Opioid analgesics are commonly administered in addition to general anesthetics to provide analgesia and to reduce the MAC of inhalation anesthetics in humans and other animals. To compare the physiological effects of inhalation anesthetics with those of combinations of inhalation anesthetics and other drugs, it is important to use doses that induce an equivalent depth of anesthesia. This has commonly been done by use of the MAC (ie, concentration of an inhalation anesthetic that prevents movement in response to a supramaximal noxious stimulus in 50% of the population), with this value determined for the inhalation anesthetic with and without administration of the other drug or drugs being evaluated. Although the combination of opioids with equipotent doses of inhalation anesthetics is thought to result in greater hemodynamic stability in dogs, com-

**Objective**—To compare hemodynamic effects in dogs anesthetized with remifentanil-isoflurane and with isoflurane alone.

**Animals**—6 adult dogs.

**Procedures**—Mechanically ventilated, isoflurane-anesthetized dogs received increasing constant rate infusions (CRIs) of remifentanil (0.15, 0.30, 0.60, and 0.90 µg/kg/min) or physiologic saline (0.9% NaCl) solution (control treatment), with a 1-week washout interval between treatments. Each CRI of remifentanil or saline solution was maintained for 60 minutes with equipotent end-tidal isoflurane concentrations that corresponded to 1.3 times the minimum alveolar concentration. Hemodynamic measurements and plasma vasopressin concentrations were determined before and at the end of each CRI and 60 minutes after the end of the infusion regimen.

**Results**—Compared with the control treatment, remifentanil CRIs significantly decreased heart rate (HR) and cardiac index (CI) and significantly increased systemic vascular resistance index (SVRI) and plasma vasopressin concentration. Greatest differences in mean values between treatments were recorded for remifentanil at 0.60 µg/kg/min (HR and CI were 55% and 47% lower, respectively, and SVRI was 91% higher than for the control treatment). Mean arterial pressure increased significantly during the highest remifentanil CRI (9% higher than for the control treatment). The increase in vascular resistance was positively correlated with increases in vasopressin concentrations (coefficient of determination, 0.65) during anesthesia with remifentanil-isoflurane.

**Conclusions and Clinical Relevance**—Anesthesia maintained with remifentanil-isoflurane may decrease tissue perfusion as a result of a decrease in CI. However, hypotension may not develop because of systemic vasoconstriction. An increase in plasma vasopressin concentration was associated with the vasoconstriction observed in dogs anesthetized with remifentanil-isoflurane. (Am J Vet Res 2010;71:1133–1141)
pared with that for the use of volatile anesthetics alone, opioid administration may cause substantial cardiovascular changes, such as bradycardia, decreased CO, and decreased arterial blood pressure. If these changes are not counteracted by the effects achieved via administration of decreased amounts of inhalation anesthetics, opioid administration may result in cardiovascular depression. 

The IV administration of high doses (1 mg/kg) of the opioid methadone to conscious dogs resulted in a 40-fold increase in plasma vasopressin concentrations and increased SVR by 165% above the baseline value. When administration of fentanyl (0.002 mg/kg, as an IV bolus) was compared with administration of halothane for maintaining anesthesia in humans receiving nitrous oxide and oxygen, the opioid caused an increase in plasma vasopressin concentrations that was blunted by prior administration of naloxone. Vasopressin has vasoconstrictive properties mediated by activation of V1 receptors within the vascular smooth muscles and may result in increased SVR, decreased CO, and decreased oxygen delivery. The relationship between vasopressin release and opioid-induced changes in hemodynamic function has not been established. In pentobarbital-anesthetized dogs that received morphine (10 to 100 μg/kg) via intracarotid injection, increases in plasma vasopressin concentrations were secondary to a decrease in arterial blood pressure induced by the opioid. However, in conscious dogs receiving methadone (0.5 to 2.5 mg/kg, IV), a dose-related increase in plasma vasopressin concentrations was not caused by decreases in arterial blood pressure and vasopressin release was attributed to a direct action of methadone.

Remifentanil is a phenylpiperidino-opioid derivative that acts as a pure agonist at μ-opioid receptors. Opioids such as remifentanil result in significant reductions in the MAC of inhalation anesthetics in humans and dogs, and this effect may be explained by CNS depression and by the analgesic action induced by pure μ-opioid receptor agonists. The main advantage of remifentanil over other phenylpiperidino-opioid derivatives (ie, fentanyl, alfentanil, and sufentanil) is the lack of accumulation in body compartments even after prolonged infusions. The objective of the study reported here was to investigate the hemodynamic effects of increases in infusion rates of remifentanil during anesthesia with equieffective concentrations of isoflurane in mechanically ventilated dogs and the possible correlation between opioid-induced changes in plasma vasopressin concentrations with some hemodynamic variables (eg, SVR). We hypothesized that remifentanil administration would result in vasopressin release in dogs and that the increase in plasma vasopressin concentration would contribute to hemodynamic changes in dogs during anesthesia with remifentanil-isoflurane.

Materials and Methods

Animals—Six healthy adult mixed-breed dogs (5 males and 1 female; mean ± SD weight, 27.7 ± 4.3 kg) were used in the study. Health status was assessed by means of physical examination and laboratory analysis (CBC, serum biochemical analyses, and blood gas analysis); all findings were within respective reference ranges. The study was approved by a local institutional animal care committee.

