The Cardiovascular Sparing Effect of Fentanyl and Atropine, Administered to Enflurane Anesthetized Dogs

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ABSTRACT

Cardiovascular effects of high dose opioid together with low dose inhalant were compared with inhalant alone to determine whether opioid/inhalant techniques were less depressant on the cardiovascular system. The effects of positive pressure ventilation and increasing heart rate to a more physiological level were also studied. Cardiovascular measurements recorded during administration of enflurane at 1.3 minimum alveolar concentration (MAC; 2.89 ± 0.02%) to spontaneously breathing dogs (time 1) and during controlled ventilation [arterial carbon dioxide tension at 40 ± 3 mmHg (time 2)] were similar. At time 2, mixed venous oxygen tension and arterial and mixed venous carbon dioxide tensions were significantly decreased, while arterial and mixed venous pH were significantly increased compared to measurements at time 1. After administration of fentanyl to achieve plasma fentanyl concentration of 71.7 ± 14.4 ng/mL and reduction of enflurane concentration to yield 1.3 MAC multiple (0.99 ± 0.01%), heart rate significantly decreased, while mean arterial pressure, central venous pressure, stroke index, and systemic vascular resistance index increased compared to measurements taken at times 1 and 2. Pulmonary arterial occlusion pressure was significantly increased compared to measurements taken at time 2. After administration of atropine until heart rate was 93 ± 5 beats/min (plasma fentanyl concentration 64.5 ± 13.5 ng/mL) heart rate, mean arterial pressure, cardiac index, oxygen delivery index, and venous admixture increased significantly and oxygen utilization ratio decreased significantly compared to values obtained at all other times. Central venous and pulmonary arterial occlusion pressures and systemic vascular resistance index were significantly decreased compared with measurements taken prior to atropine administration, but were not significantly different to those recorded at times 1 and 2. We conclude that, in healthy dogs, an anesthetic technique utilizing fentanyl/enflurane offers considerable cardiovascular sparing compared to enflurane alone, provided an anticholinergic is administered to prevent bradycardia.

RÉSUMÉ

Les effets cardio-vasculaires d'une haute dose d'opioïde combinée à une faible dose de gaz anesthésique ont été comparés à ceux du gaz anesthésique utilisé seul, afin de déterminer si les techniques anesthésiques opioïde/gaz avaient moins d'effets délétères sur le système cardiovasculaire. Les effets de la ventilation à pression positive et ceux de l'augmentation de la fréquence cardiaque à un niveau plus physiologique ont également été étudiés. Les mesures cardio-vasculaires enregistrées sur des chiens recevant de l'enflurane à 1.3 fois la concentration alvéolaire minimale (CAM; 2.89 ± 0.02%) étaient similaires pendant la respiration spontanée (temps 1) et pendant la ventilation contrôlée (pression partielle de dioxyde de carbone dans le sang artériel maintenue à 40 ± 3 mmHg) (temps 2). Au temps 2, les pressions partielles d'oxygène et de dioxyde de carbone dans le sang veineux mélangé et la pression partielle de dioxyde de carbone dans le sang artériel étaient diminuées de façon significative alors que le pH du sang artériel et veineux mélangé augmentait significativement par rapport aux mesures du temps 1. Après avoir administré du fentanyl de façon à obtenir une concentration plasmatique de fentanyl de 71.7 ± 14.4 ng/mL et diminué la concentration d'enflurane (0.99 ± 0.01%), la fréquence cardiaque diminuait significativement alors que la pression artérielle moyenne, la pression veineuse centrale, l'index d'éjection et l'index de résistance vasculaire systémique augmentaient par rapport aux mesures effectuées aux temps 1 et 2. La pression artérielle pulmonaire bloquée était significativement augmentée par rapports aux mesures prises au temps 2. Après l'administration d'atropine jusqu'à ce que la fréquence cardiaque soit de 93 ± 5 battements/min (concentration plasmatique de fentanyl 64.5 ± 13.5 ng/mL), la fréquence cardiaque, la pression artérielle moyenne, l'index cardiaque, l'index de distribution d'oxygène et l'effet de shunt augmentaient significativement et le ratio d'utilisation d'oxygène diminuait significativement comparés aux valeurs obtenues à tous les autres temps. Les mesures de la pression veineuse centrale, de la pression artérielle pulmonaire bloquée et de l'index de résistance vasculaire systémique étaient significativement diminuées par rapport aux mesures

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prises avant l'administration d'atropine mais elles n'étaient pas significativement différentes de celles enregistrées aux temps 1 et 2. Nous concluons qu'une technique anesthésique utilisant fentanyl/enflurane protège beaucoup mieux la fonction cardio-vasculaire que l'enflurane seul, à condition qu'un agent anticholinergique soit administré pour prévenir la bradycardie. ***(Traduit par Dr Phillipe Pibarot)***

