Anesthesiology
76:573–579, 1992

Ventilatory Effects of Dexmedetomidine, Atipamezole, and Isoflurane in Dogs

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Dexmedetomidine (DMED) is a novel α_2 adrenergic agonist that has been shown to have potent analgesic and anesthetic sparing effects. This study was designed to investigate the effects of DMED, both alone and combined with isoflurane, on resting ventilation, the hypercapnic response, and the hypoxic response in dogs. When given alone, 1 μg/kg decreased resting ventilation by 22% but at larger doses (10, 20, and 100 μg/kg) resting ventilation increased, doubling at 100 μg/kg. Doses of 10 μg/kg and greater caused a maximum depression of 60% in the slope of the hypercapnic response, but no dose had a significant effect on the hypoxic ventilatory response. A dose of 3 μg/kg of DMED reduced isoflurane MAC from 1.3% to 0.37%, and the ventilatory effects of this 1 MAC combination were intermediate between the awake values and those of isoflurane-anesthetized (1.3%) dogs. Atipamezole is a specific centrally acting α_2 receptor antagonist and when given with DMED in isoflurane-anesthetized dogs prevented the ventilatory depression. However, atipamezole alone also had ventilatory stimulating effects, which may indicate tonic α_2 adrenergic activity. The ventilatory depression caused by DMED, either alone or combined with isoflurane, at doses that significantly reduce anesthetic requirements are relatively mild. (Key words: Lungs, ventilation: hypercapnic response; hypoxic response. Sympathetic nervous system, α_2 agonists: dexmedetomidine. Sympathetic nervous system, α_2 antagonists: atipamezole.)

DEXMEDETOMIDINE (DMED) is a potent, selective, and specific α_2-adrenergic agonist[1] that exerts its effects by stimulating pre- and postsynaptic α_2 adrenergic receptors both centrally and peripherally. DMED has a high affinity toward α_2 binding sites, and in receptor binding experiments, its α_2/α_1 selectivity ratio has been determined to be 1,620, as compared to 220 for clonidine.[2] Like clonidine and other α_2 agonists, DMED causes sedation, analgesia, bradycardia, and a reduction in blood pressure.** In recent studies, α_2 agonists have been observed to show anesthetic sparing effects when combined with volatile anesthetics in dogs[3] and rats,[4] decrease cerebral blood flow in dogs,[5] and prevent opioid-induced muscle rigidity in rats.†† In addition, DMED relieves anxiety in humans when given as premedication.[6] Clonidine, a less specific α_2 agonist, has been shown to reduce anesthetic requirements for sufentanil, isoflurane, and halothane in animals and human patients and has been advocated for use in anesthesia.[7,8]

Atipamezole (ATI) is a centrally acting α_2-adrenergic antagonist that is specific and highly selective (α_2/α_1 selectivity ratio of 8,526) with little effect on other neurotransmitter receptors.[9] In animal studies, ATI has been shown to effectively antagonize α_2-agonist behavioral, neurochemical, and cardiovascular effects.[10]

A potential major clinical advantage of α_2 agonists is a relative lack of ventilatory depression.[11] The purpose of this study was to investigate more fully the ventilatory effects of DMED in dogs by determining: 1) the dose–response of DMED on the resting ventilation and the ventilatory responses to hypercapnia and hypoxia; 2) the amount of reduction in anesthetic requirements and the respiratory effects of DMED when it is used with isoflurane; and 3) the ability of ATI to prevent the ventilatory effects of DMED.

Materials and Methods

Twelve trained mongrel dogs having a chronic tracheotomy[12] and weighing 18–25 kg were studied in three different protocols. Each protocol used 6 dogs. Two dogs were used in all three protocols; 4 dogs were used in at least two protocols; 4 dogs were used in only one protocol; and 2 dogs were used only in the MAC determination experiments. All dogs were free of respiratory diseases, and the protocols were approved by the Animal Care and Use Committee of the University of California Los Angeles Center for Health Sciences. These dogs had been familiarized with the laboratory equipment and environment prior to being used in an experiment. All dogs remained calm even after the tracheostomy tube was inserted. No dog was used in an experiment on consecutive days, and most experiments in a dog were separated by 4–8 days.