Instrumentation—Food was withheld from all dogs for 12 hours prior to each experiment. Anesthesia was induced in each dog by the use of 5% isoflurane in oxygen (flow rate, 5 L/min) administered by means of a face mask and a circle breathing system. Endotracheal intubation was performed, and pressure-controlled mechanical ventilation was initiated to maintain eucaapnia (PaCO2 between 33 and 45 mm Hg) throughout the procedure. Samples (200 mL/min) of airway gases were obtained continuously from the proximal end of the endotracheal tube to monitor ETISO. The gas analyzer was calibrated with a standard calibration gas mixture before each experiment. An esophageal temperature probe whose tip was positioned in the thoracic portion of the esophagus was used to record body temperature, which was maintained within a narrow range (between 37.5°C and 38.5°C) by means of a forced warm air blanket and an electric heating pad. Each dog was positioned in lateral recumbency, and a 20-gauge catheter was placed into a cephalic vein for administration of fluids (lactated Ringer’s solution at a rate of 3 mL/kg/h throughout anesthesia) and drugs. Another 20-gauge catheter was inserted percutaneously into a dorsal pedal artery and connected to a pressure transducer filled with heparinized physiologic saline (0.9% NaCl) solution (5 U/mL) to enable the display of SAP, DAP, and MAP on the screen of a monitor. Accuracy of the pressure transducer was verified before each experiment with a mercury column, and the zero reference of this device was set at the manubrium of the dogs. Adhesive surface electrodes were attached to the skin in accordance with a lead II ECG to monitor HR.

An 8.5F catheter introducer was inserted in the right jugular vein, and a 7.5F pulmonary artery catheter was advanced through the introducer until the distal pressure-sensing lumen was in the pulmonary artery: confirmation of correct placement was achieved via observation of characteristic pressure waveforms. The proximal lumen of the pulmonary artery catheter (which was located 30 cm from the distal lumen) was assumed to be located in the cranial vena cava when the typical right ventricular and right atrial pressure waveforms could not be identified on the screen of the multiparametric monitor. The distal and proximal lumens of the pulmonary artery catheter were connected to pressure transducers for continuous measurements of MPAP and CVP, respectively. Intermittent measurements of PAOP were obtained by insufflating the balloon located at the tip of the pulmonary artery catheter with 0.7 mL of air. The CO was measured by injection of 10 mL of cold (1°C to 5°C) 5% dextrose solution through the proximal port of the pulmonary artery catheter. Temperature of the cold dextrose solution was measured via an in-line thermistor that was connected between the syringe containing the dextrose solution and the injection port of the pulmonary artery catheter. At each time point, 5 CO measurements were performed, the maximum and minimum values were discarded, and the 3 remaining measurements were used to calculate the mean CO value.
The BSA was calculated by use of the following equation: BSA = (body weight [in g])\(^{0.667}\)•1.01•10\(^{-4}\). Hemodynamic variables calculated by use of standard equations\(^{18}\) included CI, SV, SRV, SVRI, CAO\(_o\), and DO\(_2\). Arterial blood samples were collected for determinations of temperature-corrected blood gas concentrations,\(^b\) Hct, and concentrations of hemoglobin,\(^c\) plasma TP, and plasma vasopressin. Blood samples for plasma vasopressin measurements were collected in prechilled (in ice) heparin-coated tubes. Plasma was obtained by centrifugation (1,127 \(\times\) g) at 4°C for 15 minutes and stored at –70°C until assayed. After extraction from plasma with cold acetone and petroleum ether, vasopressin concentrations were measured by use of a specific radioimmunoassay.\(^{19}\) Recovery of vasopressin from plasma was > 89%. Vasopressin antiserum\(^d\) and \(^{125}\)I-vasopressin\(^e\) were obtained from commercial sources. Detection limit of the radioimmunoassay was 0.15 pg/mL. The intra-assay and interassay coefficients of variation were 7.7% and 11.9%, respectively.\(^{20}\)

Experimental protocol—Each dog was anesthetized twice with at least a 1-week washout interval. During 1 anesthetic episode, dogs received increasing CRIs of remifentanil (remifentanil treatment), whereas during the other anesthetic episode, dogs received increasing CRIs of physiologic saline solution (control treatment). Order in which dogs received the remifentanil or control treatments was determined by use of a random-number table.

The individual MAC values for isoflurane and for isoflurane combined with increasing CRIs of remifentanil were determined in another study\(^7\) conducted by our laboratory group 15 days prior to the onset of the study reported here with the same dogs. After the instrumentation period, the ETISO was adjusted to maintain 1.3 times the MAC value for each dog. Measurement of baseline cardiopulmonary data and collection of blood samples were performed after anesthesia for 60 minutes at a stable ETISO. After baseline data were obtained, remifentanil or saline solution were administered IV as CRIs by means of a syringe pump.\(^3\) Remifentanil\(^m\) (50 µg/mL solution) was administered at increasing CRIs (0.15, 0.30, 0.60, and 0.90 µg/kg/min). During remifentanil administration, the ETISO was adjusted for each dog to maintain equipotent isoflurane concentrations (1.3 times isoflurane MAC). Saline solution was administered at infusion rates that corresponded to the infusion rates for remifentanil. During all infusions of saline solution, the ETISO was maintained constant at the same concentration used during baseline measurements (ie, 1.3 times isoflurane MAC). No washout period was allowed between subsequent CRI rates, and each infusion was maintained for 60 minutes.