INTRODUCTION

In veterinary practice, anesthesia is usually maintained by administration of the potent inhalant anesthetic agents, methoxyflurane, halothane, or isoflurane. These agents, as well as inducing progressive depression of the central nervous system, induce cardiovascular and respiratory depression in dose-dependent fashion (1,2). While opioids induce minimal changes in cardiovascular dynamics (3,4), their ability to produce anesthesia is debated (5,6). In human beings, opioids and sedative hypnotics are often administered with low concentrations of inhalant anesthetics and muscle relaxants as a technique called "balanced anesthesia." Opioids are known to reduce the concentration of inhalant anesthetics required for anesthesia (7,8), and opioid/inhalant anesthetic techniques are thought to cause less depression of cardiovascular and other organ systems (9,10). Opioids and inhalant anesthetics interact synergistically to produce ventilatory depression (11,12) and after administration of these drugs, ventilation is usually controlled. Positive pressure ventilation may induce greater cardiovascular depression and outweigh the benefits of reduced inhalant concentration (2,13).

The study reported here was undertaken to determine whether administration of an opioid under inhalant anesthesia induced less cardiovascular depression than an equivalent level of inhalant anesthesia alone. The effects on hemodynamics of positive pressure ventilation and increasing the heart rate were also studied. All studies were undertaken in healthy dogs with cardiovascular and respiratory systems deemed normal on physical examination.

MATERIALS AND METHODS

INSTRUMENTATION

The experimental protocol was approved by the campus animal care and use committee. Ten nonconditioned, mixed-breed dogs of either sex, weighing 18.5 to 27.9 kg, were used in this study. The dogs were vaccinated against distemper, hepatitis, leptospirosis, parvovirus and rabies, held for two weeks and only included in the study if they were considered healthy by thorough physical examination. Food was withheld for 12 hours and anesthesia induced with enflurane (Ethrane, Anaquest, Madison, Wisconsin) and oxygen delivered via a face mask. Anesthesia was maintained with enflurane and oxygen administered through an orotracheal tube placed in the trachea. A catheter was passed down the lumen of the orotracheal tube so that its distal tip lay level with the tip of the orotracheal tube. This catheter was used to measure inspiratory pressure and to collect gas samples for determination of end-tidal enflurane concentration by infrared absorption (Beckman Medical Gas Analyzer LB-2, Beckman Instruments Inc., Anaheim, California). Prior to and at the completion of each experiment, the gas analyzer was calibrated with gases containing known concentrations of enflurane (1.00% and 2.89%). A Teflon catheter (2-inch, 20-gauge, Insyte, Deseret Medical Inc., Becton Dickinson & Co., Sandy, Utah) was placed percutaneously in the dorsal metatarsal artery for continuous measurement of arterial blood pressure and repeated collection of arterial blood samples for pH, blood gas, PCV and TP measurements. Another Teflon catheter was placed percutaneously in the cephalic vein for administration of fentanyl (Fentanyl citrate injection USP, Elkins-Sinn Inc., Cherry Hill, New Jersey). A balloon-tipped catheter (7.5-F, Swan Ganz thermodilution catheter, Baxter Healthcare Corp., Edwards Critical-Care Division, Irvine, California) was inserted percutaneously via the jugular vein so that the tip lay in the pulmonary artery. Correct positioning was confirmed by observation of a characteristic pulmonary arterial pressure waveform prior to balloon inflation and observation of a characteristic pulmonary arterial occlusion pressure waveform after inflation of the balloon. This catheter was used for continuous measurement of pulmonary arterial and central venous pressures, intermittent mea-

TABLE I. Cardiovascular effects of enflurane (1.3 MAC[1]) during spontaneous and controlled ventilation and of subsequent administration of fentanyl to enflurane to yield 1.3 MAC multiple in dogs (n = 10)

Variable	Time 1 Enflurane 1.3 MAC, spontaneous ventilation	Time 2 Enflurane 1.3 MAC, controlled ventilation	Time 3 Fentanyl and enflurane at 1.3 MAC multiple	Time 4 Fentanyl and enflurane at 1.3 MAC multiple and atropine administration (heart rate 80 to 100 beats/min)
Heart rate (beats/min)	114 ± 9[cd]	112 ± 9[cd]	54 ± 8[abd]	93 ± 5[abc]
Mean arterial pressure (mmHg)	59 ± 6[cd]	64 ± 7[cd]	82 ± 20[abd]	111 ± 10[abc]
Mean pulmonary arterial pressure (mmHg)	9.3 ± 1.5	8.5 ± 1.9	9.6 ± 2.3	10.6 ± 4.4
Central venous pressure (mmHg)	1.3 ± 1.4[c+]	1.8 ± 1.3[c]	3.9 ± 1.7[abd]	1.0 ± 1.4[c]
Pulmonary arterial occlusion pressure (mmHg)	5.7 ± 1.0*	4.4 ± 1.7[c+]	6.9 ± 2.0[bd]*	4.4 ± 1.2[c]*
Stroke index (ml/beat/m²)	24 ± 5[cd]	23 ± 5[cd]	42 ± 10[ab]	48 ± 11[ab]
Cardiac index (L/min/m²)	2.71 ± 0.48[d]	2.55 ± 0.57[d]	2.24 ± 0.64[d]	4.44 ± 0.96[abc]
Systemic vascular resistance index (dyne·sec/cm⁵/m²)	1738 ± 397[c+]	2010 ± 446[c]	2851 ± 626[abd]	2059 ± 494[c]
Pulmonary vascular resistance index (dyne·sec/cm⁵/m²)	100 ± 32*	103 ± 58+	94 ± 33*	105 ± 92*