The dogs were allowed to breathe spontaneously through a cuffed tracheostomy tube. Inspired and expired

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Received from the University of California Los Angeles School of Medicine, Department of Anesthesiology, Los Angeles, California. Accepted for publication December 1, 1991.

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** Bloor BC, Raybould D, Shurtliff M, Gellmann J, Stead SW: MPV-1440: An α_2 adrenergic agonist with potent anesthetic qualities (abstract). ANESTHESIOLOGY 69:A614, 1988.

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air flows were measured with an impeller flowmeter (VMM-110, Sensor Medics, Laguna Hills, CA) calibrated with a syringe pump. A mass spectrometer (1100 MGA, Perkin-Elmer Corp., Norwalk, CT) calibrated with known gas mixtures was used to measure airway O_2, CO_2, N_2, and isoflurane concentrations. All data measured were collected on a breath-by-breath basis using a data-acquisition software program, TIDAL,[13] on a PC computer (PC Limited 286, Austin, TX). Control of inspired gas concentration was achieved with computer-controlled valves adjusting the fresh gas flow into an open breathing circuit. The O_2 and CO_2 concentration of the inspired gas was adjusted on a breath-by-breath basis to follow a specified pattern. For the hypercapnic and hypoxic tests a ramp increase in the inspired CO_2 and O_2, respectively, was used. During the hypoxic ramp, isocapnia was maintained by computer closed-loop control of the PET_{CO_2}. Arterial blood samples were drawn anaerobically (Protocol 3 only) and analyzed in duplicate for Pa_{CO_2}, Pa_{O_2}, and *p*H using a calibrated *p*H/blood gas analyzer (System 1303, Instrumentation Laboratory, Inc., Lexington, MA). In anesthetized dogs, body temperature was measured by a rectal thermometer (Yellow Springs Instruments, Yellow Springs, OH) and was maintained constant at 37–38° C with a heating lamp and/or a warming blanket as required.

Experimental Protocols

The protocol time lines are shown in figure 1. Each dog was allowed to adjust to the laboratory environment for 30–60 min after placing the tip of the cuffed tracheostomy tube through the stoma. The drug doses all were injected intravenously over 1 min as a bolus diluted in 5 ml 0.9% saline solution. Breath-by-breath ventilation and end-tidal gas concentrations were measured and averaged over 5-min steady-state baseline periods prior to determination of the ventilatory response to hypercapnia or hypoxia.

Hypercapnic Response

Following equilibration with high O_2 ($FI_{O_2} > 50\%$), an initial step increase of inspired P_{CO_2} to 50 mmHg was followed by a ramp increase to a maximum inspired P_{CO_2} of 70 mmHg over 4 min. The breath-by-breath response of minute ventilation ($\dot{V}_E$) to hypercapnia was determined by linear regression: $\dot{V}_E = S \times PET_{CO_2} + I$, where S and I are the slope and intercept, respectively, of the hypercapnic response. The initial transient segment of the response was omitted, and only the linear rise segment of the ventilation during the CO_2 ramp was fitted.

