Mechanical ventilation is widely used as a lifesaving intervention to maintain eucapnia and normoxemia in critically ill patients. Mechanical ventilation is poorly tolerated in many conscious patients, which results in patient-ventilator asynchrony. Administration of sedatives; analgesics; and, in some cases, neuromuscular blocking agents, alone or in combination, is required to facilitate IPPV. Most of these pharmacologic agents induce alterations in cardiovascular function, which must be considered in patients receiving IPPV. A fundamental consequence of mechanical ventilation is the increase in pleural space pressures. This subsequent increase in intrathoracic pressure can reduce preload and compromise CO.

**Objective**—To determine the effectiveness and safety of 2 sedative-analgesic protocols to facilitate assisted ventilation in healthy dogs.

**Animals**—12 healthy dogs.

**Procedures**—Dogs were randomly assigned to 2 groups. Mean dosages for protocol 1 were diazepam (0.5 mg/kg/h [n = 3 dogs]) or midazolam (0.5 mg/kg/h [3]), morphine (0.6 mg/kg/h [6]), and medetomidine (1.0 µg/kg/h [6]). Mean dosages for protocol 2 were diazepam (0.5 mg/kg/h [n = 3]) or midazolam (0.5 mg/kg/h [3]), fentanyl (18 µg/kg/h [6]), and propofol (2.5 mg/kg/h [6]). Each dog received the drugs for 24 consecutive hours. All dogs were mechanically ventilated with adjustments in minute volume to maintain normocapnia and normoxemia. Cardiorespiratory variables were recorded. A numeric comfort score was assigned hourly to assess efficacy. Mouth care, position change, and physiotherapy were performed every 6 hours. Urine output was measured every 4 hours.

**Results**—Use of both protocols maintained dogs within optimal comfort ranges > 85% of the time. The first dog in each group was excluded from the study. Significant decreases in heart rate, oxygen consumption, and oxygen extraction ratio were evident for protocol 1. Cardiac index values in ventilated dogs were lower than values reported for healthy unsedated dogs. Oxygen delivery, lactate concentration, and arterial base excess remained within reference ranges for both protocols.

**Conclusions and Clinical Relevance**—Use of both protocols was effective for facilitating mechanical ventilation. A reduction in cardiac index was detected for both protocols as a result of bradycardia. However, oxygen delivery and global tissue perfusion were not negatively affected. (Am J Vet Res 2008;69:1351–1359)

**Abbreviations**

- ABE Arterial base excess
- ADH Antidiuretic hormone
- BFP Benzodiazipine, fentanyl, and propofol
- BMM Benzodiazipine, morphine, and medetomidine
- Ca\textsubscript{o}\textsubscript{2} Arterial oxygen content
- C\textsubscript{cv}\textsubscript{o}\textsubscript{2} Central-venous oxygen content
- CI Cardiac index
- CO Cardiac output
- CRI Constant rate infusion
- DO\textsubscript{o} Oxygen delivery
- ER\textsubscript{o}\textsubscript{2} Oxygen extraction ratio
- FI\textsubscript{o} Inspired oxygen fraction
- ICU Intensive care unit
- IPPV Intermittent positive-pressure ventilation
- MAP Mean arterial pressure
- NICO Noninvasive cardiac output
- PEEP Positive end expiratory pressure
- P\textsubscript{eto}\textsubscript{2} End-tidal partial pressure of carbon dioxide
- SVI Stroke volume index
- SVRI Systemic vascular resistance index
- VE Minute ventilation
- VO\textsubscript{o} Oxygen consumption
- VT Tidal volume
that requires mechanical ventilation must also consider the safety for such protocols with respect to the cardiovascular system. Other important considerations are the duration of action and reversibility of the sedatives and analgesics with respect to termination of ventilatory support. Patients spending an extensive period on the ventilator with uninterrupted periods of sedation develop muscle fatigue and atrophy (disuse and neurogenic) that contribute to difficulty when weaning them from the ventilator.\textsuperscript{4–11} The morbidity and cost associated with prolonged weaning have prompted a trend in human medicine to reduce overall sedation requirements and to promote the use of analgesic-based protocols that have a rapid onset of action, are easily titrated to effect, and can be readily reversed.\textsuperscript{12–15}

Although recommendations for instituting and maintaining dogs on IPPV have been described in canine patients,\textsuperscript{3,14,15} the authors are not aware of any published veterinary studies that have specifically evaluated use of sedation and analgesia protocols with potential adverse cardiovascular effects in dogs receiving IPPV. The 2 general categories of patients requiring IPPV are patients afflicted with diseases impairing ventilation but that are otherwise generally hemodynamically stable and patients with primary parenchymal disease, severe hypoxia, hypercapnia, or a combination of these as well as cardiovascular compromise.

Thus, the purpose of the study reported here was to evaluate the efficacy and safety for the use of 2 sedation and analgesia protocols to facilitate IPPV for 24 hours in healthy dogs in a typical ICU setting. One of the protocols (BMM) was deemed to have more cardiorespiratory depressive effects than the other (BFP); however, our hypothesis was that both protocols would allow IPPV with minimal impairment in cardiovascular status in healthy dogs.

**Materials and Methods**

**Animals**—Twelve healthy mixed-breed dogs (3 females and 9 males) that weighed (mean ± SD) 26.5 ± 2.91 kg were used in the study. All dogs were in ideal body condition and considered healthy on the basis of results of physical examination, a CBC, serum biochemical analysis, and thoracic radiography performed prior to enrollment into the study. The study was approved by the Animal Care Committee of the University of Guelph.

