Cardiopulmonary evaluation of the use of medetomidine hydrochloride in cats

Leigh A. Lamont, DVM; Barret J. Bulmer, DVM; Kurt A. Grimm, DVM, MS; William J. Tranquilli, DVM, MS; David D. Sisson, DVM, MS

Objective—To evaluate the cardiovascular effects of the α_2-adrenergic receptor agonist medetomidine hydrochloride in clinically normal cats.

Animals—7 clinically normal cats.

Procedure—Cats were anesthetized with isoflurane, and thermodilution catheters were placed for measurement of central venous, pulmonary, and pulmonary capillary wedge pressures and for determination of cardiac output. The dorsal pedal artery was catheterized for measurement of arterial blood pressures and blood gas tensions. Baseline variables were recorded, and medetomidine (20 µg/kg of body weight, IM) was administered. Hemodynamic measurements were repeated 15 and 30 minutes after medetomidine administration.

Results—Heart rate, cardiac index, stroke index, rate-pressure product, and right and left ventricular stroke work index significantly decreased from baseline after medetomidine administration, whereas systemic vascular resistance and central venous pressure increased. However, systolic, mean, and diastolic arterial pressures as well as arterial pH, and oxygen and carbon dioxide tensions were not significantly different from baseline values.

Conclusions and Clinical Relevance—When administered alone to clinically normal cats, medetomidine (20 µg/kg, IM) induced a significant decrease in cardiac output, stroke volume, and heart rate. Arterial blood pressures did not increase, which may reflect a predominant central α_2-adrenergic effect over peripheral vascular effects. (*Am J Vet Res* 2001;62:1745–1762)

Medetomidine hydrochloride is a synthetic α_2-adrenoceptor agonist approved for use as a sedative-analgesic in dogs by the FDA:Center for Veterinary Medicine. It is known for its selectivity, with an α_2-to-α_1-receptor binding ratio of 1,620, compared with ratios of 160, 260, and 220 for xylazine hydrochloride, detomidine hydrochloride, and clonidine hydrochloride, respectively.[1-3] In contrast to many commonly used drugs such as acepromazine maleate, ketamine hydrochloride, and isoflurane, medetomidine and other α_2-agonists have a unique spectrum of activity, inducing sedation, analgesia, anxiolysis, and muscle relaxation, while being completely reversible with specific antagonists.[4-8] The availability of atipamezole, an α_2-antagonist that is 200 to 300 times more specific for the α_2-adrenoceptor than traditional antagonists such as yohimbine, has meant that the effects of medetomidine can be reliably and safely reversed if desired.[3] The sedative effects of medetomidine are attributed to supraspinal activation of α_2-adrenoceptors located on adrenergic neurons in the locus ceruleus that mediate inhibition of norepinephrine release.[1,9] Analgesia is mediated largely at the level of the spinal cord by activation of dorsal horn α_2-adrenoceptors located presynaptically on primary afferent nociceptive fibers and postsynaptically on projection neurons. Receptor activation results in diminished release of neurotransmitters and neuronal hyperpolarization that ultimately contributes to antinociception.[10] During maximal effect, treated animals are relaxed, recumbent, and amenable to physical restraint.[2,11]

Separate from its CNS effects, medetomidine also binds peripheral α_2-adrenoceptors located in vascular smooth muscle, resulting in vasoconstriction and an increase in systemic vascular resistance.[9,12,13] In clinically normal dogs, medetomidine decreases **cardiac output (CO)** primarily as a consequence of this increase in afterload; however, the decrease in CO may be exacerbated by an accompanying and potentially profound bradycardia.[14-16] Medetomidine-induced bradycardia is a result of an initial vagal stimulation mediated through arterial baroreceptor reflexes responding to an increase in arterial blood pressure and diminished CNS sympathetic outflow.[13-16]

In cats, medetomidine has been reported to cause bradycardia[2,11,17-21] and hypertension,[19-21] followed by varying degrees of hypotension.[19,20] However, hemodynamic effects have not been extensively investigated in this species. We could only find 1 report of invasive cardiovascular measurements in cats following medetomidine administration, but these cats were anesthetized with isoflurane at the time of measurement.[21] The objective of the study reported here was to determine the hemodynamic effects of medetomidine administered alone to clinically normal cats.

