Effect of medetomidine on respiration and minimum alveolar concentration in halothane- and isoflurane-anesthetized dogs

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Objective—To evaluate the effect of medetomidine on minimum alveolar concentration (MAC), respiratory rate, tidal volume, minute volume (VM), and maximum inspiratory occlusion pressure (IOCPmax) in halothane- and isoflurane-anesthetized dogs.

Animals—6 healthy adult dogs (3 males and 3 females).

Procedure—The MAC of both inhalants was determined before and after administration of medetomidine (5 µg/kg, IV). Dogs were subsequently anesthetized by administration of halothane or isoflurane and administered saline (0.9% NaCl) solution IV or medetomidine (5 µg/kg, IV). Respiratory variables and IOCPmax were measured at specific MAC values every 15 minutes before and after administration of medetomidine while dogs breathed 0% and 10% fractional inspired carbon dioxide (FICO2). Slopes of the lines for VM/FICO2 and IOCPmax/FICO2 were then calculated.

Results—Administration of medetomidine decreased MAC of both inhalants. Slope of VM/FICO2 increased in dogs anesthetized with halothane after administration of medetomidine, compared with corresponding values in dogs anesthetized with isoflurane. Administration of medetomidine with a simultaneous decrease in inhalant concentration significantly increased the slope for VM/FICO2, compared with values after administration of saline solution in dogs anesthetized with halothane but not isoflurane. Values for IOCPmax did not differ significantly between groups.

Conclusions and Clinical Relevance—Equipotent doses of halothane and isoflurane have differing effects on respiration that are most likely attributable to differences in drug effects on central respiratory centers. Relatively low doses of medetomidine decrease the MAC of halothane and isoflurane in dogs. (Am J Vet Res 2006;67:782–789)

M ost general anesthetics that are inhaled or administered IV, as well as many anesthetic adjuncts including opioid analgesics, depress breathing.1 The inhalant anesthetics halothane and isoflurane cause dose-dependent depression of breathing in dogs, presumably by depressing central and peripheral chemical receptors, although the apneic index (the percentage of inhalant at which apnea is evident divided by the MAC) is higher for halothane.1 Medetomidine, an α2-adrenoceptor agonist, is commonly prescribed and administered as a preanesthetic medication or perianesthetic adjunct in dogs to induce sedation, analgesia, and muscle relaxation.1 The α2-adrenoceptor agonists cause most, if not all, of their pharmacologic effects through stimulation of central and peripheral α2-receptors.2 Respiratory depressant effects of medetomidine are usually attributed to depression of the central respiratory centers secondary to a decrease in catecholamine activity at central α2-receptors situated in the locus coeruleus.3 In another study4 conducted by our laboratory group, we reported that administration of medetomidine (5 and 10 µg/kg, IV) decreased respiratory drive (as measured by IOCP at 0.1 second) and VM in conscious dogs for up to 60 minutes in response to increases in FICO2.

Respiratory drive has been defined5 as the rate of respiratory motoneuron output during inspiration and can be assessed by repetitive measurement of IOCP. The IOCP is a measure of the output of the respiratory centers that, unlike more conventional measures of ventilation including RR, VT, and VM, is not dependent on airway resistance or lung compliance.5 Compared with measurements obtained by other methods (eg, electromyography of the muscles of respiration or pulmonary function tests), measurement of IOCP is relatively simple.5 The inspiratory phase of breathing can be occluded in unconscious subjects until IOCPmax is reached. Inspiratory occlusion pressure can be evaluated during rebreathing of carbon dioxide. Staged or gradual increases in FICO2 and a concurrent lack of hypoxemia allow quantification of the sensitivity of the ability of the respiratory centers to respond to the stimulus of increases in carbon dioxide.

In the study reported here, we hypothesized that medetomidine would decrease inspiratory drive in dogs. We believed that this effect would be less pronounced in dogs during halothane-induced anesthesia,
compared with the effect in dogs during isoflurane-induced anesthesia.

Materials and Methods

Animals—Six heartworm-negative adult dogs (3 males and 3 females), each of which weighed between 8 and 12 kg, were subjects in the experiments reported here. Dogs were deemed healthy on the basis of anticipated results for a CBC and physical examination, which included thorough auscultation of the thorax. The experiments were approved by the Animal Care and Use Committee of The Ohio State University.