**Anesthesia and instrumentation**—Each dog was sedated by administration of hydromorphone\textsuperscript{a} (0.05 mg/kg, IM). Thirty minutes later, a 20-gauge, 1.88-inch catheter\textsuperscript{b} was aseptically placed into a cephalic vein to allow the administration of a bolus of propofol\textsuperscript{c} (4 mg/kg). This propofol bolus was repeated as necessary to achieve heavy sedation for instrumentation. A 12-inch catheter\textsuperscript{d} was placed into a jugular vein and advanced to the level of the right atrium for collection of central venous blood samples for venous blood gas analysis, drug delivery, and measurement of central venous pressure; catheter placement was verified by examination of a lateral thoracic radiographic view. A balanced saline solution\textsuperscript{d} was continuously infused through the jugular catheter at a rate of 5 mL/kg/h. A 20-gauge, 1.88-inch catheter was placed in a dorsal pedal artery to measure systolic arterial pressure, diastolic arterial pressure, and SAP and for collection of arterial blood samples for blood gas analysis. For measurement of arterial and venous pressures, catheters were attached to an electronic transducer that was calibrated to zero at the level of the sternum and connected to a physiologic monitor.\textsuperscript{1} A rectal thermometer was used for continuous monitoring of body temperature. An indwelling urinary catheter was used to monitor urine output, and a 3-lead ECG was used to continuously monitor heart rate and rhythm.\textsuperscript{5}

All dogs were then intubated with a low-pressure cuffed endotracheal tube, and the drugs for the respective protocols were administered to facilitate IPPV. The PET\textsubscript{CO}\textsubscript{2} was monitored continuously by use of software provided with the ventilator.\textsuperscript{6} Once IPPV was initiated, measurements of NICO were determined by use of a partial CO\textsubscript{2} rebreathing noninvasive system.\textsuperscript{9} Manufacturer’s instructions were followed to obtain CO measurements, and those instructions included collection of an arterial blood sample for blood gas analysis prior to CO measurement and entering the required patient data (body weight, F\textsubscript{IO}\textsubscript{2}, P\textsubscript{A}\textsubscript{O}\textsubscript{2}, and P\textsubscript{A}\textsubscript{CO}\textsubscript{2}) into the monitor. The CO\textsubscript{2}-volume sensor was connected to each dog at a point between the endotracheal tube and the ventilation circuit system, and a pulse oximeter was placed on each dog’s tongue. The CO determinations at each interval consisted of a measurement every 3 minutes, which were completed in duplicate or triplicate to ensure that variation was ≤ 20% between measurements. Mean of all acceptable duplicate or triplicate measurements was recorded as the CO value.

**Experimental design**—Dogs were randomly allocated to 2 groups (n = 6 dogs/group). After instrumentation was completed, ventilation was initiated for a 24-hour period in the ICU setting to mimic a clinical environment. Dogs administered drugs in accordance with protocol 1 (BMM group) received a CRI of a benzodiazepine (diazepam\textsuperscript{1} [n = 3 dogs] or midazolam\textsuperscript{1} [3] at a rate of 0.3 to 0.7 mg/kg/h) and a CRI of morphine\textsuperscript{1} (0.4 to 0.8 mg/kg/h [6]). Dosages were adjusted to achieve an optimal degree of sedation and analgesia as determined on the basis of clinical judgment and a comfort score. When a short-term increase in sedation or analgesia was deemed necessary because of the reaction of a dog to noise or manipulations, morphine (0.1 mg/kg) or the benzodiazepine (0.4 mg/kg) was administered IV without a change in the CRI. When adequate sedation and patient comfort were not achieved with sedation and analgesia alone, then a bolus of medetomidine\textsuperscript{1} (0.5 µg/kg) was administered IV during a 15-second period. When 2 or more boluses of medetomidine were necessary, then a CRI of medetomidine (0.5 to 3.0 µg/kg/h) was added to the protocol. Dogs administered drugs in accordance with protocol 2 (BFP group) received a CRI of a benzodiazepine (diazepam\textsuperscript{1} [n = 3 dogs] or midazolam\textsuperscript{1} [3] at a rate of 0.3 to 0.7 mg/kg/h) and a CRI of fentanyl\textsuperscript{10} (10 to 20 µg/kg/h [6]). When short-term sedation and analgesia were deemed necessary, a bolus of fentanyl (2 µg/kg) or the benzodiazepine (0.4 mg/kg) was administered IV without a change in the CRI. When adequate sedation and patient...
comfort were not achieved with sedation and analgesia alone, then a bolus of propofol (1.0 mg/kg) was administered IV during a 15-second period. When no or more boluses of propofol were necessary, a CRI of propofol (3 to 10 mg/kg/h) was added to the protocol.