[1] Minimum alveolar concentration; * n = 9; + n = 8

[a] Significantly different from value under enflurane 1.3 MAC, spontaneous ventilation ($p < 0.05$)

[b] Significantly different from value under enflurane 1.3 MAC, controlled ventilation ($p < 0.05$)

[c] Significantly different from value under fentanyl and enflurane at 1.3 MAC multiple ($p < 0.05$)

[d] Significantly different from value under fentanyl and enflurane at 1.3 MAC multiple, with heart rate 80 to 100 beats/min ($p < 0.05$)

Data are expressed as mean ± SD

TABLE II. Oxygenation effects of enflurane (1.3 MAC[1]) during spontaneous and controlled ventilation and of subsequent administration of fentanyl to enflurane to yield 1.3 MAC multiple in dogs (n = 10)

Variable	Time 1 Enflurane 1.3 MAC, spontaneous ventilation	Time 2 Enflurane 1.3 MAC,controlled ventilation	Time 3 Fentanyl and enflurane at 1.3 MAC multiple	Time 4 Fentanyl and enflurane at 1.3 MAC multiple and atropine administration (heart rate 80 to 100 beats/min)
Partial pressure of oxygen in arterial blood (mmHg)	532.0 ± 30.7	548.6 ± 25.0	545.9 ± 17.3	528.1 ± 35.7
Hemoglobin (g/L)	141 ± 16	142 ± 14	140 ± 13	140 ± 14
Oxygen delivery index (ml/min/m2)	513 ± 129[d]	485 ± 129[d]	423 ± 146[d]	833 ± 238[abc]
Oxygen consumption index (ml/min/m2)	115 ± 31[d]	95 ± 18[+]	100 ± 16*	84 ± 18[a+]
Oxygen utilization ratio	0.23 ± 0.05[d]	0.20 ± 0.07[d+]	0.26 ± 0.09[d]*	0.11 ± 0.05[abc+]
Partial pressure of oxygen in mixed venous blood (mmHg)	70.3 ± 9.9[bc]	59.5 ± 7.0[ad+]	54.5 ± 8.8[ad]*	73.4 ± 11.1[bc+]
Venous admixture (%)	1.1 ± 0.5[d]	1.1 ± 0.5[d+]	0.9 ± 0.2[d]*	2.5 ± 0.8[abc+]

[1]Minimum alveolar concentration; * n = 9; [+] n = 8
[a] Significantly different from value under enflurane 1.3 MAC, spontaneous ventilation ($p < 0.05$)
[b] Significantly different from value under enflurane 1.3 MAC, controlled ventilation ($p < 0.05$)
[c] Significantly different from value under fentanyl and enflurane at 1.3 MAC multiple ($p < 0.05$)
[d] Significantly different from value under fentanyl and enflurane at 1.3 MAC multiple, with heart rate 80 to 100 beats/min ($p < 0.05$)
Data are expressed as mean ± SD

surement of pulmonary arterial occlusion pressure and cardiac output, and for repeated collection of blood samples for mixed venous pH and blood gas measurements. Limb leads were attached for recording the ECG (Amplifier 13 4615 55, Gould Inc., Cleveland, Ohio). Core temperature was measured from the thermistor of the balloon-tipped catheter. All measurements were recorded on a physiograph (ES 1000 recorder, Gould Inc., Cleveland, Ohio). Throughout the study, a 100 volt single twitch stimulus (Grass S48 stimulator, Grass Instruments Co., Quincy, Massachusetts) was delivered every 12 seconds to the lip.

Arterial and mixed venous oxygen (Pa_{O2}, $P\bar{v}_{O2}$) and carbon dioxide (Pa_{CO2},$P\bar{v}_{CO2}$) tensions and arterial and mixed venous pH (pHa, $pH\bar{v}$) were measured, using a blood-gas analyzer (IL system 1306, Instrumentation Laboratory Inc., Lexington, Massachusetts). All measurements were corrected for patient temperature (14). Bicarbonate concentration (mmol/L) and base deficit (mmol/L) were calculated (14,15). Hemoglobin concentration (g/L) was measured by use of the cyanmethemoglobin method and a spectrophotometer(Beckman DB, Beckman Instruments Inc.).