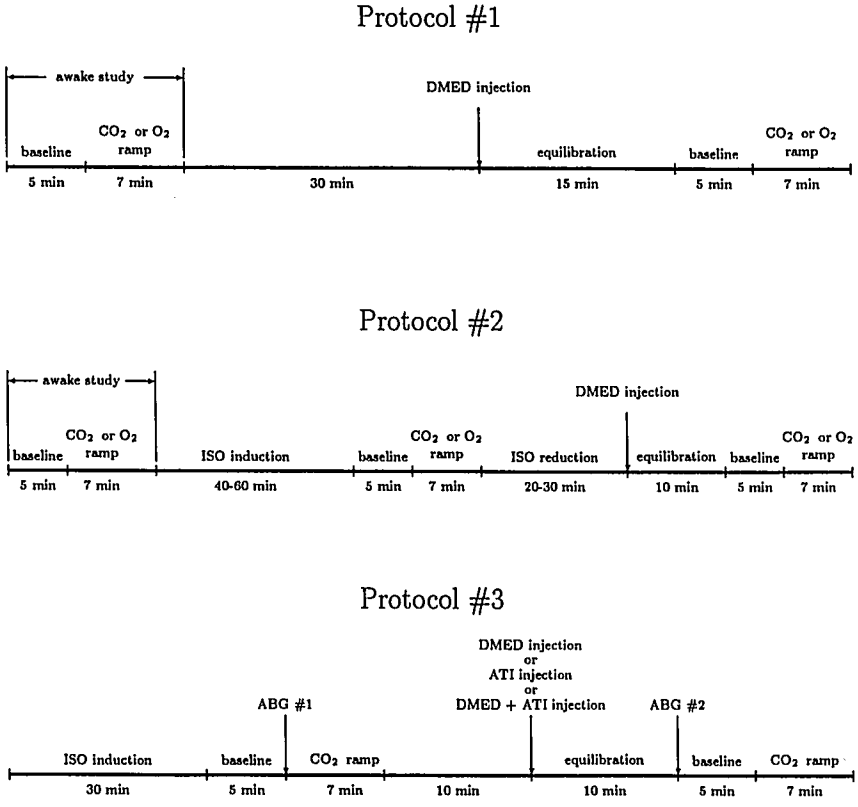

FIG. 1. Study timelines for the three protocols. See text for a complete description of the methods and measurements.

Hypoxic Response

The ventilatory response to isocapnic hypoxia was assessed by a ramp decrease in the inspired P_{O_2} from an initial value of 150 mmHg to 50 mmHg over 4 min. $P_{ET_{CO_2}}$ was kept constant at the level measured during the baseline prior to each hypoxic test by adjusting the inspired CO_2 on a breath-by-breath basis by computer control. The breath-by-breath response of $\dot{V}_E$ to hypoxia was fitted to a hyperbolic model: $\dot{V}_E = (A/P_{ET_{O_2}} - C) + B$, where A = the shape factor of the hyperbolic curve; B = the ventilation in hyperoxia; and C = the $P_{ET_{O_2}}$ asymptote. Only the data acquired during the O_2 ramp were fitted. The results of the hypoxic response are expressed as the change in ventilation from hyperoxia to a P_{O_2} of 50 mmHg; $\Delta\dot{V}_{EP50} = A/(50 - C)$.

Protocol 1: Dose–Response Ventilatory Effects

Awake measurements of baseline ventilation was followed by either a hypercapnic or a hypoxic response. A single bolus of DMED at 1, 10, 20, or 100 μg/kg was then administered intravenously, and the measurements of baseline ventilation and either the hypercapnic or hypoxic response were repeated. Only one dose was given to a dog on any 1 day. Thus, since the hypoxic and hypercapnic responses were performed on different days, each dog was studied eight times. Each dog completed both the hypercapnic and hypoxic tests in randomized order within a dose groups. The sequence of the dose groups was not completely randomized prior to the study because it was not known at what dose ventilatory changes would be seen. The 10 and 20 μg/kg dose were studied initially, with half the dogs receiving each dose first. The 1.0 μg/kg dose was given next and 100 μg/kg dose given last.