Respiratory rate, pulse oximetry, heart rate, systolic arterial pressure, diastolic arterial pressure, MAP, PETCO₂, respiratory rate, Vt, Ve, and peak inspiratory pressure were continuously monitored and recorded every hour once a stable plane of anesthesia was achieved after initial CRI of drugs (ie, baseline). Baseline (time 0) was defined as a lightly sedated dog with no evidence of ventilator-patient asynchrony, PaO₂ > 80 mm Hg, FiO₂ of 0.21, and PETCO₂ between 35 and 45 mm Hg for a minimum of 30 minutes after intubation but no sooner than 30 minutes after commencement of positive-pressure ventilation. The CO was measured at baseline and at 4-hour intervals. Arterial and central venous blood samples were collected anaerobically into heparinized syringes at baseline and every 4 hours. All samples were analyzed immediately by use of a calibrated blood gas analyzer to determine PaO₂, Paco₂, pH, and ABE. All measurements were recorded directly into a computerized data spreadsheet.

Several variables were then calculated. The value for CI was calculated as (CO/body weight) X 1,000. Stroke volume was calculated as (CO/heart rate) X 1,000. The SVI was calculated as stroke volume divided by body weight. The systemic vascular resistance was calculated as ([MAP – central venous pressure]/CO) X 80. The CaO₂ was calculated as (hemoglobin concentration X arterial hemoglobin saturation X 1.34) + (0.0031 X PaO₂). The CvCO₂ was calculated as (hemoglobin concentration X central venous hemoglobin saturation X 1.34) + (0.0031 X PcvO₂). The Vo₂ was calculated as ([CaO₂ – CvO₂] X CI)/1,000. The Do₂ was calculated as (Cao₂ X CI)/1,000. The ERO₂ was calculated as (Vo₂/Do₂) X 10.

All dogs received a balanced electrolyte solution at an initial rate of 5 mL/kg/h; the rate was adjusted every 4 hours on the basis of urine output, urine specific gravity, PCV, total protein concentration, and results of a physical examination. Our initial intent was that the fluid rate would be increased when there was a decrease in urine production to ensure adequate volume. Patterns for urine production, PCV, total protein concentration, serum sodium concentration, and results of physical examination performed every 4 hours were used to assess hydration. Furosemide (0.25 mg/kg, IV) was administered when urine output was < 0.5 mL/kg/h without a concurrent increase in PCV, total protein concentration, or serum sodium concentration; BUN concentration (as measured by use of a chemical reagent strip) was within the reference range; and there was evidence of fluid overload detected during physical examination.

Mouth care and physiotherapy were performed every 6 hours. An in-line suction device was placed, and the endotracheal tube was aspirated every 6 hours. Prior to suctioning of the endotracheal tube, each dog was oxygenated by administration of 100% oxygen for a minimum of 1 minute. Each dog was rotated through sternal, left lateral, and right lateral positions. Positional changes were made every 6 hours; changes were made at < 6 hours when needed to maintain patient comfort. Body temperature was maintained between 37° and 38°C with blankets and external warming devices.

IPPV—All dogs were mechanically ventilated in a volume target mode (ie, synchronous intermittent mandatory ventilation) with an automated flow and a PEEP of 5 cm H₂O by use of a ventilator with spirometry capabilities. All dogs were initially ventilated at an FiO₂ of 1.0 until stable; the FiO₂ was then reduced to 0.21. Initial Vt and respiratory rate were set at 10 ml/kg and 15 breaths/min, respectively. Additional adjustments of Vt and respiratory rate were made as needed to maintain patient comfort. PaO₂ > 80 mm Hg, and Paco₂ between 35 and 45 mm Hg while ensuring that plateau airway pressures did not exceed 25 cm H₂O. In-line evaluations of PETCO₂ and pulse oximetry were used to detect changes in Paco₂ and arterial hemoglobin saturation, respectively. Weaning from IPPV began at the completion of data collection after ventilation for 24 hours. All dogs were continuously monitored by at least 1 investigator (MRE or KAM) or a registered veterinary technician trained in the use of mechanical ventilation.

Comfort score—Optimal comfort was defined as a lightly sedated dog with no signs of anxiety (assessed by evidence of agitation) or patient-ventilator asynchrony. Efficacy of each sedation and analgesia protocol was determined by use of a comfort score for agitation and sedation that was a modification of the Ramsay score and a comfort scale used in ventilated adult and pediatric humans16,17 (Appendix). Dogs were continuously observed, and the highest score assigned for any specific hour was recorded. A score of 2 or 3 (scale of 1 to 5) was considered acceptable for sedation, whereas a score of 1 (scale of 1 to 5) was acceptable for agitation. All other scores were considered outside of the target comfort range. In response to an unacceptable score, ventilation variables (as assessed on the basis of results of blood gas analysis) and potential causes of patient discomfort (body and head position) were addressed first, and when necessary, appropriate changes in drug dosages were made in response to the scores obtained.

Diagnostic imaging—Orthogonal thoracic radiographs were obtained in the ICU by use of a portable radiographic machine between hours 4 and 6 and between hours 20 and 22 of IPPV for all dogs. These radiographs were compared with radiographs obtained before the study and at baseline. The same board-certified veterinary radiologist, who was unaware of the sedation and analgesia protocol for each dog and time at which the radiograph was obtained, evaluated all radiographs. Placement of the central jugular catheter, lung volume, parenchymal changes, and mediastinal shift were evaluated on all radiographs. When abnormalities were detected, additional radiographs were obtained after completion of the IPPV to evaluate changes once that dog was weaned from IPPV and allowed to resume spontaneous respiration.