After baseline data were collected, measurement of cardiopulmonary variables and collection of blood samples were performed 60 minutes after the beginning of each CRI of remifentanil or saline solution (time points T1, T2, T3, and T4, respectively). After recording cardiopulmonary data and collecting blood samples at the highest CRI of remifentanil or saline solution, the CRI was stopped; measurement of cardiopulmonary data and blood sample collection were performed again 60 minutes later (time point T5). The ETISO maintained at T5 for the control treatment was the same as the ETISO used throughout the experiment (ie, 1.3 times isoflurane MAC). Remifentanil is rapidly eliminated and has no significant residual effects on MAC by 80 minutes after the end of a CRI at a rate of 0.90 µg/kg/min.\(^{27}\) Thus, the ETISO was increased to a value corresponding to the baseline value (ie, 1.3 times isoflurane MAC) immediately after the end of the opioid infusion. The last data and blood collection (ie, T5) was performed after the ETISO was stable at this new state for 60 minutes. After the last measurements, isoflurane administration was stopped and the dogs were allowed to recover from anesthesia.

Interval from endotracheal intubation until completion of the instrumentation phase and total duration of anesthesia (time elapsed from intubation until isoflurane administration was stopped) were recorded. Recovery from anesthesia was assessed by recording the time until removal of the orotracheal tube (considered as the point at which the swallowing reflex returned), until sternal recumbency, and until regaining a standing position. The aforementioned times were considered as the interval elapsed from cessation of isoflurane administration until the observation of the specific event.

Statistical analysis—Comparisons between the remifentanil and control treatments were performed by use of a 2-way repeated-measures ANOVA with time (baseline, T1, T2, T3, T4, and T5) and treatment (saline solution or remifentanil) as main factors. When a significant treatment effect was detected, treatment comparison was performed by use of a Bonferroni correction for multiple pairwise comparisons to identify the time points at which the 2 treatments differed. To evaluate the time-related effects of progressive increases in infusion rates of saline solution or remifentanil, a 1-way repeated-measures ANOVA was performed within each treatment. When a significant effect was detected, values at each time point (T1 through T3) were compared with baseline values by use of a Dunnett test. Plasma vasopressin concentrations were analyzed by use of Friedman, Dunn, and Wilcoxon matched pairs tests. Duration of anesthesia and times recorded during recovery from anesthesia were compared by use of a paired \(t\) test. Differences were considered significant at values of \(P<0.05\). Least squares regression analysis was used to evaluate the correlation between SVR and plasma vasopressin concentrations and between SVR and ETISO.

Results

The mean ± SD ETISO maintained throughout the experiment (from baseline through T5) for the control treatment was 1.61 ± 0.23 volume percent (values corresponding to 1.3 times isoflurane MAC at 1 atmosphere). These ETISO values were also maintained for the remifentanil treatment before (baseline) and after the end (T3) of the remifentanil infusions. For maintaining equipotent ETISO (1.3 times isoflurane MAC) during the increasing remifentanil CRIs, mean ± SD percentage reductions from baseline ETISO were 43 ± 10%, 59 ± 10%, 66 ± 9%, and 71 ± 9% during the
administration of remifentanil at 0.15, 0.30, 0.60, and 0.90 µg/kg/min, respectively.

Cardiopulmonary data and variables determined from arterial blood samples did not differ between the control and remifentanil treatments at baseline (Figure 1; Table 1). For the control treatment, SI and CI increased significantly over time (increases above baseline values recorded for T3 through T5 for SI and for T4 and T5 for CI). Heart rate did not change significantly over time for the control treatment. All infusion rates of remifentanil significantly decreased HR from the baseline value. Compared with baseline values, CI significantly decreased during administration of remifentanil at 0.15, 0.30, and 0.60 µg/kg/min but not during administration of remifentanil at the highest rate (0.90 µg/kg/min). At the highest remifentanil CRI, mean SI values

Figure 1—Mean ± SD values for hemodynamic variables recorded in 6 dogs anesthetized with equipotent concentrations (1.3 MAC) of isoflurane (control treatment [black circles]) or isoflurane combined with increasing doses of remifentanil (white triangles). Baseline data were recorded after anesthesia for 60 minutes at a stable ETISO. Remifentanil was administered at increasing CRI (0.15, 0.30, 0.60, and 0.90 µg/kg/min); saline (0.9% NaCl) solution was administered at infusion rates that corresponded to the infusion rates for remifentanil. Each infusion was maintained for 60 minutes. Measurement of cardiopulmonary variables and collection of blood samples were performed 60 minutes after the beginning of each CRI of remifentanil or saline solution (time points T1, T2, T3, and T4, respectively) and 60 minutes after the CRI was stopped (time point T5). *Within a treatment, value differs significantly (P < 0.05; Dunnett test) from the baseline value. †Within a time point, value differs significantly (P < 0.05; Bonferroni correction for multiple pairwise comparisons) from the value for the control treatment.
were significantly increased, compared with baseline values and compared with values for the control treatment. Heart rate and CI were significantly lower for the remifentanil treatment than for the control treatment during all infusion rates; maximum differences in mean values were recorded during infusion of remifentanil at a rate of 0.60 µg/kg/min (HR and CI were 59% and 47% lower, respectively, than for the control treatment). After the remifentanil infusion was stopped (ie, T5), HR and CI were higher than baseline values and values for the control treatment.