Protocol 2: Ventilatory Effects of Dexmedetomidine Combined with Isoflurane

MAC Determination

Prior to the ventilatory measurements, isoflurane MAC before and after administration of 3 μg/kg DMED was determined. MAC was determined by the tail-clamping method.[14] The test isoflurane concentration in each dog was allowed to equilibrate for 20–30 min. A tail clamp was applied within 3 cm of the base of the tail for 1 min. The isoflurane concentration was then gradually reduced by increments of 0.1% followed by tail clamping until a purposeful movement was observed, after which tail clamping was repeated with the isoflurane concentration increasing by 0.1% until no movement was observed. The 1 MAC isoflurane concentration was determined from the average of the two isoflurane concentrations. The average isoflurane MAC of the 6 dogs used in this protocol was 1.3%.

Once 1 MAC isoflurane was determined, the inspired isoflurane concentration was reduced to 0.6% and allowed to equilibrate for 15–20 min. DMED 3.0 μg/kg was then injected, and after 5 min the above procedure was repeated to determine 1 MAC anesthesia for isoflurane in combination with 3.0 μg/kg DMED. All determinations were made within 20 min after injection. An average MAC of 0.37% was found. This 70% reduction in MAC is comparable to the 90% reduction in halothane MAC with 10 μg/kg medetomidine found by Vickery *et al.*[15]

Ventilatory Measurement

After awake measurements (similar to protocol 1) were determined, the dogs were anesthetized with 1.3% isoflurane in air *via* the tracheostomy, and the same set of measurements was repeated (*i.e.*, on any 1 day, baseline followed by either the hypercapnic or the hypoxic test). The end-tidal isoflurane concentration was held constant by manually adjusting inspired isoflurane throughout the tests. While the dogs were asleep and undisturbed, the inspired isoflurane was gradually reduced to approach 0.37% inspired over a 20–30-min period. DMED 3.0 μg/kg was given and the isoflurane stabilized at 0.37%. The ventilatory measurements were then repeated.

Protocol 3: Dexmedetomidine in Combination with Atipamezole

During preliminary experiments it was found that the dogs anesthetized with 1.3% isoflurane awoke following ATI and required 1.5% isoflurane to stabilize the ventilation for postdrug measurements. A protocol for ventilatory measurements similar to that in other protocols was used except that hypoxic responses were not performed. Arterial blood gas measurements were obtained from a femoral arterial catheter at the end of the baseline period. Three conditions were studied; DMED, ATI, and the combination. Two dose combinations were used: 3.0 μg/kg DMED and 0.3 mg/kg ATI, or 20.0 μg/kg DMED and 0.5 mg/kg ATI. The isoflurane concentration was maintained at 1.5% throughout the study. Intravenous administration of DMED, ATI, or the combination of DMED and ATI at the specified dose were studied separately. The two drugs were administered simultaneously in the combined-drug experiment.

Statistical Analysis

Differences between control and postdrug values were analyzed with unweighted means analysis of variance (Solo Statistical Software, Los Angeles, CA). Intragroup differences were determined by Newman-Keuls *post hoc* analysis.

TABLE 1. Results for Protocol 1

	Awake Control	1 μg/kg DMED	Awake Control	10 μg/kg DMED	Awake Control	20 μg/kg DMED	Awake Control	100 μg/kg DMED
$\dot{V}_E$ (l·min^{-1})	2.8 (0.8)	2.2* (0.5)	2.2 (0.8)	2.7* (1.0)	2.5 (0.7)	3.7* (2.0)	2.5 (0.8)	5.2* (2.0)
PET_{CO_2} (mmHg)	39.9 (2.5)	39.6 (2.4)	39.6 (1.8)	38.8 (2.6)	39.6 (1.6)	36.4* (4.9)	40.6 (1.2)	32.5* (4.3)
PET_{O_2} (mmHg)	97.5 (4.0)	97.7 (5.5)	92.0 (8.2)	95.5 (6.9)	93.6 (5.3)	97.7* (8.5)	94.7 (4.4)	105.2* (8.6)
$\Delta\dot{V}_{EP_{50}}$ (l·min^{-1})	10.3 (3.4)	9.1 (5.3)	6.1 (3.2)	5.6 (3.3)	6.3 (3.7)	4.5 (1.9)	10.5 (4.6)	8.2 (3.0)
S (l·min^{-1}·mmHg^{-1})	0.95 (0.34)	0.76* (0.30)	1.01 (0.20)	0.53* (0.30)	0.75 (0.34)	0.30* (0.13)	0.97 (0.25)	0.55* (0.3)