Equipment and calibration—Oxygen and carbon dioxide were delivered via a circle anesthetic breathing system. Inhalant anesthetics were delivered by out-of-circle, calibrated halothane or isoflurane vaporizers. End-tidal concentration of inhaled anesthetic, FIO2, and FICO2, were measured by use of a respiratory gas analyzer. The gas analyzer was calibrated before each experiment with known concentrations of halothane (or isoflurane), oxygen, and carbon dioxide.

Airflow and airway pressures were measured by use of a wire-mesh pneumotachograph flowmeter and an attached differential pressure transducer positioned between the dog and breathing system. The pressure transducer was calibrated at 0 and 10 cm H2O. Calibration of equipment was performed at the start of each experiment. Changes in Vt were obtained by electrical integration of the flow signal. Gas flow, RR, Vt, Vm, intratracheal pressure, and an ECG were simultaneously recorded by use of a computer-based data acquisition system.

The IOCP was determined by temporarily rapidly inflating a pneumatically controlled balloon positioned in the inspiratory limb of the breathing circuit. This technique permitted the measurement of IOCPmax, reaching during occlusion throughout a complete respiratory cycle. The inflated balloon completely occluded the inspiratory limb of the breathing circuit, which prevented gas flow.

Experimental protocol—The study was conducted in accordance with a randomized crossover design. Each dog was subjected to 4 treatments. Dogs were anesthetized by administration of halothane and injected IV with saline (0.9% NaCl) solution or medetomidine (5 µg/kg) and similarly were anesthetized by administration of isoflurane and injected IV with saline solution or medetomidine (5 µg/kg). Order of treatments for each dog was randomized. There was a minimum of 7 days between successive treatments for each dog.

MAC determination—In a preliminary study, we found that IV administration of medetomidine at a dosage of 5 µg/kg to dogs maintained at a constant inhalant anesthetic concentration of 1.4 MAC eliminated all response to an increase in inspired carbon dioxide, which suggested marked depression of central respiratory drive. Medetomidine has potent anesthetic-sparing qualities, which result in a marked reduction in the amount of isoflurane required to induce a surgical plane of anesthesia. Therefore, in preliminary experiments, we determined the MAC required to maintain anesthesia with halothane or isoflurane before and after the IV administration of medetomidine at a dosage of 5 µg/kg. The noxious stimulus used to determine MAC in those preliminary experiments was continuous airway occlusion for 60 seconds while breathing FICO2 of 15%. This amount of carbon dioxide was selected because it was greater than the maximum FICO2 administered to dogs during the study reported here. Gross purposeful movements, including but not limited to paddling, head lifting, and gagging on the endotracheal tube, were considered positive responses to this noxious stimulus; MAC was determined immediately before and 5, 30, and 60 minutes after administration of medetomidine (5 µg/kg, IV).

Collection of respiratory and IOCP data—Anesthesia was induced by administering inhalant anesthetic via a tight-fitting face mask attached to the circle system with the vaporizer set at 5%. After induction, dogs were orotracheally intubated with an appropriately sized, cuffed endotracheal tube. Dogs were placed on a circulating warm water blanket during anesthesia. During the experiments, dogs breathed specific concentrations of oxygen and carbon dioxide and were administered halothane or isoflurane at selected multiples of MAC. Two gas flow meters were independently used to control delivery of oxygen and carbon dioxide into the breathing circuit and to adjust the required FICO2 to steady-state values.

Equilibration to achieve steady-state carbon dioxide values required approximately 10 minutes. Steady-state values for RR, gas flow, and end-tidal carbon dioxide concentration were confirmed before data collection and were achieved ≤5 minutes after carbon dioxide had equilibrated. Respiratory variables were recorded 15 minutes before administration of medetomidine or saline solution. Ten to 20 minutes was required for the amount of carbon dioxide and any concomitant increase in sympathetic tone to return to preadministration steady-state values.