The SVRI was significantly decreased at T4 and T5 from the baseline value for the control treatment. During remifentanil infusion at rates ranging from 0.15 to 1.25 µg/kg/min, systemic vascular resistance decreased significantly compared with baseline values at T1, T2, T3, T4, and T5.

Table 1—Mean ± SD values for physiologic variables recorded in 6 dogs anesthetized with equipotent concentrations (1.3 MAC) of isoflurane and administered increasing CRIs of remifentanil (remifentanil treatment) or saline (0.9% NaCl) solution (control treatment).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Treatment</th>
<th>Baseline</th>
<th>T1</th>
<th>T2</th>
<th>T3</th>
<th>T4</th>
<th>T5</th>
</tr>
</thead>
<tbody>
<tr>
<td>SI (mL/beat/m²)</td>
<td>Control</td>
<td>28 ± 6</td>
<td>27 ± 5</td>
<td>29 ± 6</td>
<td>30 ± 5</td>
<td>32 ± 5</td>
<td>32 ± 6</td>
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<tr>
<td></td>
<td>Remifentanil</td>
<td>27 ± 7</td>
<td>33 ± 5</td>
<td>35 ± 6</td>
<td>35 ± 6</td>
<td>41 ± 9T</td>
<td>34 ± 7</td>
</tr>
<tr>
<td>SAP (mm Hg)</td>
<td>Control</td>
<td>107 ± 15</td>
<td>111 ± 14</td>
<td>114 ± 18</td>
<td>114 ± 16</td>
<td>116 ± 16T</td>
<td>118 ± 15T</td>
</tr>
<tr>
<td></td>
<td>Remifentanil</td>
<td>110 ± 16</td>
<td>130 ± 10T</td>
<td>142 ± 11T</td>
<td>155 ± 14T</td>
<td>169 ± 17T</td>
<td>110 ± 16</td>
</tr>
<tr>
<td>DAP (mm Hg)</td>
<td>Control</td>
<td>99 ± 6</td>
<td>59 ± 7</td>
<td>59 ± 8</td>
<td>58 ± 8</td>
<td>60 ± 8</td>
<td>60 ± 8</td>
</tr>
<tr>
<td></td>
<td>Remifentanil</td>
<td>59 ± 8</td>
<td>56 ± 9</td>
<td>57 ± 9</td>
<td>57 ± 8</td>
<td>60 ± 9</td>
<td>60 ± 12</td>
</tr>
<tr>
<td>CVP (mm Hg)</td>
<td>Control</td>
<td>4 ± 1</td>
<td>4 ± 1</td>
<td>4 ± 1</td>
<td>4 ± 1</td>
<td>5 ± 1</td>
<td>4 ± 1</td>
</tr>
<tr>
<td></td>
<td>Remifentanil</td>
<td>4 ± 1</td>
<td>8 ± 11T</td>
<td>9 ± 11T</td>
<td>10 ± 21T</td>
<td>11 ± 21T</td>
<td>10 ± 11T</td>
</tr>
<tr>
<td>PAOP (mm Hg)</td>
<td>Control</td>
<td>6 ± 2</td>
<td>8 ± 1</td>
<td>6 ± 1</td>
<td>6 ± 1</td>
<td>6 ± 1</td>
<td>6 ± 2</td>
</tr>
<tr>
<td></td>
<td>Remifentanil</td>
<td>6 ± 1</td>
<td>8 ± 1</td>
<td>10 ± 21T</td>
<td>11 ± 21T</td>
<td>11 ± 21T</td>
<td>6 ± 2</td>
</tr>
<tr>
<td>MPAP (mm Hg)</td>
<td>Control</td>
<td>13 ± 1</td>
<td>13 ± 1</td>
<td>13 ± 2</td>
<td>13 ± 2</td>
<td>13 ± 2</td>
<td>13 ± 2</td>
</tr>
<tr>
<td></td>
<td>Remifentanil</td>
<td>13 ± 2</td>
<td>14 ± 2</td>
<td>15 ± 2</td>
<td>16 ± 21T</td>
<td>17 ± 21T</td>
<td>15 ± 2</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>Control</td>
<td>12.7 ± 0.7</td>
<td>12.6 ± 0.9</td>
<td>12.2 ± 0.7</td>
<td>11.9 ± 0.9</td>
<td>11.6 ± 0.71</td>
<td>11.8 ± 0.81</td>
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<tr>
<td></td>
<td>Remifentanil</td>
<td>12.1 ± 0.8</td>
<td>13.0 ± 1.9</td>
<td>14.7 ± 2.4T</td>
<td>15.7 ± 1.8T</td>
<td>15.9 ± 2.3T</td>
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<td>Hct (%)</td>
<td>Control</td>
<td>38 ± 2</td>
<td>35 ± 2</td>
<td>35 ± 2</td>
<td>35 ± 2</td>
<td>34 ± 2</td>
<td>34 ± 2</td>
</tr>
<tr>
<td></td>
<td>Remifentanil</td>
<td>38 ± 3</td>
<td>38 ± 5</td>
<td>42 ± 7T</td>
<td>47 ± 11T</td>
<td>46 ± 11T</td>
<td>39 ± 5</td>
</tr>
<tr>
<td>Plasma TP (g/dL)</td>
<td>Control</td>
<td>5.6 ± 0.4</td>
<td>5.4 ± 0.4T</td>
<td>5.3 ± 0.4T</td>
<td>5.2 ± 0.4T</td>
<td>5.1 ± 0.4T</td>
<td>5.1 ± 0.4T</td>
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<tr>
<td></td>
<td>Remifentanil</td>
<td>5.7 ± 0.5</td>
<td>5.5 ± 0.5T</td>
<td>5.5 ± 0.4T</td>
<td>5.3 ± 0.5T</td>
<td>5.3 ± 0.6T</td>
<td>5.2 ± 0.6T</td>
</tr>
<tr>
<td>pH</td>
<td>Control</td>
<td>7.39 ± 0.03</td>
<td>7.41 ± 0.01</td>
<td>7.40 ± 0.02</td>
<td>7.41 ± 0.01</td>
<td>7.40 ± 0.02</td>
<td>7.41 ± 0.02</td>
</tr>
<tr>
<td></td>
<td>Remifentanil</td>
<td>7.41 ± 0.02</td>
<td>7.38 ± 0.02</td>
<td>7.37 ± 0.03</td>
<td>7.36 ± 0.02T</td>
<td>7.36 ± 0.04T</td>
<td>7.42 ± 0.05</td>
</tr>
<tr>
<td>Paco₂ (mm Hg)</td>
<td>Control</td>
<td>38.7 ± 1.5</td>
<td>37.9 ± 2.3</td>
<td>38.9 ± 4.1</td>
<td>37.3 ± 3.2</td>
<td>38.0 ± 3.3</td>
<td>38.3 ± 2.0</td>
</tr>
<tr>
<td></td>
<td>Remifentanil</td>
<td>38.9 ± 3.2</td>
<td>40.7 ± 3.2</td>
<td>38.2 ± 4.5</td>
<td>37.8 ± 3.5</td>
<td>37.4 ± 4.7</td>
<td>35.1 ± 4.7</td>
</tr>
<tr>
<td>HCO₃⁻ (mEq/L)</td>
<td>Control</td>
<td>23.3 ± 1.5</td>
<td>24.2 ± 1.0</td>
<td>23.8 ± 2.2</td>
<td>23.8 ± 0.8</td>
<td>23.8 ± 1.0</td>
<td>24.2 ± 0.4</td>
</tr>
<tr>
<td></td>
<td>Remifentanil</td>
<td>23.5 ± 1.2</td>
<td>23.4 ± 0.9</td>
<td>22.1 ± 2.5</td>
<td>21.0 ± 1.21T</td>
<td>21.3 ± 1.41T</td>
<td>23.2 ± 2.0</td>
</tr>
</tbody>
</table>