Mean (SD) given for n = 6 dogs. $\dot{V}_E$, PET_{CO_2}, and PET_{O_2} comparisons are for two experiments per dog; $\Delta\dot{V}_{EP_{50}}$ and S are for one experiment per dog. $\Delta\dot{V}_{EP_{50}}$ is a measurement of the hypoxic ventilatory response, and S is the hypercapnic response slope (see text). DMED = dexmedetomidine.
* $P < 0.05$ comparing awake control with postdrug within each group.

All data are given as mean ± SD. A P value ≤ 0.05 was considered to be statistically significant.

Results

PROTOCOL 1 (TABLE 1)

The baseline data from both the hypercapnic and hypoxia experiments at a given dose level were combined for statistical analysis. Although there was considerable variation among the awake control values for the different dose groups, only the variation in $\Delta\dot{V}_{EP50}$ was significant ($P = 0.03$; intergroup differences could not be isolated with Newman-Keuls *post hoc* analysis). When compared to the awake baseline measurements within each dose group, $\dot{V}_E$ decreased slightly at a 1 μg/kg DMED. Doses greater than 10 μg/kg, however, caused a progressive increase in $\dot{V}_E$. At the 20 μg/kg and 100 μg/kg concentrations, PET_{CO_2} decreased with a corresponding increase in PET_{O_2}. All four doses caused a decrease in the slope of the hypercapnic response, but there was no significant change in hypoxic response at any of the four doses. Intergroup comparison showed a clear dose response for ventilation ($P < 0.05$), but the slopes after 10, 20, or 100 μg/kg were not different from each other.

PROTOCOL 2 (TABLE 2)

At 1 MAC isoflurane (1.3%) anesthesia, $\dot{V}_E$ and PET_{O_2} were not greatly affected, although the small consistent increase in PET_{CO_2} was statistically significant. Ventilatory responses to both hypoxia and hypercapnia were significantly decreased from awake measurements.

At 1 MAC combination anesthesia (0.37% isoflurane and 3 μg/kg DMED), changes in PET_{CO_2} and PET_{O_2} were minor but consistent and statistically significant when compared with awake and 1 MAC isoflurane alone. The ventilatory responses to hypoxia and hypercapnia during 1 MAC isoflurane combined with DMED were between and not statistically different from either the responses of those during awake measurement or during 1 MAC isoflurane alone.

PROTOCOL 3

3.0 μg/kg Dexmedetomidine + 0.3 mg/kg Atipamezole (Table 3)

DMED at 3 μg/kg during 1.5% isoflurane anesthesia caused a nonsignificant decrease in ventilation, but the small increase in the Pa_{CO_2} and decrease in the slope of the hypercapnic response were significant when compared to 1.5% isoflurane alone. ATI at 0.3 mg/kg caused a significant increase in ventilation without a significant decrease in Pa_{CO_2}. It is noteworthy that the Pa_{O_2} did increase significantly. The slope of the hypercapnic response was mildly, but significantly, increased. The combination of DMED and ATI given simultaneously did not cause a significant increase in ventilation, whereas the relatively

TABLE 2. Results for Protocol 2

	Awake	1.3% Isoflurane	0.37% Isoflurane + 3 μg/kg DMED
$\dot{V}_E$ (l·min^{-1})	3.00 (0.97)	2.71 (0.70)	3.03 (0.89)
PET_{CO_2} (mmHg)	40 (2.2)	41* (2.5)	39†‡ (2.3)
PET_{O_2} (mmHg)	100 (4.3)	98 (3.4)	104†‡ (4.5)
$\Delta\dot{V}_{EP_{50}}$ (l·min^{-1})	9.85 (3.6)	5.20* (2.49)	8.07 (3.91)
S (l·min^{-1}·mmHg^{-1})	0.84 (0.24)	0.26* (0.19)	0.46 (0.48)