Mean arterial, mean pulmonary arterial, pulmonary arterial occlusion, airway and central venous pressures (all, mmHg) were measured, using pressure transducers (Gould disposable transducer, T4812AD-R, Oxnard, California). Prior to each study, all pressure transducers were calibrated against a mercury manometer, with zero level set at the thoracic inlet in laterally recumbent dogs.

Cardiac output was measured by thermodilution (Cardiac output computer COM-1, American Edwards Laboratories, Irvine, California). Five milliliters of a 0.9% sodium chloride solution at room temperature were injected under pressure via the right atrium (Thermal dilution injector, Lexington, Massachusetts). This procedure was repeated five times, and values obtained were averaged and divided by body surface area [(body weight, kg)$^{0.667}$/10] to obtain cardiac index (L/min/m^2).

Systemic vascular resistance index (dyne·sec/cm^5/m^2), pulmonary vascular resistance index (dyne·sec/cm^5/m^2), arterial and mixed venous blood oxygen content (Ca_{O2} and $C\bar{v}_{O2}$, mL/L), venous admixture (%), oxygen consumption index (mL/min/m^2), oxygen delivery index (mL/min/m^2), and oxygen utilization ratio were calculated from measured values (14,16,17).

EXPERIMENTAL PROTOCOL

After instrumentation and with the dogs breathing spontaneously, the end-tidal enflurane concentration was maintained between 2.84 and 2.92% [1.3 minimum alveolar concentration (MAC)] for 20 minutes and measurements were taken (time 1-enflurane, spontaneously breathing). Throughout the study, all pressure measurements, except pulmonary arterial occlusion pressure, were continuously recorded. Mechanical ventilation was then instituted and continued for the remainder of the study to maintain the Pa_{CO2} at 40 ± 3 mmHg with an inspiratory pressure < 8 mmHg. End-tidal enflurane concentration was maintained at 1.3 MAC for a further 20 minutes and measurements were taken (time 2-enflurane,controlled ventilation). Fentanyl was then administered intravenously, using a loading (15.9 μg/kg/min for 20 minutes) and infusion dose (1.065 μg/kg/min), to maintain the arterial plasma fentanyl concentration at > 30 ng/mL for 60 minutes. At the same time, the enflurane end-tidal concentration was decreased by 65% (0.99-1.02%, 1.3 MAC multiple) and held constant for 60 minutes. A third set of measurements was then taken (time 3-fentanyl and enflurane). Atropine sulfate (Atropine sulfate injection USP, Elkins-Sinn Inc., 0.01 to 0.02 mg/kg) was then administered intravenously until the heart rate was 80 to 100 beats/min, while continuing the fentanyl infusion and maintaining the end-tidal enflurane concentration at 0.99 to 1.02%. Once heart rate was 80 to 100 beats/min, a fourth set of measurements was taken (time 4-fentanyl, enflurane and atropine). Arterial blood samples for determination of plasma fentanyl levels using radioimmunoassay (18) were collected prior to measurement 3 and after measurement 4.

STATISTICAL ANALYSIS

Data were analyzed, using ANOVA for repeated measures to determine ventilation and drug effects. When a significant effect was detected, pairwise comparisons of means were made, using a two-tailed *t*-test. All results are

TABLE III. Acid–base effects of enflurane (1.3 MAC[1]) during spontaneous and controlled ventilation and of subsequent administration of fentanyl to enflurane to yield 1.3 MAC multiple in dogs (n = 10)

Variable	Time 1 Enflurane 1.3 MAC, spontaneous ventilation	Time 2 Enflurane 1.3 MAC,controlled ventilation	Time 3 Fentanyl and enflurane at 1.3 MAC multiple	Time 4 Fentanyl and enflurane at 1.3 MAC multiple and atropine administration (heart rate 80 to 100 beats/min)
pHa (U)	7.250 ± 0.069[bcd]	7.358 ± 0.031[a]	7.341 ± 0.045[a]	7.357 ± 0.038[a]
Partial pressure of carbon dioxide in arterial blood (mmHg)	53.9 ± 8.6[bcd]	40.7 ± 1.1[a]	41.4 ± 1.7[a]	40.9 ± 2.0[a]
Bicarbonate concentration (mmol/L)	22.4 ± 1.6	21.9 ± 1.7	21.4 ± 2.1	21.9 ± 2.1
Base deficit (mmol/L)	−4.2 ± 2.3	−1.9 ± 1.9	−2.6 ± 2.6	−1.8 ± 2.5
$pH\bar{v}$(U)	7.213 ± 0.064[bcd]	7.299 ± 0.021[a*]	7.294 ± 0.047[a*]	7.316 ± 0.041[a*]
Partial pressure of carbon dioxide in mixed venous blood (mmHg)	62.4 ± 8.2[bcd]	49.0 ± 2.6[a*]	50.2 ± 3.0[a*]	46.3 ± 1.4[a*]

[1] Minimum alveolar concentration; * n = 9; * n = 8
[a] Significantly different from value under enflurane 1.3 MAC, spontaneous ventilation ($p < 0.05$)
[b] Significantly different from value under enflurane 1.3 MAC, controlled ventilation ($p < 0.05$)
[c] Significantly different from value under fentanyl and enflurane at 1.3 MAC multiple ($p < 0.05$)
[d] Significantly different from value under fentanyl and enflurane at 1.3 MAC multiple, with heart rate 80 to 100 beats/min ($p < 0.05$)
Data are expressed as mean ± SD

expressed as mean ± SD, and differences were considered significant if $p < 0.05$.

