recovery from anesthesia may have affected the evaluation of urine retention. However, voluntary voiding was observed in all dogs after recovery from anesthesia. One possible mechanism of urine retention following epidural opioid administration is interference with the detrusor reflex.[1] Hansen[1] has suggested that although most dogs develop some degree of urine retention following epidural morphine administration, most are able to urinate without assistance if they are able to walk outside. Therefore, in our study, we considered that the presence of voluntary voiding would indicate an absence of clinically important urine retention.

Results of the present study suggest that cardiorespiratory depression should be considered a possible complication of epidural administration of a combination of morphine and fentanyl in dogs anesthetized with sevoflurane. A dose of 0.1 mg/kg is probably the dose most widely used for epidural administration of morphine in dogs, and morphine seems to have minimal cardiorespiratory depressant effects when administered at this dose. The optimum dose for epidural administration of fentanyl and the dose-related cardiorespiratory and analgesic effects of epidural fentanyl administration in dogs are unclear.

[a]EC-5520-P, Arrow International, Reading, Pa.
[b]MTC-6210, Nihon Kohden, Tokyo, Japan.
[c]BSM-3101, Nihon Kohden, Tokyo, Japan.
[d]AP-641G, Nihon Kohden, Tokyo, Japan.
[e]Handy Corder, NEC san-ei, Tokyo, Japan.
[f]Gastat 3, Techno Medica, Tokyo, Japan.
[g]Capnox, Colin, Komaki, Japan.
[h]Takeda, Osaka, Japan.
[i]Sankyo, Tokyo, Japan.

References

1. Hansen BD. Epidural catheter analgesia in dogs and cats: technique and review of 182 cases (1991–1999). *J Vet Emerg Crit Care* 2001;11:95–103.

2. Troncy E, Junot S, Keroack S, et al. Results of preemptive epidural administration of morphine with or without bupivacaine in dogs and cats undergoing surgery: 265 cases (1997–1999). *J Am Vet Med Assoc* 2002;221:666–672.

3. Popilskis S, Kohn DF, Danilo P. Efficacy of epidural morphine versus intravenous morphine for post-thoracotomy pain in dogs. *J Vet Anaesth* 1993;20:21–25.

4. Pascoe PJ, Dyson DH. Analgesia after lateral thoracotomy in dogs. Epidural morphine vs intercostal bupivacaine. *Vet Surg* 1993; 22:141–147.

5. Hendrix PK, Raffe MR, Robinson EP, et al. Epidural administration of bupivacaine, morphine, or their combination for postoperative analgesia in dogs. *J Am Vet Med Assoc* 1996;209:598–607.

6. Skarda RT. Local and regional anesthetic and analgesic techniques: dogs. In: Thurman JC, Tranquilli WJ, Benson GJ, eds. *Lumb and Jones' veterinary anesthesia*. 3rd ed. Baltimore: The Williams & Wilkins Co, 1996;426–447.

7. Hardie EM, Kyles A. Pain management in the small animal patient. In: Bojrab MJ, ed. *Current techniques in small animal surgery*. 4th ed. Baltimore: The Williams & Wilkins Co, 1998;3–17.

8. Tanaka M, Watanabe S, Matsumiya N, et al. Enhanced pain management for post-gastrectomy patients with combined epidural morphine and fentanyl. *Can J Anaesth* 1997;44:1047–1052.

9. Dobromylskyj P, Flecknell PA, Lascelles BD, et al. Management of postoperative and other acute pain. In: Flecknell PA, Waterman-Pearson A, eds. *Pain management in animals*. London: WB Saunders Co, 2000;81–145.

10. Duke T, Cox A-MK, Remedios AM, et al. The cardiopulmonary effects of placing fentanyl or medetomidine in the lumbosacral epidural space of isoflurane-anesthetized cats. *Vet Surg* 1994;23:149–155.

11. Steffey EP, Gillespie JR, Berry JD, et al. Circulatory effects of halothane and halothane-nitrous oxide anesthesia in the dog: controlled ventilation. *Am J Vet Res* 1974;35:1289–1293.

12. Hansen B. Epidural analgesia. In: Bonagura JD, ed. *Kirk's current veterinary therapy XIII. Small animal practice*. Philadelphia: WB Saunders Co, 2000;126–131.

13. Justins DM, Knott C, Luthman J, et al. Epidural versus intramuscular fentanyl. Analgesia and pharmacokinetics in labour. *Anaesthesia* 1983;38:937–942.

14. Valverde A, Conlon PD, Dyson DH, et al. Cisternal CSF and serum concentrations of morphine following epidural administration in the dog. *J Vet Pharmacol Ther* 1992;15:91–95.

15. Durant PAC, Yaksh TL. Distribution in cerebrospinal fluid, blood, and lymph of epidurally injected morphine and inulin in dogs. *Anesth Analg* 1986;65:583–592.

16. Negre I, Gueneron JP, Ecoffey C, et al. Ventilatory response to carbon dioxide after intramuscular and epidural fentanyl. *Anesth Analg* 1987;66:707–710.

17. Valverde A, Dyson DH, Cockshutt JR, et al. Comparison of the hemodynamic effects of halothane alone and halothane combined with epidurally administered morphine for anesthesia in ventilated dogs. *Am J Vet Res* 1991;52:505–509.

18. Keegan RD, Greene GA, Weil AB. Cardiovascular effects of epidurally administered morphine and a xylazine-morphine combination in isoflurane-anesthetized dogs. *Am J Vet Res* 1995;56: 496–500.

19. Bailey PL, Stanley TH. Intravenous opioid anesthetics. In: Miller RD, ed. *Anesthesia*. 4th ed. New York: Churchill Livingstone Inc, 1994;291–387.

20. Gissen AJ, Gugino LD, Datta S, et al. Effects of fentanyl and sufentanil on peripheral mammalian nerves. *Anesth Analg* 1987;66: 1272–1276.

21. Goodarzi M, Narasimhan RR. The effect of large-dose intrathecal opioids on the autonomic nervous system. *Anesth Analg* 2001;93:456–459.

22. Rothe CF, Flanagan AD, Maass-Moreno R. Reflex control of vascular capacitance during hypoxia, hypercapnia, or hypoxic hypercapnia. *Can J Physiol Pharmacol* 1990;68:384–391.

23. White DA, Reitan JA, Kien ND, et al. Decrease in vascular resistance in the isolated canine hind limb after graded doses of alfentanil, fentanyl, and sufentanil. *Anesth Analg* 1990;71:29–34.