Mean (SD) given for n = 6 dogs. $\dot{V}_E$, PET_{CO_2}, and PET_{O_2} comparisons are for two experiments per dog; $\Delta\dot{V}_{EP_{50}}$ and S are for one experiment per dog. See table 1 for explanation of symbols. DMED = dexmedetomidine.
* $P \leq 0.05$ for isoflurane *versus* awake.
† $P \leq 0.05$ for conbination *versus* awake.
‡ $P \leq 0.05$ for combination *versus* isoflurane.

TABLE 3. Results for Protocol 3: Low Dose of Dexmedetomidine

	Group 1		Group 2		Group 3	
	1.5% Isoflurane	3.0 μg/kg DMED, 1.5% Isoflurane	1.5% Isoflurane	0.3 mg/kg ATI, 1.5% Isoflurane	1.5% Isoflurane	3.0 μg/kg DMED, 0.3 mg/kg ATI, 1.5% Isoflurane
$\dot{V}_E$ (l·min^{-1})	3.47 (0.76)	3.14 (0.36)	2.70 (0.44)	3.27* (0.69)	2.88 (0.59)	3.37 (0.60)
PET_{CO_2} (mmHg)	36.4 (3.7)	41.2* (3.7)	39.3 (4.3)	37.9 (4.1)	40.4 (4.8)	38.0* (4.0)
PET_{O_2} (mmHg)	105.9 (7.5)	96.3* (7.6)	100.6 (5.1)	104.8* (4.2)	98.2 (8.0)	108.1 (16.4)
Pa_{CO_2} (mmHg)	41 (4)	46* (4)	45 (4)	44 (3)	44† (2)	43* (3)
Pa_{O_2} (mmHg)	86 (7)	80 (8)	80 (8)	91* (5)	79† (5)	93† (16)
*p*H	7.32 (0.02)	7.28* (0.03)	7.30 (0.03)	7.30 (0.03)	7.33† (0.05)	7.31† (0.02)
S (l·min^{-1}·mmHg^{-1})	0.49 (0.13)	0.16* (0.11)	0.35 (0.15)	0.44* (0.15)	0.39 (0.13)	0.49 (0.13)

Mean (SD) given for n = 6 dogs, except n = 5 for blood gas data in group 3. See table 1 for explanation of symbols. DMED = dexmedetomidine; ATI = atipamezole.

* $P \leq 0.05$ compared to 1.5% isoflurane alone within the same group.

small changes in blood gases were significant. Comparison across dose groups showed no significant differences among the 1.5% isoflurane control measurements. After the injection there again were no differences, except that the slope of the hypercapnic response was significantly lower in group 1. The results from the blood gas sample were lost in one of the dogs in the DMED and ATI combination group.

20.0 μg/kg Dexmedetomidine + 0.5 mg/kg Atipamezole (Table 4)

DMED at 20.0 μg/kg caused a significant increase in Pa_{CO_2} and a significant decrease in Pa_{O_2}. In two of the dogs, a stable breathing pattern could not be obtained to measure the baseline ventilation, and $\dot{V}_E$ was significantly decreased in the other four dogs. In four of the six dogs, no detectable response to hypercapnia could be found; in the other two dogs, the slope was 0.11 and 0.15 l·min^{-1}·mmHg^{-1}, respectively. The administration of ATI at 0.5 mg/kg did not cause significant changes in ventilation and blood gases, but the hypercapnic response was increased approximately 3-fold and was comparable to the slope seen in awake dogs (tables 1 and 2). However, when both drugs were given in combination, no significant changes were observed. Comparisons across the 1.5% isoflurane control measurements showed some inconsistent minor differences; PET_{CO_2} was significantly larger in group 2, and Pa_{CO_2} was significantly larger in group 3. Comparison across the groups after the injection showed that the slope was significantly larger in group 2; the PET_{CO_2} and Pa_{CO_2} both were significantly increased in group 1; ventilation was increased in group 2; and the Pa_{O_2} and PET_{CO_2} were significantly lower in group 1.