Data analysis—Statistical analyses were performed by use of commercially available software. All data were reported as mean ± SD. A Shapiro-Wilk test was
performed to determine normality of the data. To compare the physiologic variables among treatment groups over time, an ANOVA for repeated measures with an appropriate covariance structure was used, with treatment and time of data collection as main factors. When the overall F test was significant for the main effects of treatment or time or there was a treatment-by-time interaction, pairwise comparisons were used. A Dunnett correction was performed to evaluate variables within a treatment over time, compared with baseline values. A general linear model accounting for random effect of dog was used to determine the frequency of target sedation range attained within each protocol. Values of P < 0.05 were considered significant for all analyses.

**Results**

The first dog within each protocol was not treated in accordance with the algorithm designed for the study. Because of these protocol violations, both of these dogs were removed from the study. Thus, results are based on 10 dogs (5 dogs in each group).

All dogs eventually required continuous infusions of all 3 drugs of their respective protocols to facilitate mechanical ventilation. The mean CRI dosages and total number of boluses used to facilitate mechanical ventilation during the 24-hour period for each protocol were determined (Table 1). Mean number of boluses for any dog for protocol 1 was 6.8, whereas the mean number of boluses for any dog for protocol 2 was 3.4. Mean dosage of each drug for each protocol was calculated to determine the overall protocol mean for the continuous infusion of each drug during the 24-hour period. Although triglyceride concentrations were not measured, lipemia was not detected in any blood sample during or following administration of propofol in dogs for protocol 2.

Ventilation settings used to maintain variables within designated limits (ie, PaO₂ > 80 mm Hg and PaCO₂ of 35 to 45 mm Hg) did not differ significantly between protocols. A pattern for an increase in Vt requirement over time within each protocol was evident (Table 2, Figure 1).

Mean ± SD values for ventilatory variables recorded during a 24-hour period in mechanically ventilated dogs sedated and anesthetized by administration of drugs in accordance with protocol 1 (BMM [n = 5]) and protocol 2 (BFP [5]).

### Table 1—Mean ± SD CRI for each drug and the total combined number of boluses administered during a 24-hour period in mechanically ventilated dogs sedated and anesthetized by administration of drugs in accordance with protocol 1 (BMM [n = 5]) and protocol 2 (BFP [5]).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Protocol 1</th>
<th>Protocol 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Benzodiazepine* (mg/kg/h)</td>
<td>Morphine (mg/kg/h)</td>
</tr>
<tr>
<td>Mean rate</td>
<td>0.5 ± 0.1</td>
<td>0.6 ± 0.1</td>
</tr>
<tr>
<td>No. of boluses</td>
<td>13</td>
<td>7</td>
</tr>
</tbody>
</table>

* Dogs received diazepam or midazolam.

### Table 2—Mean ± SD values for ventilatory variables recorded during a 24-hour period in mechanically ventilated dogs sedated and anesthetized by administration of drugs in accordance with protocol 1 (BMM [n = 5]) and protocol 2 (BFP [5]).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Protocol 1</th>
<th>Protocol 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Protocols Vt (mL/kg)</td>
<td>Protocols Respiratory rate (breaths/min)</td>
</tr>
<tr>
<td>Vt (mL/kg)</td>
<td>15 ± 1</td>
<td>14 ± 1</td>
</tr>
<tr>
<td>Vt (mL/kg/min)</td>
<td>242 ± 21</td>
<td>246 ± 47</td>
</tr>
<tr>
<td>Respiratory rate (breaths/min)</td>
<td>17 ± 2</td>
<td>18 ± 4</td>
</tr>
<tr>
<td>Peak inspiratory pressure (cm H₂O)</td>
<td>13 ± 1</td>
<td>13 ± 1</td>
</tr>
<tr>
<td>PaO₂ (mm Hg)</td>
<td>84 ± 4</td>
<td>90 ± 3</td>
</tr>
<tr>
<td>PaCO₂ (mm Hg)</td>
<td>45 ± 2</td>
<td>42 ± 2</td>
</tr>
</tbody>
</table>

Higher in dogs administered drugs in accordance with protocol 1, compared with values for dogs administered drugs in accordance with protocol 2. Cardiopulmonary variables did not change significantly over time relative to hour 1 within a protocol group, except for a significant increase in CI and Do₂ at hour 13 (Table 4).

The percentage of time that dogs were within the target range for sedation was 91% for protocol 1 and 95% for protocol 2; for agitation, the percentage was 90% for protocol 1 and 97% for protocol 2. When sedation and agitation were combined, the combined percentage of time that dogs were within the target sedation and agitation range was 87% for protocol 1 and 93% for protocol 2. However, no overall significant difference was detected between groups when variation of individual dogs was considered.

All dogs were successfully weaned from assisted ventilation after completion of the study. Spontaneous breathing was detected within 1 hour after discontinuation of drug administration, regardless of sedation and analgesia protocol. Administration of acepromazine (0.02 mg/kg, IV) was required to avoid dysphoria during recovery from sedation and analgesia in 4 dogs administered drugs in accordance with protocol 1 and 3 dogs administered drugs in accordance with protocol 2.