*Baseline data were recorded after anesthesia for 60 minutes at a stable ETISO. Remifentanil was administered at increasing CRIs (0.15, 0.30, 0.60, and 0.90 µg/kg/min); saline solution was administered at infusion rates that corresponded to the infusion rates for remifentanil. Each infusion was maintained for 60 minutes. Measurements of cardiopulmonary variables and collection of blood samples were performed 60 minutes after the beginning of each CRI of remifentanil or saline solution (time points T1, T2, T3, and T4, respectively) and 60 minutes after the CRI was stopped (time point T5). Within a treatment, value differs significantly (*P < 0.05; Dunnett test) from the baseline value. Within a time point, value differs significantly (**P < 0.05; Bonferroni correction for multiple pairwise comparisons) from the value for the control treatment.

HCO₃⁻ = Arterial bicarbonate concentration. pH = Arterial pH.

Figure 2—Box-and-whisker plots of plasma vasopressin concentrations recorded in 6 dogs anesthetized with equipotent concentrations (1.3 MAC) of isoflurane (control treatment); A) isoflurane combined with increasing doses of remifentanil (B). Each box represents the interquartile range (ie, central 50% of the values), and the median value is the horizontal line within each box. The upper and lower whiskers represent the upper and lower range of values, respectively. *Within a treatment, value differs significantly (**P < 0.05; Friedman and Dunn tests) from the baseline value. Within a time point, value differs significantly (**P < 0.05; Wilcoxon matched pairs test) from the value for the control treatment. See Figure 1 for remainder of key.
0.60 µg/kg/min, SVRI was significantly increased, compared with the baseline value and the value for the control treatment. Maximum differences in mean values were recorded during infusion of remifentanil at a rate of 0.60 µg/kg/min (SVRI was 91% higher than the value for the control treatment).

For the control treatment, SAP increased from the baseline value at T4 and T5, whereas MAP, DAP, and CVP did not change over time. All remifentanil CRIs increased SAP and CVP, compared with the baseline values and values for the control treatment; MAP was increased, compared with the baseline value and the value for the control treatment, only during the CRI at 0.90 µg/kg/min (MAP was 9% higher than for the control treatment). After the remifentanil infusion was stopped (ie, T5), SAP, MAP, and CVP returned to baseline values and did not differ from values for the control treatment. During remifentanil administration, there were morphological changes in the arterial blood pressure waveform, with steep systolic upstrokes and narrow systolic peaks; these changes were no longer evident after cessation of remifentanil administration.