RESULTS

Throughout the study, model conditions were preserved with no significant changes in temperature, packed cell volume or total protein between measurement times. There was no significant difference in end-tidal enflurane concentration between spontaneous ventilation (2.89 ± 0.02%) and controlled ventilation (2.89 ± 0.02%). Both these values were significantly different compared to the end-tidal enflurane concentrations at both measurement times during infusion of fentanyl. There was no significant difference in the end-tidal enflurane concentration during infusion of fentanyl with enflurane (0.99 ± 0.01%) and similar conditions with heart rate increased to 80 to 100 beats/min (0.99 ± 0.01%). Plasma fentanyl concentration at time 3 (71.7 ± 14.4 ng/mL) was not significantly different from that at time 4 (after atropine administration; 64.5 ± 13.5 ng/mL).

Institution of positive pressure ventilation (time 2) did not significantly change any of the cardiovascular measurements compared to measurements taken during spontaneous ventilation (time 1; Table I). The mixed venous oxygen tension and the arterial and mixed venous carbon dioxide tensions were significantly decreased, while the arterial and mixed venous pH were significantly increased at time 2 compared to time 1 (Tables II and III).

Administration of fentanyl and reduction of enflurane to yield 1.3 MAC multiple (time 3) induced a significant decrease in heart rate, while mean arterial pressure, central venous pressure, stroke index, and systemic vascular resistance index increased compared to measurements taken at times 1 and 2. Mixed venous oxygen and carbon dioxide tensions and arterial carbon dioxide tension were significantly decreased, while arterial and mixed venous pH were significantly increased at time 3 compared to values recorded at time 1 (Tables II and III). Pulmonary arterial occlusion pressure was significantly increased at time 3 compared to time 2 (Table I).

After atropine administration, heart rate increased significantly from 54 ± 8 to 93 ± 5 beats/min (Table I). Mean arterial pressure, cardiac index, oxygen delivery index, and venous admixture were increased significantly and oxygen utilization ratio decreased significantly compared to values obtained at times 1, 2 and 3 (Tables I and II). Central venous and pulmonary arterial occlusion pressures and systemic vascular resistance index were significantly decreased compared to measurements taken at time 3, but not different to those at times 1 and 2 (Table I). Oxygen consumption index at time 4 was significantly less than that measured at time 1, while stroke index was significantly greater than that measured at times 1 and 2, but not different from that measured at time 3. Mixed venous oxygen tension measured at time 4 was significantly increased compared to the values measured at times 2 and 3, but not different from the value obtained at time 1.

DISCUSSION

This study was designed to investigate whether opioid/inhalant anesthetic techniques, using high dose fentanyl infusion with low concentration of enflurane, were less depressant on cardiovascular function than standard inhalant techniques. Hypoventilation and a decrease in heart rate usually occur when high dose opioid infusions are administered during inhalant anesthesia in dogs. To prevent hypoventilation, respiration is usually controlled to maintain arterial carbon dioxide at about 40 mmHg, but the decrease in heart rate may not be treated if arterial blood pressure is well maintained. Thus, the effects of positive pressure ventilation and of increasing heart rate to a higher level were also studied.

The study was undertaken in dogs, since in veterinary practice opioid/inhalant anesthetic techniques are more commonly administered to that species than other domestic species. Fentanyl was selected for study, as it is frequently used in opioid/inhalant anesthetic techniques in dogs (19,20), its pharmacokinetic profile and MAC reduction potential have been reported in dogs under enflurane anesthesia (7,21), plasma concentrations of the drug can be easily assayed (18), the pharmacodynamic/pharmacokinetic profile indicates a relationship between effect and plasma concentration (22) and this profile suits administration as an infusion. A loading