Materials and Methods

Animals—This study was approved by the Office of Laboratory Animal Care of the University of Illinois. It was conducted in compliance with local and federal guidelines governing laboratory animal care and housing. Seven cats (5 males, 2 females) weighing between 3.6 and 6.8 kg and ranging in age from 2 to 7 years were studied. The mean weight was 5.1 kg, and the mean age was 4 years. Prior to the study, all cats were determined to be clinically normal on the basis of routine physical examinations, ECG, and echocardiography.

Received Dec 11, 2000.
Accepted Feb 28, 2001.
From the Department of Veterinary Clinical Medicine, College of Veterinary Medicine, University of Illinois, Urbana, IL 61801.
Supported in part by the Department of Veterinary Clinical Medicine, University of Illinois, Urbana, Ill, and Pfizer Animal Health, New York, NY.
The authors thank Genia Sarr and Anglia Hicks for technical assistance.

Cardiac and arterial catheterization—Anesthesia was induced with isoflurane in oxygen in an induction chamber, followed by endotracheal intubation. A light surgical plane of anesthesia was maintained, using a pediatric circle breathing circuit to deliver isoflurane and oxygen. Cats were positioned in right lateral recumbency, and a 5-F thermodilution catheter was introduced into the left jugular vein and connected to a saline (0.9% NaCl) solution-filled calibrated pressure transducer [a] placed at the level of the manubrium for measurement of **systolic**, **diastolic**, and **mean pulmonary arterial pressures (SPAP, DPAP**, and **MPAP**, respectively), **central venous pressures (CVP)**, **pulmonary capillary wedge pressures (PCWP)**, and CO. The catheter was advanced under fluoroscopic guidance until the distal port was positioned in the pulmonary artery and the characteristic pulmonary arterial pressure waveform was displayed on the oscilloscope. All pressure data were recorded on a multiple channel physiograph,[b] and CO was measured, using a thermodilution CO computer.[c] The technique used for obtaining PCWP has been outlined previously.[22] A 22-gauge catheter was placed percutaneously in the dorsal pedal artery of each cat to facilitate measurement of **systolic**, **diastolic**, and **mean arterial blood pressures (SAP, DAP**, and **MAP**, respectively)[d] and for collection of samples to measure arterial blood gas tensions.[e] The blood gas machine was calibrated prior to sample introduction. Catheters were secured in place, and isoflurane was discontinued. The cats were allowed to recover in a calm and quiet environment for a minimum of 30 minutes after extubation and prior to baseline data collection.

Study protocol—For collection of baseline data, each unsedated cat was minimally restrained in right lateral recumbency. Values for **heart rate (HR)**, SAP, DAP, MAP, SPAP, DPAP, MPAP, CVP, PCWP, and CO were recorded, and an arterial blood gas sample was collected anaerobically and stored on ice for later analysis. Cardiac output was determined by injecting 1 ml of ice-cold saline (0.9% NaCl) solution into the proximal port of the thermodilution catheter. Three injections were made 1 minute apart, and measurements were averaged to obtain a mean CO for each recording period. These baseline conditions closely simulated periods of physical restraint needed to facilitate noninvasive diagnostic procedures such as radiography or ultrasonography, which are common clinical procedures.

After baseline measurements were made, medetomidine (20 µg/kg of body weight, IM) was injected, and cats were left undisturbed for 15 minutes. Hemodynamic measurements were recorded 15 and 30 minutes following injection. At the conclusion of the study, catheters were removed, and butorphanol tartrate (0.4 mg/kg, IM) was administered.