Fifteen minutes after baseline values were recorded, medetomidine or saline solution was administered IV. Time of IV injection was designated as time 0. Respiratory variables were then recorded 5, 30, and 60 minutes after administration of medetomidine or saline solution. All recorded variables were obtained at an FICO2 of 0% followed by an FICO2 of 10% to generate response data for changes in carbon dioxide concentrations. Order of delivery for FICO2 was not randomized (ie, dogs were always subjected to an FICO2 of 0% and then subsequently to an FICO2 of 10%). Inhalant concentration for halothane and isoflurane was 1.4 MAC at baseline and at all times after administration of saline solution. Inhalant concentration for halothane and isoflurane was 0.4, 0.6, and 1.2 MAC at 5, 30, and 60 minutes after administration of medetomidine, respectively. Respiratory data were recorded beginning 5 breaths before the first of 3 airway occlusions, which were performed at each time point and each value of FICO2.

The IOCPmax was directly measured after the experiments from computer printouts of tracheal pressure recorded during each occlusion. The IOCPmax and Vt were plotted as functions of FICO2. The slope of the line was calculated for each time point in accordance with the following equations:

\[
\text{IOCP}_{\text{max}} = \text{IOCP}_{\text{max}} \times \text{FICO}_2^{0.05}
\]

\[
\text{Vt} = \text{Vt} \times \text{FICO}_2^{0.05}
\]

Statistical analysis—Data for IOCP and respiratory variables were analyzed by use of a 2-way ANOVA for repeated measures. Data were analyzed by use of a statistical software package. Differences within and among groups were detected by use of the Tukey multiple comparison post hoc test. Results were considered significant at values of P ≤ 0.05.

Results

Effects of medetomidine on MAC of halothane and isoflurane—Mean ± SD MAC was 0.9 ± 0.1% for halothane and 1.2 ± 0.1% for isoflurane. Mean MAC multiple (ie, actual percentage of inhalant divided by the MAC) required to result in no physical response (ie, no gross purposeful movement) to the noxious stimulus in all dogs was 1.4 ± 0.1% for both inhalant anesthetics (1.3 ± 0.1% for halothane and 1.7 ± 0.1% for isoflurane). There were no differences in the reduc-
Anesthesia—Total duration of anesthesia for collection of respiratory data (including IOCPmax) was approximately 2.5 hours, which included stabilization of each dog, baseline measurements, a 15-minute interval before administration of medetomidine or saline solution, and 60 minutes after injection. Body temperature did not decrease significantly during this time, and dogs were extubated within 15 minutes after the end of each experiment.

Effects of FICO2 on respiratory variables—Anesthesia achieved by use of isoflurane or halothane at 1.4 MAC did not significantly alter RR, compared with an RR of 18 breaths/min in conscious dogs; however, administration of isoflurane did cause RR to have slightly lower values. The RR was generally higher when dogs were anesthetized with halothane, compared with RR for dogs when anesthetized with isoflurane. Breathing an FICO2 of 10% did not significantly increase RR, compared with the RR when breathing an FICO2 of 0% (Table 1).

Anesthesia achieved by administration of halothane and isoflurane resulted in a significant decrease in mean ± SD Vt (halothane, 91 ± 8 mL; isoflurane, 109 ± 6 mL), compared with Vt for conscious dogs (171 ± 11 mL). Regardless of inhalant, Vt always increased significantly when dogs breathed an FICO2 of 10%, compared with Vt when they breathed an FICO2 of 0% (Table 1).

The Vm was generally lower in dogs anesthetized by administration of isoflurane, compared with the Vm for dogs anesthetized by use of halothane, regardless of FICO2, and was significantly lower at an FICO2 of 10% (Figure 1). The Vm was always significantly increased when dogs breathed an FICO2 of 10%, compared with Vm when dogs breathed an FICO2 of 0%. Slope of the Vm/FICO2 response line was significantly greater when dogs were anesthetized by administration of halothane, compared with the slope for the response line when dogs were anesthetized by administration of isoflurane.

Effects of medetomidine on respiratory variables—The RR was decreased after the IV administration of medetomidine in halothane- and isoflurane-anesthetized dogs. The RR was not affected by medetomidine when the FICO2 was 10% (Table 1). Medetomidine did not significantly decrease Vt from the baseline value. Regardless of treatment group, Vt always increased significantly when dogs breathed an FICO2 of 10%, compared with Vt when dogs breathed an FICO2 of 0%. Regardless of the FICO2, Vt was greater in dogs anesthetized by administration of halothane and administered medetomidine, compared with Vt for all other treatment groups.