dose, as well as a 60 minute infusion of fentanyl, were administered to ensure a steady state had been reached. Although enflurane is rarely administered to veterinary patients, it is commonly administered to human beings. In the present study, enflurane was selected for study because the maximal anesthetic MAC reduction for fentanyl in dogs had been reported for enflurane but not for other inhalants (7). We think that these results can be extrapolated to other inhalants, although the degree of cardiovascular sparing may be less with agents such as isoflurane which induce less myocardial depression. The end-tidal anesthetic concentration prior to fentanyl administration was maintained at 2.89 ± 0.02%, a value equal to 1.3 × MAC. This value was selected as one which would provide surgical anesthetic levels. Throughout the study, a supramaximal single twitch stimulus was applied to the lip of the dogs every 12 seconds to act as a noxious stimulus and simulate surgical conditions and to negate some of the depressant effects of the inhalants (23,24). Maximal reduction in enflurane concentration of 65% has been reported at plasma fentanyl concentrations of 30 ng/mL, with no further significant reduction at 97.0 ng/mL (7). In our study, the 65% reduction was applied to 1.3 × MAC so that the end-tidal enflurane concentration was decreased to 0.99 ± 0.01% and held at that level during infusion of fentanyl. Loading and infusion doses of fentanyl were calculated from pharmacokinetic data (21) to achieve plasma concentrations of ⩾ 30 ng/mL (25). Plasma fentanyl levels measured in this study were approximately twice as high as those desired. This was not considered to affect the experimental results, as higher levels do not produce a greater reduction in enflurane MAC (7). It appeared that the loading dose was responsible for the high plasma levels, as plasma fentanyl levels from samples collected at the completion of administration of the loading dose in four dogs, indicated that the high plasma level had already been reached. The entire study, including instrumentation, took approximately three hours to complete, and as we did not measure the cardiovascular changes under enflurane alone for this duration we are unable to comment on time-related changes in cardiovascular function. Hemodynamic adaptation to prolonged inhalant anesthesia has been reported in dogs (26) but is unlikely to have influenced our results as no changes in cardiac index were found between times 1 and 3. The significant difference occurred between times 3 and 4, measurement times which were separated by less than 15 minutes.

The cardiovascular and respiratory effects of enflurane during both spontaneous and controlled ventilation are similar to those published previously (27). No differences in cardiovascular measurements were found between spontaneous and controlled respiration at 1.5 MAC (27), a similar result to that found in the present study at 1.3 MAC. Mixed venous oxygen tension decreased significantly during controlled ventilation in our study; the importance of this is unknown as oxygen delivery index and oxygen utilization ratio were unchanged. Although not found in this study, greater cardiovascular depression during positive pressure ventilation has been reported previously due in part to the effects of ventilation on venous return (13), as well as to the maintenance of a normal arterial carbon dioxide tension and therefore lack of sympathetic stimulation (2). In our study, respiratory depression induced by enflurane alone was significant (Pa_{co2} 53.9 ± 8.6 mmHg), and since apnea, has been reported when fentanyl was administered to dogs already under inhalant anesthesia (28), controlled ventilation is necessary with opioid/inhalant techniques.

When fentanyl was administered and enflurane reduced to 1.3 MAC multiple, heart rate decreased significantly compared with administration of enflurane alone. Mu-receptor agonist opioids induce bradycardia, which is reportedly more marked in anesthetized than conscious human beings (29). In the study reported here, the plasma fentanyl concentration attained was 71.7 ± 14.4 ng/mL rather than the desired concentration of 30 ng/mL. Although it is possible that a lower plasma fentanyl concentration might not have induced such a decrease in heart rate, the maximal analgesic action appears to coincide with maximal changes in respiratory and cardiovascular systems at a plasma fentanyl level of approximately 30 ng/mL (30). The mechanism of fentanyl-induced bradycardia, while not completely understood, is most likely due to stimulation of the vagal nucleus in the medulla (31). Blockade of sympathetic chronotropic action may also play a minor role (31). In our study, there was a significant increase in mean arterial pressure due to an increase in peripheral vascular resistance. In dogs, peripheral vascular resistance does not change under enflurane (27,32), and perhaps this increase is a compensatory response for the decrease in heart rate and cardiac output. Stroke index increased significantly, but cardiac index did not change due to the decrease in heart rate. Despite the increase in stroke index, both central venous and pulmonary arterial occlusion pressures increased significantly, possibly because the heart was incapable of pumping the increased volume. Since fentanyl alone appears to have minimal effects on myocardial contractility (3,30,33), while enflurane induces dose-dependent myocardial depression, we expected the hemodynamics to improve as the level of enflurane decreased.

In the present study, administration of atropine to increase heart rate to 93 ± 5 beats/min during administration of fentanyl and enflurane, increased cardiac index causing an increase in mean arterial pressure, oxygen delivery index and a decrease in oxygen utilization ratio. From this response, it would appear that the cardiovascular sparing effects of administering fentanyl and decreasing enflurane concentration were present only when heart rate was increased. In a previous study in dogs, fentanyl alone was found not to depress myocardial contractility and thus cardiac output was maintained because of a compensatory increase in stroke volume (34). With other potent opioids however, significant decreases in cardiac output, which were attenuated by atropine, have been reported (35,36,37). In normal hearts, not under the influence of drugs,cardiac output appeared to be independent of heart rate, except at the very extremes (38,39), whereas, in abnormal hearts with impairment of ventricular function, stroke volume appeared to be fixed and cardiac output became dependent on heart rate (40). In our study, it appeared that ventricular impairment limited the increase in stroke volume in response to the fentanyl-induced bradycardia so that cardiac output was maintained at levels similar to those with enflurane alone. The significant increase in central venous and pulmonary arterial occlusion pressure are further evidence for impairment of ven-