Discussion

α_2 Agonists represent a new class of drugs found to have analgesic and sedative properties. A potential advantage of these drugs is the minimal respiratory depression observed with their use.[11] This study was designed to investigate the ventilatory effects of DMED over a wide dose range alone and when combined with isoflurane. We used three techniques to study the effects on ventilation: the resting ventilation and PET_{CO_2} or Pa_{CO_2} and the PET_{O_2} or Pa_{O_2}; the ventilatory response to hypercapnia; and the ventilatory response to hypoxia. As illustrated by the results of this study and other studies of drug effects

TABLE 4. Results for Protocol 3: High Dose of Dexmedetomidine

	Group 1		Group 2		Group 3	
	1.5% Isoflurane	20 μg/kg DMED, 1.5% Isoflurane	1.5% Isoflurane	0.5 mg/kg ATI, 1.5% Isoflurane	1.5% Isoflurane	20 μg/kg DMED, 0.5 mg/kg ATI, 1.5% Isoflurane
$\dot{V}_E$ (l·min^{-1})	3.02 (0.53)	2.36* (0.77)	3.55 (0.56)	4.87 (1.67)	3.01 (0.91)	3.16 (0.63)
PET_{CO_2} (mmHg)	38.3 (2.7)	48.5* (2.1)	36.1 (2.3)	35.1 (3.7)	40.4 (5.4)	39.3 (3.3)
PET_{O_2} (mmHg)	102.0 (5.1)	77.8* (12.2)	108.8 (7.6)	113.3 (6.5)	97.9 (8.3)	100.7 (3.4)
Pa_{CO_2} (mmHg)	44 (2)	53* (7)	44 (3)	43 (1)	47 (3)	46 (4)
Pa_{O_2} (mmHg)	84 (2)	60* (11)	79 (5)	80 (6)	81 (5)	86 (8)
*p*H	7.30 (0.04)	7.27 (0.15)	7.32 (0.03)	7.32 (0.04)	7.32 (0.04)	7.32 (0.04)
S (l·min^{-1}·mmHg^{-1})	0.40 (0.10)	See text	0.33 (0.10)	0.93* (0.53)	0.30 (0.14)	0.28 (0.12)

Mean (SD) given for n = 6 dogs, except for $\dot{V}_E$, PET_{CO_2}, and PET_{O_2} in group 1 (n = 4) after dexmedetomidine (DMED) and group 2 (n = 5) after DMED. ATI = atipamezole.

* $P \leq 0.05$ compared to 1.5% isoflurane alone within the same group.

on the control of breathing,[16] each of these ways of assessing ventilatory drive can be differently affected by a drug. The resting ventilatory drive is determined by multiple factors, specifically the input from the chemoreceptors, but is also influenced by factors such as sleep state, body temperature, pain, and metabolic rate. The CO_2 concentration at the central chemoreceptors may have a primary role in determining resting ventilation; this is especially true under anesthesia when other inputs are minimized or absent. The hypercapnic and hypoxic ventilatory responses are best thought of as protective reflexes that become important in specific situations.

In interpreting the results of this study, consideration must be given to the pharmacokinetics of the drugs studied as well as the ventilatory variability seen among animals and across experimental days. Protocol 1 illustrates the considerable day-to-day variability seen in awake dogs. The variability seen in this study is similar to that found by Hirshman *et al.*[17] Because of this variability, control experiments were performed on each day, but because of the relatively long half-life of DMED,[18] the control experiments always preceded the administration of DMED. Thus, there could be a time effect not detected by our study design. The long half-life of DMED does ensure relatively consistent drug effects over the time period that the ventilatory tests were made, even after a bolus injection. The effects of isoflurane may also change with time; however, the results of Hirshman *et al.*[17] after 3 h of isoflurane are comparable to ours after 60–90 min of isoflurane.