In isoflurane-anesthetized dogs, administration of medetomidine caused little change in the slope of Vm in response to an FICO2 of 10%, compared with the slope of Vm in response to an FICO2 of 10% when dogs were administered saline solution. The slope of the Vm/FICO2 line for halothane-anesthetized dogs administered medetomidine was greater than the slope of the Vm/FICO2 response line in halothane-anesthetized dogs administered saline solution or isoflurane-anesthetized dogs administered medetomidine or saline solution (Figure 1).

Table 1—Mean ± SD values for RR and Vt in response to changes in FICO2 in dogs anesthetized by administration of halothane or isoflurane 15 minutes before (baseline) and 5, 30, and 60 minutes after IV administration*. Values are in mL/kg or saline (0.9% NaCl) solution.

<table>
<thead>
<tr>
<th>IV injection</th>
<th>FICO2 (%)</th>
<th>Time (min)</th>
<th>RR (breaths/min)</th>
<th>Vt (mL)</th>
<th>RR (breaths/min)</th>
<th>Vt (mL)</th>
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<tr>
<td>Saline solution</td>
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<td>91 ± 8</td>
<td>15 ± 7</td>
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<td>5</td>
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<tr>
<td></td>
<td></td>
<td>30</td>
<td>32 ± 21</td>
<td>87 ± 10t</td>
<td>19 ± 8</td>
<td>113 ± 6</td>
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<tr>
<td></td>
<td></td>
<td>60</td>
<td>27 ± 111</td>
<td>128 ± 91t</td>
<td>19 ± 7</td>
<td>103 ± 6</td>
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<tr>
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<td>253 ± 265</td>
<td>18 ± 5</td>
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<td>16 ± 7</td>
<td>208 ± 301,II</td>
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</table>

*Time of injection was designated as time 0. Within a row, value differs significantly (P ≤ 0.05) from the value for isoflurane. Within a row, value differs significantly (P ≤ 0.05) from the value for saline. IV within an inhalant, value differs significantly (P ≤ 0.05) from the corresponding value for FICO2 of 0%. IV within an inhalant, value differs significantly (P ≤ 0.05) from the corresponding value for saline solution.
Effects of inhalants, FICO₂, time, and medetomidine on IOCPmax—The IOCPmax (range, 12.4 to 19.2 mm H₂O) did not differ significantly when dogs breathed an FICO₂ of 0%, regardless of inhalant anesthetic and administration of medetomidine (Figure 2). The IOCPmax always increased in response to an increase in FICO₂, regardless of inhalant or administration of medetomidine. The IOCPmax and slope of IOCPmax/FICO₂ response line were generally lower when dogs were anesthetized by administration of halothane (IOCPmax range, 32.1 to 38.1 mm H₂O), compared with results when dogs were anesthetized by administration of isoflurane (IOCPmax range, 31.9 to 48.2 mm H₂O). Administration of medetomidine did not affect slope of the IOCPmax/FICO₂ response line in halothane-anesthetized dogs, whereas administration of medetomidine generally decreased, although not significantly, the slope of the IOCPmax/FICO₂ response line in isoflurane-anesthetized dogs.

Effects of time on IOCPmax and Vₐ—the IOCPmax did not differ significantly over time when dogs were anesthetized by administration of halothane, regardless of administration of medetomidine or FICO₂. The IOCPmax did not differ significantly over time when dogs anesthetized by use of isoflurane were administered saline solution, regardless of FICO₂, and when isoflurane-anesthetized dogs were administered medetomidine and breathed an FICO₂ of 10%. The increase in IOCPmax after dogs anesthetized by use of isoflurane were administered medetomidine and breathed an FICO₂ of 0% was significantly different 30 minutes after injection of medetomidine, compared with IOCPmax at baseline. By 60 minutes after injection, IOCPmax in this group was decreasing and was no longer significantly different from the baseline value.

The Vₐ also did not change significantly over time when dogs were anesthetized by administration of halothane and breathed an FICO₂ of 0%, regardless of administration of medetomidine. The Vₐ also did not change significantly over time when halothane-anesthetized dogs were administered saline solution and breathed an...
FICO2 of 10%. There was a significant decrease in VM at 60 minutes when halothane-anesthetized dogs were administered medetomidine and breathed an FICO2 of 10%, compared with the VM at baseline. There was no difference in VM over time in dogs anesthetized by administration of isoflurane, regardless of FICO2 or administration of medetomidine.