Calculations and statistical analyses—**Cardiac index (CI)**, **stroke volume (SV)**, **stroke index (SI)**, **rate-pressure product (RPP)**, **right ventricular stroke work index (RVSWI)**, **left ventricular stroke work index (LVSWI)**, **systemic vascular resistance (SVR)**, and **pulmonary vascular resistance (PVR)** were calculated for each period according to the following formulas:

$$CI\ (L/min/m^2) = CO/BSA$$
$$SV\ (ml/beat) = CO/HR$$
$$SI\ (ml/beat/m^2) = SV/BSA$$
$$RPP\ (beats/min \times mm\ Hg) = HR \times SAP$$
$$RVSWI\ (g \times m/m^2) = 1.36 \times ([MPAP - CVP]/100) \times SI$$
$$LVSWI\ (g \times m/m^2) = 1.36 \times ([MAP - PCWP]/100) \times SI$$
$$SVR\ (dynes \times [s/cm^5]) = ([MAP - CVP]/CO) \times 80$$
$$PVR\ (dynes \times [s/cm^5]) = ([MPAP - PCWP]/CO) \times 80$$

where body surface area (**BSA**) is calculated according to the formula:

$$BSA\ (m^2) = (10.0 \times [body\ weight\ in\ g]^{2/3})/10^4.$$

Mean values for all hemodynamic variables over time were compared by use of a 1-way ANOVA for repeated measures. When significant ($P \leq 0.05$) differences were detected, a pairwise comparison was performed between means, using the Tukey test.

Results

Cats recovered well from isoflurane anesthesia and cardiac catheterization. During baseline data collection, all cats were amenable to handling and did not struggle. One of the cats vomited approximately 3 minutes after medetomidine administration, but all cats became sedate, relaxed, and laterally recumbent after receiving the drug. None of the cats required restraint during subsequent data collection, and all recovered smoothly from the sedative effects of the drug. No cats required atipamezole administration after completion of the study, and all were alert, responsive, and ready to return to their cage 1 hour after medetomidine injection.

Heart rate decreased significantly ($P < 0.001$) to 58% of the baseline value 15 minutes after medetomidine administration and remained at 62% of baseline value at 30 minutes (**Fig 1**; **Table 1**). Systemic vascular resistance increased from baseline; however, the difference was only significant ($P = 0.002$) at 15 minutes. There was no significant change in SAP, MAP, and DAP over time. In 4 of the 7 cats, small decreases in blood pressure were recorded over time, whereas in the remaining 3 cats, blood pressure increased slightly after medetomidine administration. Cardiac index decreased significantly ($P < 0.001$) to 37% of baseline at 15 minutes and remained at 50% of baseline 30 minutes after medetomidine administration (**Fig 2**). Stroke

Table 1—Hemodynamic effects of medetomidine hydrochloride adminsitration (20 µg/kg of body weight, IM) in 7 clinically normal cats

	Time		
Variables	**Baseline**	**15 min**	**30 min**
HR (beats/min)	194 ± 4	113 ± 8*	121 ± 6*
SAP (mm Hg)	177 ± 7	167 ± 11	156 ± 11
MAP (mm Hg)	139 ± 6	140 ± 10	130 ± 10
DAP (mm Hg)	113 ± 6	121 ± 9	110 ± 9
PAP (mm Hg)	16.0 ± 0.9	15.9 ± 1.4	16.0 ± 1.1
CVP (mm Hg)	4.2 ± 1.1	8.0 ± 1.1*	7.6 ± 1.3*
PCWP (mm Hg)	2.9 ± 0.6	5.6 ± 1.5	5.2 ± 1.1
CO (L/min)	1.30 ± 0.09	0.49 ± 0.10*	0.64 ± 0.09*
CI (L/min/m^2)	4.42 ± 0.40	1.64 ± 0.28*	2.19 ± 0.35*
SV (ml/beat)	6.8 ± 0.565	4.4 ± 0.707*	5.3 ± 0.627
SI (ml/beat/m^2)	23.0 ± 2.1	14.9 ± 2.2*	18.3 ± 2.5
SVR (dynes × s/cm^5)	8506 ± 589	27229 ± 5616*	17968 ± 3367
PVR (dynes × s/cm^5)	844 ± 94	2094 ± 428*	1469 ± 234
RPP (beats/min × mm Hg)	34232 ± 1063	18907 ± 1891*	18741 ± 1318*
RVSWI (g × m/m^2)	0.0036 ± 0.00032	0.0016 ± 0.00028*	0.0022 ± 0.00051*
LVSWI (g × m/m^2)	0.042 ± 0.0041	0.026 ± 0.0033*	0.030 ± 0.0039*