During the 24-hour period, we detected a reduction in urine production and an increase in urine specific gravity but no significant changes in PCV and total protein, BUN, and serum sodium concentrations. Physical examination revealed peripheral edema as assessed by loss of anatomic detail in the distal portions of limbs; a noticeable increase in skin turgor over the thorax, head, and neck; and chemosis. A single dose of furosemide was administered to 1 dog in group BMM, whereas 4 dogs in group BFP required a single dose of furosemide. Mean ± SD volume of fluid administered to each dog during the 24-hour period was 121 ± 18 mL/kg for protocol 1 and 122 ± 10 mL/kg for protocol 2. Mean urine
Discussion

In the study reported here, we evaluated the safety and efficacy for use of 2 sedation and analgesia protocols in healthy dogs that were mechanically ventilated for a 24-hour period. The optimal sedation comfort range was achieved by use of both protocols (87% of the study period for protocol 1 [BMM] and 93% for protocol 2 [BFP]). This resulted in lightly sedated dogs that could breathe spontaneously without signs of anxiety or patient-ventilator asynchrony. Considering that the dogs were continuously monitored and that the degree of sedation comfort was adjusted accordingly, it is likely that the amount of time outside the optimal range was overestimated because the score recorded every hour corresponded to the highest score, regardless of interventions.

The ICU setting, which included activity of staff and noises that were likely to disturb sedated dogs, was selected to mimic conditions encountered routinely in clinical environments. For the same reason, physiotherapy, mouth care, and suctioning of the endotracheal tube were performed routinely in these dogs.

The personality or disposition observed for each dog prior to the study was also reflected in the overall sedation requirements. Calmer, more passive dogs typically required lower overall dosages of the drugs during the 24-hour period, whereas nervous, more active dogs required higher dosages. Dogs that received drugs in accordance with protocol 1 were more likely to awaken or dynamically change from an acceptable sedation state as a result of activity or noise in the ICU; thus, more boluses of medetomidine were required. It has been reported\(^{19,20}\) that animals receiving medetomidine may have an increase in sensitivity to sounds and tactile stimulation. Therefore, depending on the ICU environment, medetomidine combinations may not provide sufficient sedative and anxiolytic effects to facilitate IPPV.

Propylene glycol toxicity is a reported complication in patients receiving IV administration of certain benzodiazepines. Propylene glycol is the vehicle used to deliver diazepam; therefore, patients receiving prolonged administration of diazepam may be at risk of toxic effects, such as hyperosmolality, hemolysis, cardiac arrhythmia, seizure, and coma.\(^{21}\) An unexplained increase in anion gap and decrease in serum bicarbonate concentration secondary to an increase in lactic acidosis is often the first sign of propylene glycol accumulation. During the 24-hour infusions used in the study reported here, no significant differences were detected between serum lactate concentrations or measured anion gap in dogs receiving diazepam versus midazolam. Although no toxic effects were evident with the use of diazepam in the study, dogs exposed to larger dosages or longer durations of diazepam infusions should be monitored for potential adverse effects.

In human patients receiving IPPV, daily weaning trials for short periods are recommended to reduce morbidity associated with long-term IPPV and sedation. To facilitate this, several strategies have been recommended. These include reducing the overall degree of sedation, avoiding use of neuromuscular blocking agents, emphasizing the use of analgesic-based protocols, and selecting short-acting drugs that allow for rapid reversal and reinstitution of sedation.\(^{10-13,22-23}\) Drugs included in both protocols in our study have a relatively short duration of action and most have specific antagonists.

Table 3—Mean ± SD values for cardiorespiratory variables recorded during a 24-hour period in mechanically ventilated healthy dogs sedated and anesthetized by administration of drugs in accordance with protocol 1 (BMM [n = 5]) and protocol 2 (BFP [5]).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Reference values*</th>
<th>Protocol 1</th>
<th>Protocol 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (beats/min)</td>
<td>87 ± 22</td>
<td>53 ± 101</td>
<td></td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>103 ± 15</td>
<td>79 ± 11</td>
<td></td>
</tr>
<tr>
<td>CI (mL/kg/min)</td>
<td>165 ± 43</td>
<td>141 ± 30</td>
<td></td>
</tr>
<tr>
<td>SVI (mL/beat/kg)</td>
<td>1.9 ± 0.5</td>
<td>2.7 ± 0.4</td>
<td></td>
</tr>
<tr>
<td>SVRI (mm Hg/mL/min/kg)</td>
<td>0.6 ± 0.2</td>
<td>0.6 ± 0.11</td>
<td></td>
</tr>
<tr>
<td>DO2 (mL of O2/min/kg)</td>
<td>29.5 ± 6.8</td>
<td>25.2 ± 4.4</td>
<td></td>
</tr>
<tr>
<td>VO2 (mL of O2/min/kg)</td>
<td>6.0 ± 2.8</td>
<td>5.0 ± 1.67</td>
<td></td>
</tr>
<tr>
<td>ER1 (%)</td>
<td>20.5 ± 5.7</td>
<td>20.4 ± 5.7</td>
<td></td>
</tr>
</tbody>
</table>

*Represents reference values for unsedated normovolemic dogs in another study.†Value differs significantly (P < 0.05) from the value for protocol 1.

output during the same period was 49 ± 11 mL/kg for protocol 1 and 32 ± 14 mL/kg for protocol 2. Marked polyuria and return to prestudy physical findings were evident in all dogs within 12 hours after weaning from IPPV at the completion of the study.