tricular function. The most likely reason for ventricular impairment in our study is depression of myocardial contractility by the inhalant anesthetic. Enflurane is reported to induce potent, direct, dose-dependent depression of myocardial contractility (41,42). Thus, although a lower concentration of enflurane was administered with the opioid infusion technique, cardiac output was not spared because ventricular impairment was still sufficient, in the face of a decrease in heart rate, to limit stroke volume. When atropine was administered and heart rate increased to more physiological levels, the cardiovascular sparing effect became evident, with a significant increase in cardiac index, mean arterial pressure, mixed venous oxygen tension, oxygen delivery index and a decrease in oxygen utilization ratio. The cardiac index at this time was similar to the value reported for normal, nonpremedicated, conscious dogs (43) and, when compared with the value for enflurane alone, attests to the cardiovascular sparing effect. Thus, the cardiovascular sparing effect of this opioid/inhalant technique is only present if an anticholinergic is administered to prevent the drug-induced decrease in heart rate.

REFERENCES

1. **STEFFEY EP, HOWLAND D Jr.** Isoflurane potency in the dog and cat. Am J Vet Res 1977; 38: 1833–1849.
2. **STEFFEY EP, GILLESPIE JR, BERRY JD, EGER EI, RHODE EA.** Circulatory effects of halothane and halothane-nitrous oxide anesthesia in the dog: spontaneous ventilation. Am J Vet Res 1975; 36: 197–200.
3. **STANLEY TH, WEBSTER LR.** Anesthetic requirements and cardiovascular effects of fentanyl-oxygen and fentanyl-diazepam-oxygen anesthesia in man. Anesth Analg 1978; 57: 411–416.
4. **SEBEL PS, BOVILL JG.** Cardiovascular effects of sufentanil anesthesia. Anesth Analg 1982; 61: 115–119.
5. **LOWENSTEIN E, PHILBIN DM.** Narcotic "anesthesia" in the eighties (editorial). Anesthesiology 1981; 55: 195–197.
6. **WONG KC.** Narcotics are not expected to produce unconsciousness and amnesia (editorial). Anesth Analg 1983; 62: 625–626.
7. **MURPHY MR, HUG CC Jr.** The anesthetic potency of fentanyl in terms of its reduction of enflurane MAC. Anesthesiology 1982; 57: 485–488.
8. **HALL RI, SZLAM F, HUG CC Jr.** The enflurane-sparing effect of alfentanil in dogs. Anesth Analg 1987; 66: 1287–1291.
9. **HAMM D, FREEDMAN B, PELLOM G, EVERSON C, KNOX J, WECHSLER A, CHRISTIAN C.** The maintenance of myocardial contractility by fentanyl during enflurane administration. Anesthesiology 1983; 59: A86.
10. **FREEDMAN B, HAMM D, PELLOM G, EVERSON C, KNOX J, WECHSLER A, CHRISTIAN C.** Fentanyl-halothane anesthesia maintains myocardial contractility. Anesthesiology 1983; 59: A35.
11. **SMITH TC.** Pharmacology of respiratory depression. Int Anesthesiol Clin 1971; 9: 125–143.
12. **SMITH TC, MASON H, KULP R.** Interaction of fentanyl and enflurane during surgery as expressed by respiratory response to carbon dioxide. Abstract of Scientific Papers, ASA Annual General Meeting 1975: 381–382.
13. **CARR DT, ESSEX HE.** Certain effects of positive pressure respiration on circulatory and respiratory systems. Am Heart J 1946; 31: 53–73.
14. **RUIZ BC, TUCKER WE, KIRBY RR.** A program for calculation of intrapulmonary shunts, blood-gas and acid-base values with a programmable calculator. Anesthesiology 1975; 42: 88–95.
15. **GABEL RA.** Algorithms for calculating and correcting blood-gas and acid-base variables. Respir Physiol 1980; 42: 211–232.
16. **NELSON LD.** Application of venous saturation monitoring. In: Civetta JM, Taylor RW, Kirby RR, eds. Critical Care. Philadelphia: JB Lippincott, 1988: 327–334.
17. **ILKIW JE, HASKINS SC, PATZ JD.** Cardiovascular and respiratory effects of thiopental administration in hypovolemic dogs. Am J Vet Res 1991; 52: 576–580.
18. **MICHIELS M, HENDRIKS R, HEYKANTS J.** A sensitive radioimmunoassay for fentanyl. Plasma levels in dogs and man. Eur J Clin Pharmacol 1977; 12: 153–158.
19. **WILLIAMSON HA, CUMMING DVE, COBB MA, PATTISON CW, YACOUB MH, CLAYTON JONES DG.** Development of an opiate-based anaesthetic technique for use in dogs with cardiomyopathy. Vet Rec 1991; 129: 398–400.