The PAOP and MPAP values did not change significantly over time for the control treatment. Remifentanil infusion increased PAOP and MPAP, compared with the baseline values and values for the control treatment; increases were recorded at infusion rates ranging from 0.30 to 0.90 µg/kg/min for PAOP and at infusion rates of 0.60 and 0.90 µg/kg/min for MPAP.

For the control treatment, there was a decrease over time in Cao2, Hct, and hemoglobin concentration, whereas Do2I was increased at T4. Remifentanil infusion rates ranging from 0.30 to 0.90 µg/kg/min increased Cao2, Hct, and hemoglobin concentration, compared with the baseline values and values for the control treatment. Infusion rates of remifentanil ranging from 0.30 to 0.90 µg/kg/min decreased Do2I, compared with the baseline value and values for the control treatment. After the infusion of remifentanil was stopped (ie, T5), Do2I was significantly increased, compared with the baseline value and the value for the control treatment.

For the control and remifentanil treatments, plasma TP concentration decreased over time. Mean arterial pH and bicarbonate concentration decreased significantly at remifentanil CRIs of 0.60 and 0.90 µg/kg/min, compared with the baseline values and values for the control treatment. Mean arterial pH and bicarbonate concentration as well as other blood gas variables remained within the expected physiologic ranges for dogs (pH between 7.35 and 7.45 and bicarbonate concentration between 19 and 24 mmol/L). After the remifentanil infusion was stopped (ie, T5), arterial pH and bicarbonate returned to baseline values. The PaCO2 did not differ between treatments, with mean values within physiologic ranges for dogs (35 to 45 mm Hg). The PaO2 did not differ between treatments and remained close to values (300 mm Hg) compatible with animals breathing 100% oxygen.

Baseline vasopressin concentrations did not differ between treatment groups (Figure 2). Except for 1 dog that had a high baseline vasopressin concentration (baseline vasopressin concentration, 8.1 pmol/L; reference range, 1 to 6 pmol/L21), all other plasma vasopressin concentrations for the control treatment were within the reference range for dogs. Plasma vasopressin concentration was significantly decreased from the baseline value at T4 for the control treatment.

Remifentanil administration increased plasma vasopressin concentrations (Figure 2). However, there was a poor correlation (r = 0.47) between the CRI of remifentanil and the magnitude of the increases in plasma vasopressin concentrations. In 5 of 6 dogs for the remifentanil treatment, baseline vasopressin concentrations were within the reference range. In these 5 dogs, remifentanil administration increased plasma vasopressin concentrations by at least 10- to 20-fold above baseline values (highest recorded value, 90.3 pmol/L for the 0.30 µg/kg/min infusion rate); vasopressin concentrations returned to the reference range after remifentanil infusion was stopped (ie, T5). In 1 dog for the remifentanil treatment, baseline plasma vasopressin concentration (15.0 pmol/L) was above the reference range, and

![Figure 3](image-url)
concentrations of vasopressin were decreased from this value during remifentanil administration (range, 4.6 to 9.4 pmol/L) and at T5 (1.4 pmol/L); this dog was the same one that had a high vasopressin concentration at baseline for the control treatment. Statistical analysis revealed that administration of remifentanil at a rate of 0.60 µg/kg/min significantly increased the plasma vasopressin concentration, compared with the baseline value. Plasma vasopressin concentrations were higher for all remifentanil infusion rates, compared with concentrations for the control treatment.

Linear regression analysis revealed a positive correlation ($r = 0.81$) between plasma vasopressin concentrations and SVR when dogs were treated with remifentanil. A negative correlation ($r = -0.72$) was detected between ETISO and SVR (Figure 3).

The amount of time required for completion of the instrumentation phase and total duration of anesthesia did not differ between treatments. Pooled data for both treatments revealed that completion of instrumentation was achieved in (mean ± SD) 85 ± 16 minutes, and mean total duration of anesthesia was 8.9 ± 0.3 hours. Recovery from anesthesia was uncomplicated, and values for recovery variables did not differ between treatments. Mean ± SD time until orotracheal tube removal, sternal recumbency, and a standing position were 9 ± 3 minutes, 17 ± 7 minutes, and 25 ± 7 minutes, respectively (pooled data for both treatments).