Body temperature decreased to less than the acceptable limit of 37°C in most dogs in both groups, which necessitated active warming. None of the dogs had hyperthermia. Body temperature of dogs in both groups was maintained within similar ranges (mean ± SD, 37.0 ± 0.1°C for protocol 1 and 37.3 ± 0.29°C for protocol 2).
These properties allow ease of titration to achieve the desired degree of sedation and comfort in dogs and also facilitate use of daily trials to wean dogs from IPPV. Propofol, although not reversible, has a short duration of action and minimal cumulative effects. Because emphasis was placed on the cardiovascular safety for use of the protocols evaluated here, healthy dogs were used. This allowed us to evaluate the combined effects of IPPV and the specific pharmacologic effects for each protocol without the confounding problems associated with ill patients. The only prospective IPPV study in dogs was one in which investigators determined electrolyte and metabolite concentrations elicited during 1 to 21 days of constant anesthesia with pentobarbital or pentobarbital and propofol. Although cardiovascular function was not evaluated, fatalities and complications were common, with dogs developing pneumothorax, sepsis, and cardiovascular failure of unknown causes.24

Cardiovascular variables in the study reported here were maintained within acceptable values for anesthetized dogs and were slightly lower than reference values for conscious dogs. Bradycardia (heart rate < 60 beats/min) was detected for both protocols. Use of drugs in accordance with protocol 1 (BMM) resulted in a lower heart rate over time, compared with results obtained when drugs were used in accordance with protocol 2 (BFP). Opioids and α2-adrenergic receptor agonists both induce bradycardia, and their combination exacerbates this effect,25 which was evident in dogs receiving morphine and medetomidine in accordance with protocol 1. Opioid-induced bradycardia results from stimulation of the vagal nuclei within the brainstem, central inhibition of the sympathetic chronotropic action, and a possible direct effect on cardiac opioid receptors.26–27 The α2-adrenergic receptor agonists induce bradycardia by a direct reduction in sympathetic tone and a secondary increase in systemic vascular resistance.19,28 However, low doses of medetomidine, such as those used in our study reported here, do not typically result in hypertension.28 Fentanyl administration in dogs receiving drugs in accordance with protocol 2 was likely the cause of bradycardia because propofol infusions have not been associated with bradycardia.29 However, propofol may have an additive effect when concurrently administered with vagotonic drugs such as opioids, which suggests a potential combined effect from propofol and fentanyl.30,31

The mean CI was slightly lower for both protocols (125 mL/kg/min for protocol 1 and 141 mL/kg/min for protocol 2) than the reference value (165 mL/kg/min) reported for conscious dogs.32 However, in anesthetized dogs, CI decreases to 60 to 100 mL/kg/min for acceptable minimum alveolar concentrations of inhalant anesthetic agents.31–33 Although CI was consistently lower in dogs for protocol 1 than for protocol 2 at all time

<table>
<thead>
<tr>
<th>Variable</th>
<th>Protocol</th>
<th>1</th>
<th>5</th>
<th>9</th>
<th>13</th>
<th>17</th>
<th>21</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (beats/min)</td>
<td>1</td>
<td>47 ± 3</td>
<td>42 ± 7</td>
<td>39 ± 11</td>
<td>42 ± 8</td>
<td>41 ± 12</td>
<td>47 ± 4</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>51 ± 12</td>
<td>46 ± 8</td>
<td>61 ± 4</td>
<td>57 ± 7</td>
<td>55 ± 9</td>
<td>49 ± 11</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>1</td>
<td>88 ± 3</td>
<td>87 ± 12</td>
<td>87 ± 9</td>
<td>87 ± 4</td>
<td>87 ± 5</td>
<td>84 ± 19</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>75 ± 8</td>
<td>78 ± 7</td>
<td>76 ± 18</td>
<td>82 ± 13</td>
<td>75 ± 9</td>
<td>80 ± 11</td>
</tr>
<tr>
<td>CI (mL/min/kg)</td>
<td>1</td>
<td>122 ± 37</td>
<td>110 ± 17</td>
<td>128 ± 8</td>
<td>141 ± 16</td>
<td>115 ± 21</td>
<td>130 ± 21</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>121 ± 30</td>
<td>125 ± 35</td>
<td>146 ± 23</td>
<td>168 ± 29</td>
<td>148 ± 20</td>
<td>143 ± 19</td>
</tr>
<tr>
<td>SVI (mL/beat/kg)</td>
<td>1</td>
<td>2.7 ± 0.3</td>
<td>2.4 ± 0.3</td>
<td>3.1 ± 0.5</td>
<td>3.1 ± 0.7</td>
<td>2.8 ± 0.8</td>
<td>2.7 ± 0.6</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>2.6 ± 0.4</td>
<td>2.7 ± 0.1</td>
<td>2.6 ± 0.5</td>
<td>2.7 ± 0.1</td>
<td>2.8 ± 0.4</td>
<td>3.0 ± 0.4</td>
</tr>
<tr>
<td>SVRI (mm Hg/mL/min/kg)</td>
<td>1</td>
<td>0.8 ± 0.2</td>
<td>0.8 ± 0.2</td>
<td>0.7 ± 0.1</td>
<td>0.6 ± 0.1</td>
<td>0.8 ± 0.1</td>
<td>0.7 ± 0.3</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>0.6 ± 0.1</td>
<td>0.7 ± 0.2</td>
<td>0.6 ± 0.1</td>
<td>0.5 ± 0.1</td>
<td>0.5 ± 0.1</td>
<td>0.6 ± 0.1</td>
</tr>
<tr>
<td>Lactate (mmol/L)</td>
<td>1</td>
<td>1.1 ± 0.4</td>
<td>1.1 ± 0.4</td>
<td>0.8 ± 0.3</td>
<td>0.7 ± 0.2</td>
<td>0.8 ± 0.5</td>
<td>0.8 ± 0.2</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>0.9 ± 0.2</td>
<td>1.2 ± 0.4</td>
<td>1.3 ± 0.8</td>
<td>0.9 ± 0.5</td>
<td>0.7 ± 0.6</td>
<td>0.7 ± 0.4</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>1</td>
<td>13.8 ± 1.2</td>
<td>14.6 ± 1.1</td>
<td>15.8 ± 1.6</td>
<td>14.5 ± 0.7</td>
<td>14.1 ± 1.0</td>
<td>14.2 ± 1.7</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>12.3 ± 1.5</td>
<td>12.5 ± 2.3</td>
<td>12.7 ± 1.0</td>
<td>13.4 ± 1.0</td>
<td>14.4 ± 1.4</td>
<td>14.0 ± 0.7</td>
</tr>
<tr>
<td>DO2 (mL/kg/min)</td>
<td>1</td>
<td>22.5 ± 6.9</td>
<td>21.5 ± 2.1</td>
<td>27.0 ± 1.8</td>
<td>26.7 ± 2.1</td>
<td>22.8 ± 2.8</td>
<td>24.4 ± 2.2</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>22.7 ± 4.6</td>
<td>23.5 ± 3.1</td>
<td>26.7 ± 5.3</td>
<td>28.6 ± 4.01</td>
<td>25.4 ± 4.9</td>
<td>24.2 ± 3.2</td>
</tr>
<tr>
<td>ABE (mmol/L)</td>
<td>1</td>
<td>−2.5 ± 2.5</td>
<td>−1.7 ± 2.3</td>
<td>−0.9 ± 2.5</td>
<td>−1.2 ± 2.3</td>
<td>−1.1 ± 2.5</td>
<td>−1.0 ± 2.5</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>−2.4 ± 1.8</td>
<td>−2.3 ± 2.1</td>
<td>−1.5 ± 1.6</td>
<td>0.2 ± 1.4</td>
<td>0.4 ± 1.1</td>
<td>1.1 ± 1.1</td>
</tr>
</tbody>
</table>