Discussion

In the study reported here, increases in FICO2 generally caused increases in VT, VM, and IOPCmax in isoflurane- and halothane-anesthetized dogs. These changes reflect an increase in output from the respiratory centers in the brain in response to a known stimulus of those respiratory centers.8 Administration of a relatively low dose of medetomidine (5.0 µg/kg, IV) caused decreases in the concentration of inhalant anesthetic required to maintain anesthesia and, in general, had minimal effects on respiratory variables. Duration of anesthesia played a minor role, with changes in respiratory variables being closely related to the decrease in inhalant concentration when medetomidine was administered.

Dogs anesthetized with halothane or isoflurane, and without other drugs, had an increase in RR, VT, VM, and IOPCmax in response to an increase in FICO2. However, dogs administered isoflurane had a lower RR, similar VT, and decreased VM compared with results for halothane-anesthetized dogs. The VM in response to carbon dioxide challenge was greater with halothane than isoflurane. This finding is consistent with other studies involving dogs and people9,10 in which isoflurane had a greater respiratory depressant effect than was evident for halothane.

Repetitive measurement of IOPC is the current standard for quantification of electrical output of the respiratory centers.5 When the airway of a spontaneously breathing unconscious animal is occluded at the end of expiration, there is no flow or volume change during the inspiratory phase that follows, and a negative pressure is generated in the airway when the subject attempts to inspire.11 Because there is no lung inflation, there is a lack of sensory input from pulmonary stretch receptors.12 Inspiratory occlusion also allows the measurement of output under an infinite load.13 This method of evaluating the control signal is independent of resistance (because there is no flow) and elastance (because there is no change in volume). This results in uniform impedance allowing comparisons of IOPC, and therefore respiratory center output, among subjects and experimental conditions.5 However, there are limitations to this technique. The act of occlusion is not a typical action of the muscles of respiration, and this may trigger reflexes that are not generally associated with breathing. Also, diseases of the lungs, muscles of respiration, or chest wall can alter pressures generated within the airways through changes in resistance.

Increases in FICO2 stimulate the respiratory centers by activating central chemoreceptors located in the
brainstem, with approximately 20% of sensory input originating from peripheral chemoreceptors leading to increases in RR, V_T, and V_M. Stimulation of α_2-adrenoreceptors in the locus coeruleus causes sedation in dogs, and experimentally created lesions within the loci coerulei of cats attenuated the response of cranial blood flow during hypercapnia. Nerve fibers extend from the locus coeruleus to other parts of the brainstem and are generally excitatory in nature because they have norepinephrine as a neurotransmitter. Inhibition of excitatory stimuli to the respiratory centers would explain the decreased ventilatory drive detected after the administration of medetomidine.

Halothane is considered to be unique among the currently available inhalant anesthetics because, contrary to other inhalants, V_M and IOCP are not reduced in humans. When medetomidine was not administered, V_M was consistently lower when dogs were anesthetized with isoflurane, compared with V_M when dogs were administered halothane at equipotent doses (ie, similar MAC multiples). In 1 study in which investigators evaluated respiratory variables in dogs anesthetized with isoflurane and halothane, V_T tended to be higher in isoflurane-anesthetized dogs and RR was consistently higher in halothane-anesthetized dogs (V_M was not measured or calculated). Calculation of minute ventilation from the mean V_T and RR values reported in that study reveals that V_M was consistently higher in the halothane-anesthetized dogs, compared with V_M for the isoflurane-anesthetized dogs.

However, it is not possible to determine whether these values differed significantly without examination of the original data. Compared with effects of halothane, isoflurane causes greater depression of ventilation (V_T and V_M) in humans, as determined by end-tidal carbon dioxide concentration and IOCP. In humans, halothane allows increases in central respiratory output in response to the increase in carbon dioxide, compared with increases in response to isoflurane. Analysis of these data suggests that isoflurane causes more respiratory depression than does halothane.