**Discussion**

Analysis of results of the study reported here revealed that anesthesia maintained with remifentanil and isoflurane resulted in more substantial cardiovascular changes than for equipotent anesthetic concentrations of isoflurane alone. Although remifentanil induced bradycardia (defined as HR < 60 beats/min) and caused mean CI values to decrease by 26% to 42% below baseline values, MAP did not decrease because of increases in SVRI. This vasoconstrictor response detected during anesthesia with remifentanil-isoflurane was explained in part by increases in plasma vasopressin (concentrations 10- to 20-fold greater than values recorded during baseline conditions for most dogs). The finding that vasopressin concentrations returned to baseline values after the remifentanil infusion was stopped and that it decreased over time for the control treatment supports the hypothesis that vasopressin concentrations increased as a result of remifentanil administration and not because of other stimuli. These results are in agreement with those in another report in which vasopressin concentrations increased in dogs anesthetized with remifentanil-isoflurane, compared with concentrations for the awake state. However, it was not clear in that report whether the increases in vasopressin concentration were attributable to remifentanil because similar increases in vasopressin concentrations were also recorded during anesthesia induced by administration of nitrous oxide-isoflurane. Vasopressin is released into the circulation as a result of decreased baroreceptor activity during hypotensive or shock states and as a result of increases in plasma osmolality. Pure µ-opioid receptor agonists may cause the release of vasopressin, albeit the mechanism of vasopressin release under these circumstances is poorly understood. The increase in vasopressin concentrations could have been attributed to a direct action of remifentanil at µ-opioid receptors located in the CNS, or it could have been a physiologic response to the decrease in arterial blood pressure (associated with the decrease in CO) induced by remifentanil.

Isoflurane causes vasodilatation and dose-related decreases in arterial blood pressure. Even though the isoflurane requirement was reduced by 43% to 71% with increasing CRIs of remifentanil, a consistent increase in MAP was not evident (MAP increased 14% from the baseline value only at the highest remifentanil CRI) because CI was significantly decreased during remifentanil administration. The increase in SVRI (36% to 76% higher than the baseline value) recorded during increasing remifentanil infusion rates was attributed in part to the decrease in ETISO, which may have attenuated the intensity of isoflurane-induced vasodilation. This hypothesis is reinforced by the negative linear correlation ($r = -0.72$) detected between the ETISO and SVR. However, it is evident that the decrease in ETISO alone was not the sole factor responsible for the increase in SVRI above baseline values during remifentanil administration. Vasopressin release during remifentanil administration also appeared to contribute to the increase in SVR, as indicated by the strong positive linear correlation ($r = 0.81$) between the plasma vasopressin concentrations and SVR.

Other vasopressor hormones, such as catecholamines and angiotensin II, might have been involved in the mechanisms underlying the increase in SVRI during anesthesia with remifentanil-isoflurane. At the doses used in the present study (1.3 MAC), it is unlikely that isoflurane caused an increase in circulating catecholamine concentrations because inhalation anesthetics cause dose-related inhibition of central sympathetic outflow. In dogs, plasma catecholamine concentrations were not increased from those during the awake state during anesthesia achieved by administration of remifentanil (0.5 µg/kg/min) and isoflurane (0.8% end-tidal concentration) or during anesthesia achieved by administration of nitrous oxide and isoflurane. In that report, plasma vasopressin concentrations were also increased during anesthesia with remifentanil-isoflurane; however, most of the increases in SVR were attributed to increases in plasma angiotensin II concentrations. It is possible that the increase in SVRI detected during anesthesia with remifentanil-isoflurane anesthesia in the present study might have been caused by the release of vasopressin into the circulation and by an increase in plasma angiotensin II concentrations.

Large interindividual variations in plasma vasopressin concentrations were detected when dogs received remifentanil at progressively increasing infusion rates. One dog that had higher baseline vasopressin concentrations was excited during induction of anesthesia and struggled while isoflurane was being delivered via facemask. Thus, there may have been a stress-related release of vasopressin in that dog during induction of anesthesia, and this may explain the high baseline vasopressin concentrations for that particular dog. However, it is unclear why a decrease in vasopressin concentrations...
over time was detected during increasing remifentanil infusion rates in that dog.

The increase in Hct and hemoglobin concentration recorded during increasing remifentanil infusion rates may have been caused by contraction of the spleen as a result of increased plasma vasopressin concentrations. This hypothesis is supported by the fact that the increase in Hct and hemoglobin concentrations coincided with the increase in plasma vasopressin concentrations during administration of remifentanil at infusion rates ranging from 0.30 to 0.90 µg/kg/min; 60 minutes after the remifentanil infusion was stopped, plasma vasopressin concentrations, Hct, and hemoglobin concentrations returned to baseline values and did not differ from those for the control treatment. The increase in hemoglobin concentration was the cause for the higher Cao, during anesthesia with remifentanil-isoflurane. Despite greater Cao, associated with increasing remifentanil infusions, Do, was decreased, compared with the value for the control treatment, primarily because of a decrease in CI. A reduction in overall tissue oxygenation caused by increases in SVRI and decreases in Do, during remifentanil administration might have contributed to the small but significant decrease in bicarbonate concentrations recorded during the 2 highest remifentanil infusion rates.

Administration of another phenylpiperidine-opioid derivative (fentanyl) to dogs anesthetized with enflurane (1.3 MAC) in another study resulted in hemodynamic changes that were qualitatively similar to the changes recorded in the study reported here. Fentanyl reduced the MAC of enflurane by 65%; however, CI and HR were decreased and MAP and SVRI were increased, compared with values recorded during anesthesia with enflurane alone. It was suggested that the increase in SVRI recorded during anesthesia with fentanyl-enflurane was the result of a compensatory response to the decrease in CI and HR induced by the opioid because when CI was returned to near physiologic values after atropine administration, SVRI returned to values recorded during anesthesia with enflurane alone.