*Time 0 was defined as a lightly sedated dog with no evidence of ventilator-patient asynchrony, PaO2 > 80 mm Hg, FIO2 of 0.21, and PTCO2 between 35 and 45 mm Hg for a minimum of 30 minutes after intubation but no sooner than 30 minutes after commencement of positive-pressure ventilation. Within a row, value differs significantly (P < 0.05) from the value for hour 1.
intervals, except at the 1-hour time point, the values did not differ significantly.

The study reported here was not designed to determine the components that altered CI. Preload, which is one of the main determinants of CI, is negatively affected by positive intrathoracic pressure and is further reduced by sufficient PEEP.6,7 We used 5 cm H2O of PEEP, which may have contributed to the lower CI. Cardiac index is the product of heart rate and SVI; because heart rate was decreased for both protocols and SVI was similar for both protocols and increased when compared with values for conscious dogs,18 the most likely cause of the lower CI was bradycardia. Two studies22,43 in which investigators used similar dosages of medetomidine also resulted in decreases in CI secondary to bradycardia. Both propofol and medetomidine affect SVRI. Propofol decreases SVRI36–38 and medetomidine increased SVRI35; consequently, SVRI was higher in dogs for protocol 1 than for protocol 2. An increase in SVRI can also decrease CI and may have contributed to the reduced CI for protocol 1.

A gradual increase in CI from baseline was detected during the 24-hour period. Interestingly, the highest CI values recorded for both protocols coincided at 13 hours, which was also approximately the time of the highest heart rate recorded for each protocol. This phenomenon was associated with administration of the lowest dosage of medetomidine (protocol 1) and propofol (protocol 2) as a result of titration of the CRIs to obtain the optimal degree of sedation comfort. Interestingly, this period was approximately midnight and was when the ICU was generally the quietest.

The effects of a reduction in CI on global tissue perfusion can be assessed with indicators such as DO2, VO2, blood lactate concentrations, and ABE. The DO2 was slightly lower for both protocols (24.2 mL of O2/kg/min for protocol 1 and 25.2 mL of O2/kg/min for protocol 2) than for reference values (29.5 mL of O2/kg/min), although lactate concentrations and ABE were similar for both protocols and the reference values. Because hemoglobin concentration and PaO2 were within their respective reference ranges and did not change during the study for either protocol, the reduction in DO2 was primarily attributed to the reduction in CI. The VO2 was significantly higher in dogs for protocol 1; consequently, ERO2 was also significantly higher. A possible cause for the higher VO2 included the accuracy of the sampling technique because the Ccvo2 was measured from the right atrium instead of from the pulmonary artery; however, the usefulness of Ccvo2 measurements for representing mixed-venous oxygen content has been validated,29 and the same discrepancy was not detected for protocol 2. A more likely explanation is that because both groups had a similar SVI, increased myocardial contractility was required in dogs treated in accordance with protocol 1 to maintain SVI despite the increase in SVRI. The increased myocardial VO2 necessary to maintain or increase contractility also increased global VO2. Conversely, in another study23 in which investigators used spontaneously breathing healthy dogs sedated with a similar infusion rate of medetomidine and fentanyl, the expected lower VO2 was reported, compared with values for dogs at baseline. Despite this unexpected finding in our study, all values for assessing oxygen transport and global tissue perfusion were still maintained within an acceptable range. Thus, it appears that tissue perfusion was not compromised for either protocol in our study.