20. **MOON PF, ILKIW JE.** Surface-induced hypothermia in dogs: 19 cases (1987–1989). J Am Vet Med Assoc 1993; 202: 437–444.
21. **MURPHY MR, OLSON WA, HUG CC Jr.** Pharmacokinetics of ^{3}H-fentanyl in the dog anesthetized with enflurane. Anesthesiology 1979; 50: 13–19.
22. **SCOTT JC, PONGANIS KV, STANSKI DR.** EEG quantitation of narcotic effect: The comparative pharmacodynamics of fentanyl and alfentanil. Anesthesiology 1985; 62: 234–241.
23. **HALL LW, CLARKE KW.** General pharmacology of the inhalation anaesthetics. In: Veterinary Anaesthesia, Edition 9. London: Baillière Tindall, 1991: 98–112.
24. **FRANCE CJ, PLUMER MH, EGER EI, WAHRENBROCK EA.** Ventilatory effects of isoflurane (Forane) or halothane when combined with morphine, nitrous oxide and surgery. Br J Anaesth 1974; 46: 117–120.
25. **WAGNER JG.** A safe method for rapidly achieving plasma concentration plateaus. Clin Pharmacol Therap 1974; 16: 691–700.
26. **STEFFEY EP, FARVER TB, WOLINER MJ.** Cardiopulmonary functon during 7 h of constant-dose halothane and methoxyflurane. J Appl. Physiol 1987; 63: 1351–1359.
27. **STEFFEY EP, HOWLAND D Jr.** Potency of enflurane in dogs: Comparison with halothane and isoflurane. Am J Vet Res 1978; 39: 573–577.
28. **EISELE JH, REITAN JA, TORTEN M, MILLER CH.** Myocardial sparing effect of fentanyl during halothane anaesthesia in dogs. Br J Anaesth 1975; 47: 937–940.
29. **TAMMISTO T, TAKKI S, TOIKKA P.** A comparison of the circulatory effects in man of the analgesics fentanyl, pentazocine and pethidine. Br J Anaesth 1970; 42: 317–324.
30. **ARNDT JO, MIKAT M, PARASHER C.** Fentanyl's analgesic, respiratory, and cardiovascular actions in relation to dose and plasma concentration in unanesthetized dogs. Anesthesiology 1984; 61: 355–361.
31. **REITAN JA, STENGERT KB, WYMORE ML, MARTUCCI RW.** Central vagal control of fentanyl-induced bradycardia during halothane anesthesia. Anesth Analg 1978; 57: 31–36.
32. **KLIDE AM.** Cardiopulmonary effects of enflurane and isoflurane in the dog. Am J Vet Res 1976; 37: 127–131.
33. **HAMM D, FREEDMAN B, PELLOM G, EVERSON C, KNOX J, WECHSLER A, CHRISTIAN C.** The effect of fentanyl on left ventricular function. Anesthesiology 1983; 59: A37.
34. **De HERT SG.** Study on the effects of six intravenous anesthetic agents on regional ventricular function in dogs (thiopental, etomidate, propofol, fentanyl, sufentanil, alfentanil). Acta Anaesthesiol Belg 1991; 42: 3–49.
35. **STANLEY TH, LIU WS, WEBSTER LR, JOHANSEN RK.** Haemodynamic effects of intravenous methadone anaesthesia in dogs. Can Anaesth Soc J 1980; 27: 52–57.
36. **REDDY P, LIU WS, PORT D, GILLMOR S, STANLEY TH.** Comparison of haemodynamic effects of anaesthetic doses of alphaprodine and sulfentanil in the dog. Can Anaesth Soc J 1980; 27: 345–350.
37. **COPLAND VS, HASKINS SC, PATZ JP.** Cardiovascular and pulmonary effects of atropine reversal of oxymorphone-induced bradycardia in dogs. Vet Surg 1992; 21: 414–417.
38. **MILLER DE, GLEASON WL, WHALEN RE, MORRIS JJ, McINTOSH HD.** Effect of ventricular rate on the cardiac output in the dog with chronic heart block. Circ Res 1962; 10: 658–663.
39. **WARNER HR, TORONTO AF.** Regulation of cardiac output through stroke volume. Circ Res 1960; 8: 549–552.
40. **McGREGOR M, KLASSEN GA.** Observations on the effect of heart rate on cardiac output in patients with complete heart block at rest and during exercise. Circ Res 1964; 24–25 (Suppl 2): 215–221.
41. **HOUSMANS PR, MURAT I.** Comparative effects of halothane, enflurane, and isoflurane and equipotent anesthetic concentrations on isolated ventricular myocardium of the ferret. I. Contractility. Anesthesiology 1988; 69: 451–463.
42. **BROWN BR, CROUT JR.** A comparative study of the effects of five general anesthetics on myocardial contractility: I. Isometric conditions. Anesthesiology 1971; 34: 236–245.
43. **O'ROURKE RA, BISHOP VS.** Cardiovascular hemodynamics in the conscious dog. Am Heart J 1971; 81: 55–60.