At an FICO_2 of 0%, IOCP_max did not differ among groups. For anesthesia achieved by administration of isoflurane, baseline IOCP_max was greater when dogs were administered saline solution, compared with values when dogs were administered medetomidine. This was attributable to an outlier for the medetomidine injection in which the measured IOCP_max was 19 mm H2O for 1 dog. Values for the remainder of the dogs ranged from 33 to 43 mm H2O. In general, IOCP_max values were consistent for each dog. We have no explanation for the outlier. The values of IOCP_max were higher with isoflurane-induced anesthesia, compared with values of IOCP_max for halothane-induced anesthesia, when FICO_2 was 10%. Similarly, the slope of IOCP_max/FICO_2 was significantly higher when dogs were anesthetized with isoflurane, compared with the slope of IOCP_max/FICO_2 when they were anesthetized with halothane.

Slope of the inspiratory pressure wave, although consistent during undisturbed conscious breathing,
can be affected by anesthetic agents. Halothane can have varying effects on ventilatory drive and can cause a steeper initial portion of the occlusion pressure waveform in dogs and people, compared with effects for enflurane, the stereoisomer of isoflurane. The lower RR evident during isoflurane-induced anesthesia may allow more time for inspiration and thus more time to generate a higher IOP. In the study reported here, RR at an \textit{FICO}_2 of 10% was significantly higher in halothane-anesthetized dogs, which may account for the difference we observed in \textit{IOP}_{max}.

Marked inhalant anesthetic-sparing effects were evident after IV administration of medetomidine (5 µg/kg) to isoflurane- or halothane-anesthetized dogs, resulting in large reductions in the concentration of inhalant required to maintain a similar depth of anesthesia 5 and 30 minutes after medetomidine injection. By 60 minutes after medetomidine injection, MAC was much closer to baseline values. This can be explained by the waning effects of medetomidine because temperature, which has a major impact on MAC, did not change significantly in the dogs of our study. In another study, it was reported that medetomidine administered to conscious dogs at a dosage of 5 µg/kg has a clinical effect for 60 minutes, which is similar to values reported here.

Medetomidine has an MAC-sparing effect in isoflurane-anesthetized dogs. Because we did not determine MAC by any other method, we cannot reach conclusions about comparisons with other techniques used for determining MAC. Also, it was not possible to determine MAC with absolute accuracy within 5 minutes after medetomidine administration because periods of stability between stimulation were required. We partially extrapolated backward from the MAC at 30 minutes after medetomidine administration (0.6 MAC) to obtain a MAC multiple that was practical and consistent for collecting respiratory data at the time point 5 minutes after medetomidine administration.

Sensitivity of respiratory centers can be assessed by evaluating the slope of the curve of any respiratory variable (such as RR or \textit{IOP}_{max}) plotted against changes in carbon dioxide concentration. A decrease in the slope from baseline values indicates a decrease in sensitivity of the respiratory centers, assuming that the lungs and nervous system are not affected by disease. Administration of medetomidine increased \textit{VM} in halothane-anesthetized dogs, compared with results for control dogs, but did not affect the slope of the \textit{IOP}_{max}/\textit{FICO}_2 response. The percentage of inhalant had been decreased at that time, which likely accounted for this difference. Interestingly, this is in contrast to the results we observed when isoflurane was administered but no change was seen in \textit{VM} despite the decrease in inhalant. There is evidence that dogs anesthetized with halothane have an increase in the contribution of rib cage expansion during rebreathing, which may allow dogs to compensate through recruitment of parasternal intercostal muscles for decreases expected as a result of inhalant anesthesia. The exact mechanism for this compensation is unclear, but because separate groups of medullary inspiratory and expiratory neurons drive the motor neurons of inspiratory and expiratory muscle groups, a differential effect of halothane on central respiratory centers may explain such recruitment.

Medetomidine is licensed for use as a sedative and preanesthetic medication in dogs at a dosage of 40 µg/kg, although analysis of data suggests avoiding such high doses during anesthesia, particularly in older dogs. The decrease in respiratory center output resulting from the administration of medetomidine at a dosage of 5 µg/kg in isoflurane-anesthetized dogs reveals that medetomidine contributes to respiratory depression. The decreased MAC required to maintain a similar depth of anesthesia for halothane- and isoflurane-anesthetized dogs in the study reported here emphasizes the MAC-sparing properties of medetomidine. It is advisable to closely monitor anesthetic depth, respiration, and pulmonary gas exchange in halothane- or isoflurane-anesthetized dogs administered medetomidine.