In the present study, HR values remained < 60 beats/min during all remifentanil CRIs. Because SI was unchanged or increased during remifentanil infusion, the decrease in CI during all CRIs of remifentanil was attributable to the negative chronotropism induced by this opioid. The lowest HR values (32 beats/min recorded during remifentanil CRIs ranging from 0.30 to 0.90 µg/kg/min) were detected in 1 dog that had a baseline HR of 82 beats/min. Despite the fact remifentanil caused severe bradycardia and substantial decreases in CI in that dog (decreases of 43% to 62%, compared with the baseline values), MAP was not substantially altered during opioid infusion because of increases in SVRI (MAP ranged from 67 to 76 mm Hg during remifentanil infusion, compared with 76 mm Hg at baseline).

The major determinants of MAP are CO (or CI) and SVR (or SVRI), as determined in accordance with the following equation:

\[ MAP = CI \times SVRI \]

With the exception of an increase in MAP of 14% above baseline values recorded during the highest remifentanil CRI, MAP did not change during infusion rates ranging from 0.15 to 0.60 µg/kg/min because during these CRIs, the decreases recorded in CI were compensated for by increases in SVRI. In contrast with the lack of changes in MAP during most remifentanil CRIs, SAP was significantly increased during remifentanil infusion at all rates (SAP increased by 18% to 50% above baseline values).

Whereas SAP and DAP are derived from the highest and lowest points of the arterial pressure waveform, respectively, MAP values are derived from the area under the arterial pressure waveform divided by the time interval of a single cardiac cycle. The morphological characteristics of the arterial pressure waveform recorded during remifentanil infusion (steep systolic upstrokes and narrow systolic peaks) associated with increased SAP values did not result in increases in MAP because the narrow systolic peaks did not result in changes in the area under the pressure curve used for calculating MAP. The increased SAP values during remifentanil-isoflurane anesthesia could be caused by increases in SVRI (vasoconstriction) or by a systolic overshoot attributable to an underdamping of the arterial blood pressure waveform. Although we did not conduct dynamic response testing to rule out underdamping as a source of bias, this confounder probably did not influence our results because arterial blood pressures were obtained under identical conditions for both treatments.

After remifentanil administration was stopped (ie, T5), mean CI values increased, compared with baseline values (56%) and with values at the same time point for the control treatment (36%). The increase in CI after the opioid infusion was stopped was attributable in part to an increase in HR, which was 24% higher than the baseline value and 31% higher than the value for the control treatment at T5. At T5, SVRI was decreased by 55% from the previous value at T4, and this vasodilatory effect may have stimulated baroreceptor-mediated increases in HR, which probably prevented a decrease in arterial blood pressure induced by vasodilatation. Increases in ETISO (from 0.47% at T4 to 1.61% at T5) and decreases in plasma vasopressin concentrations (from a median of 16.2 pmol/L [interquartile range, 9.3 to 61.3 pmol/L] at T4 to a median of 2.1 pmol/L [interquartile range, 1.4 to 3.4 pmol/L] at T5) appeared to contribute to the decrease in SVRI and the reflex increase in HR observed after cessation of the remifentanil infusion. In addition to the reflex increase in HR, a temporal effect may also have contributed to the increase in CI after the remifentanil infusion was stopped because when the same dogs received the control treatment (isoflurane alone), CI and SI were significantly increased over time. Qualitatively similar temporal changes during prolonged (7 hours) anesthesia with halothane in dogs have been reported.

High doses of phenylpiperidine-opioid derivatives have been used to maintain anesthesia in humans and other animals for many years and may be considered as an alternative to use of high doses of hypnotic agents (eg, inhalation or injectable anesthetics) because of the cardiovascular stability provided by opioids. In the present study, equipotent isoflurane concentrations (1.3 MAC) were used during anesthesia maintained with isoflurane alone and anesthesia maintained with...
isoflurane combined with increasing remifentanil infusion rates. A similar depth of anesthesia, determined on the basis of isoflurane MAC values that were determined for each of the dogs with and without administration of remifentanil, was used in the study reported here because the empirical adjustment in ST680 could have resulted in different degrees of cardiopulmonary depression that would have invalidated comparisons between treatments.

Despite the administration of a high cumulative dose of remifentanil (mean ± SD, 133 ± 5 μg/kg) and the effects of prolonged anesthesia (mean duration, 9 hours), all dogs of the present study rapidly regained a standing position after termination of anesthesia (mean, 25 minutes) and did not have complications from anesthesia. The time to recover from anesthesia with remifentanil-isoflurane did not differ from the time to recover from anesthesia maintained with isoflurane alone; this observation is consistent with the non-cumulative nature of remifentanil in dogs.

Increased with anesthesia maintained with isoflurane alone, anesthesia maintained with remifentanil-isoflurane may decrease overall tissue perfusion as a result of decreases in CI and increases in SVRI. However, prevention or treatment of opioid-induced bradycardia by administration of an anticholinergic agent, which has the potential for improving CI, was not investigated in the study reported here. Evidence that anesthesia with remifentanil-isoflurane is associated with an increase in vasopressin concentration and that vasopressin may contribute to some hemodynamic changes (ie, increased SVRI) detected with the use of this anesthetic technique was provided in the present study. Further studies are required to determine whether the increase in vasopressin concentrations is attributable to a direct action of remifentanil or whether the increase in vasopressin concentration is a physiologic response to a decrease in arterial pressure (secondary to a decrease in CO) induced by remifentanil.

References