DMED, when given to awake dogs, seemed to have opposing dose-related effects on the resting ventilation. This stimulation at the high doses is interesting, because the dogs remained apparently asleep, and could result from a central α_1 agonist effect. However, in protocol 3, when 20.0 μg/kg DMED was combined with 1.5% isoflurane, a substantial depression in ventilation with a 9-mmHg increase in Pa_{CO_2} (over 1.5% isoflurane alone) was found. Thus, whatever was causing the ventilatory stimulation at the higher doses was abolished by isoflurane. The effects of DMED on resting ventilation when given alone or combined with a low or high dose of isoflurane are relatively small. This is similar to the lack of increase in Pa_{CO_2} in rats when similar doses of DMED were used alone or in combination with alfentanil.[19]

The effects of DMED on the hypoxic and hypercapnic ventilatory reflexes are very important because depression of these reflexes may increase the risk of ventilatory failure. The hypoxic drive was relatively unaffected, even at the highest doses. As also found by Hirshman *et al.*,[17] isoflurane reduced the hypoxic response by almost half. The 1 MAC combination of isoflurane and DMED produced a hypoxic response intermediate between the awake controls and the isoflurane response. Although these data indicate relatively little effect on the hypoxic response, there may be species variations in drug effects of the hypoxic ventilatory response. α_2 Receptors have been found in the carotid body of the cat, and the α_2 agonist guanabenz reduced the hypoxic ventilatory response.[20] In humans, 1 MAC isoflurane essentially eliminates the hypoxic response,[16] so it would not be appropriate to extrapolate the results of this study directly to the human hypoxic response. The role of the α_2 receptors in the hypoxic ventilatory response in different species needs to be explored more fully.

The response to hypercapnia has been traditionally used as a sensitive test of ventilatory depression. DMED alone caused a decrease in the slope of the hypercapnic response, but there was a plateau in the amount of depression as the dose increased (table 1). This may be due to a countering effect of the same mechanism that caused the stimulation of resting ventilation seen at the high doses. Thus, when this stimulating effect was abolished by 1.5% isoflurane in protocol 3, a clearer dose-related decrease in slope was seen. At 20 μg/kg DMED, four of the six dogs showed no response to hypercapnia at all.

Because DMED is a highly receptor-specific drug, it is possible to reverse its effects selectively with a specific α_2 receptor antagonist like ATI. When given alone to isoflurane-anesthetized dogs, ATI caused a mild stimulation of resting ventilation, and a more pronounced increase in the slope of the CO_2 response. This could be due to a nonspecific analeptic effect of ATI (we did see an arousal effect when lower levels of isoflurane was used) or could be due to a tonic stimulation of α_2 receptors under isoflurane anesthesia. The central pharmacology of α-adrenergic receptors is quite complex, and it is possible that ATI acting on presynaptic α_2 receptors caused an increased release of central norepinephrine that stimulated ventilation through unblocked α_1 receptors. In any case, this effect of ATI alone complicates our interpretation of its ability to reverse DMED. Although the combination of DMED and ATI had essentially no ventilatory effects, this could be interpreted simply as an additive result of the two drugs and not a specific reversal of DMED. Further studies are needed to investigate fully this central interaction of α_2 agonists and antagonists during inhalational anesthesia.

In conclusion, we investigated several aspects of the ventilatory effects of a wide dose range of DMED in dogs. The ventilatory depression seen was mild, although when a relatively large dose was combined with 1.5% isoflurane, significant depression of the hypercapnic response was seen. However, reduction of the isoflurane concentration to maintain a constant MAC level resulted in less depres-

sion than that with isoflurane alone, and thus DMED may be a useful adjunct to isoflurane anesthesia.

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