Analysis of the data reported here emphasizes the inhalant anesthetic-sparing effects of medetomidine in dogs. Evaluation of differences between the effects of halothane and isoflurane on respiratory variables suggests they are likely a result of differences in drug effect on central respiratory centers. Additional studies are required to fully elucidate the precise differences for the mechanisms involved.

References
7. Canet J, Sanchis J, Zegri A, et al. Effects of halothane and during isoflurane-induced anesthesia may allow more time for inspiration and thus more time to generate a higher IOP. In the study reported here, RR at an \textit{FICO}_2 of 10% was significantly higher in halothane-anesthetized dogs, which may account for the difference we observed in \textit{IOP}_{max}.

Marked inhalant anesthetic-sparing effects were evident after IV administration of medetomidine (5 µg/kg) to isoflurane- or halothane-anesthetized dogs, resulting in large reductions in the concentration of inhalant required to maintain a similar depth of anesthesia 5 and 30 minutes after medetomidine injection. By 60 minutes after medetomidine injection, MAC was much closer to baseline values. This can be explained by the waning effects of medetomidine because temperature, which has a major impact on MAC, did not change significantly in the dogs of our study. In another study, it was reported that medetomidine administered to conscious dogs at a dosage of 5 µg/kg has a clinical effect for 60 minutes, which is similar to values reported here.

Medetomidine has an MAC-sparing effect in isoflurane-anesthetized dogs. Because we did not determine MAC by any other method, we cannot reach conclusions about comparisons with other techniques used for determining MAC. Also, it was not possible to determine MAC with absolute accuracy within 5 minutes after medetomidine administration because periods of stability between stimulation were required. We partially extrapolated backward from the MAC at 30 minutes after medetomidine administration (0.6 MAC) to obtain a MAC multiple that was practical and consistent for collecting respiratory data at the time point 5 minutes after medetomidine administration.

Sensitivity of respiratory centers can be assessed by evaluating the slope of the curve of any respiratory variable (such as RR or \textit{IOP}_{max}) plotted against changes in carbon dioxide concentration. A decrease in the slope from baseline values indicates a decrease in sensitivity of the respiratory centers, assuming that the lungs and nervous system are not affected by disease. Administration of medetomidine increased \textit{VM} in halothane-anesthetized dogs, compared with results for control dogs, but did not affect the slope of the \textit{IOP}_{max}/\textit{FICO}_2 response. The percentage of inhalant had been decreased at that time, which likely accounted for this difference. Interestingly, this is in contrast to the results we observed when isoflurane was administered but no change was seen in \textit{VM} despite the decrease in inhalant. There is evidence that dogs anesthetized with halothane have an increase in the contribution of rib cage expansion during rebreathing, which may allow dogs to compensate through recruitment of parasternal intercostal muscles for decreases expected as a result of inhalant anesthesia. The exact mechanism for this compensation is unclear, but because separate groups of medullary inspiratory and expiratory neurons drive the motor neurons of inspiratory and expiratory muscle groups, a differential effect of halothane on central respiratory centers may explain such recruitment.

Medetomidine is licensed for use as a sedative and preanesthetic medication in dogs at a dosage of 40 µg/kg, although analysis of data suggests avoiding such high doses during anesthesia, particularly in older dogs. The decrease in respiratory center output resulting from the administration of medetomidine at a dosage of 5 µg/kg in isoflurane-anesthetized dogs reveals that medetomidine contributes to respiratory depression. The decreased MAC required to maintain a similar depth of anesthesia for halothane- and isoflurane-anesthetized dogs in the study reported here emphasizes the MAC-sparing properties of medetomidine. It is advisable to closely monitor anesthetic depth, respiration, and pulmonary gas exchange in halothane- or isoflurane-anesthetized dogs administered medetomidine.

Analysis of the data reported here emphasizes the inhalant anesthetic-sparing effects of medetomidine in dogs. Evaluation of differences between the effects of halothane and isoflurane on respiratory variables suggests they are likely a result of differences in drug effect on central respiratory centers. Additional studies are required to fully elucidate the precise differences for the mechanisms involved.

References
20. Hellebrekers LJ. Comparison of isoflurane and halothane as inhalation anesthetics in the dog. Vet Q 1986;8:183–188.