Ventilation values required to maintain adequate PaO2 and Paco2 in the study reported here were similar to those recommended to correct hypoventilation in patients with normal pulmonary parenchyma.3,14 Maintaining Paco2 and Petco2 within the reference ranges by use of IPPV was also important to increase the accuracy of the NICO method used for CO determinations and validated in dogs.37

Throughout the 24-hour period, increases in Ve were required to maintain adequate PaO2 and Paco2. Potential causes of hypoxemia and hypercarbia in patients receiving IPPV include alveolar hypoventilation, ventilation-perfusion mismatch, diffusion impairment, and shunting. Radiographically, there was no evidence of parenchymal changes to account for these increased requirements in Ve, and CI was not affected throughout the study. Although atelectasis was not detectable radiographically, it is plausible that there was early atelectasis causing ventilation-perfusion mismatch that was subsequently eliminated by the increased Ve attained by changes in respiratory rate and Vt.

Within a short period after initiation of IPPV, all dogs in the study retained fluid, as determined on the basis of peripheral edema, chemois, and reduced urine output relative to the rate of fluids administered. All criteria of inappropriate antidiuresis were not evaluated (eg, hyponatremia with hypotonic plasma, urine osmolality > plasma osmolality, increased renal sodium excretion, lack of edema or volume depletion, and normal renal and adrenal gland function), and ADH concentrations were not measured. However, inappropriate antidiuresis has been reported40–42 after IPPV as well as after opioid use. Use of IPPV and PEEP may decrease venous return, which thereby reduces atrial stretch.42,43 Subsequent stimulation of baroreceptors leads to an increase in secretion of ADH and fluid retention.42,43 Reductions in release of atrial natriuretic peptide and stimulation of the renin-angiotensin-aldosterone system also are evidence of a response to stimulation of low-pressure baroreceptors. Furthermore, antidiuresis has been linked to certain opioids through direct stimulation of ADH or via inhibition of neurotransmitter uptake, such as serotonin.41,42 It is common for IPPV to be used to treat patients with severe pulmonary parenchymal disease and subsequent respiratory failure. Fluid retention may exacerbate an already compromised patient, which results in further respiratory failure and potentially death or discontinuation of treatment. Therefore, on the basis of clinical findings, quantification of urine output and monitoring for signs of fluid overload should be performed periodically each day when IPPV is used for prolonged periods. Administration of a low dose of furosemide (0.25 mg/kg) was effective in mobilizing excess fluid retained in the dogs in the study reported here. A greater number of dogs required furosemide administration for protocol 2 than for protocol 1. Medetomidine can cause diuresis, in part, by suppressing ADH42 and may be the reason for the reduced
requirement of furosemide in dogs administered drugs in accordance with protocol 1. All dogs were successfully weaned from mechanical ventilation and had spontaneous respiration within 1 hour after discontinuation of drug infusions, regardless of protocol. Although not objectively measured, attempts in the first 2 dogs for reversal of drugs with specific antagonists generally resulted in a rougher recovery and a more dysphoric dog. In the remaining dogs, when indicated, the use of low doses of acepromazine (0.02 mg/kg, IV) resulted in a smooth recovery with no negative hemodynamic effects detected with continuous monitoring. Further recovery is required to objectively evaluate the recovery phase for both protocols as well as the most appropriate method to ease transition to an awake patient with spontaneous respiration.

Cardiorespiratory effects were acceptable for this study population and potentially those clinical patients with a stable cardiovascular system. However, dosages of drugs used in this study may not reflect those required in unstable clinical patients with pathologic conditions. Furthermore, tolerance can also develop to the various drugs during prolonged periods of administration (ie, > 24 hours). Therefore, dosages reported are only guidelines, and the response of each specific patient to drugs administered over time must be considered.

The most noticeable change detected for both protocols in the study reported here was a decrease in CI administered over time must be considered. Despite protocols in the study reported here was a decrease in CI, dosages reported are only guide lines, and the response of each specific patient to drugs administered over time must be considered.

The most noticeable change detected for both protocols in the study reported here was a decrease in CI as a result of bradycardia. An increase in VO₂ was also evident with the use of the BMM combination. Despite these findings, administration of drugs in accordance with both protocols was effective for facilitating IPPV and was tolerated well in healthy dogs.

References

26. Hughes JM, Nolan AM. Total intravenous anesthesia in grey-

Appendix

<table>
<thead>
<tr>
<th>Score</th>
<th>Sedation</th>
<th>Agitation (anxiety)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Deeply asleep</td>
<td>Calm</td>
</tr>
<tr>
<td>2</td>
<td>Lightly asleep</td>
<td>Slightly anxious</td>
</tr>
<tr>
<td>3</td>
<td>Drowsy</td>
<td>Anxious</td>
</tr>
<tr>
<td>4</td>
<td>Fully awake</td>
<td>Extremely anxious</td>
</tr>
<tr>
<td>5</td>
<td>Hyperalert</td>
<td>Panicky</td>
</tr>
</tbody>
</table>

Comfort score for sedation and agitation in dogs as determined by use of a Ramsay score and comfort scale used in ventilated adult and pediatric humans.46,17