Data are reported as mean ± SEM.
*Significantly ($P < 0.05$) different from baseline value.
HR = Heart rate. SAP = Systolic arterial pressure. MAP = Mean arterial pressure. DAP = Diastolic arterial pressure. PAP = Mean pulmonary arterial pressure. CVP = Central venous pressure. PCWP = Pulmonary capillary wedge pressure. CO = Cardiac output. CI = Cardiac index. SV = Stroke volume. SI = Stroke index. SVR = Systemic vascular resistance. PVR = Pulmonary vascular resistance. RPP = Rate pressure product. RVSWI = Right ventricular stroke work index. LVSWI = Left ventricular stroke work index.

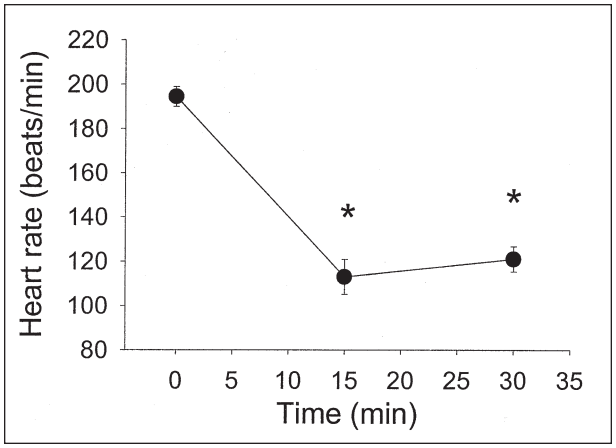

Figure 1—Mean (± SEM) heart rate in 7 cats before and after administration of medetomidine hydrochloride (20 µg/kg of body weight, IM). *Significantly ($P < 0.05$) different from baseline value.

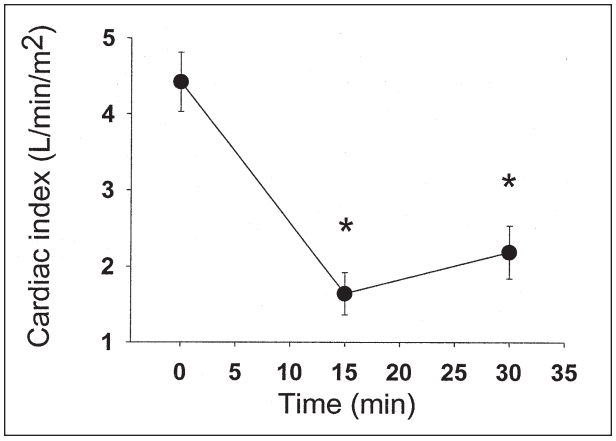

Figure 2—Mean (± SEM) cardiac index in 7 cats before and after medetomidine (20 µg/kg, IM) administration. *See* Figure 1 for key.

index also decreased significantly to 65% of baseline at 15 minutes, and although it remained less than the baseline value at 30 minutes, this difference was not significant (**Fig 3**). Mean pulmonary arterial pressure remained unchanged over time, whereas CVP increased significantly ($P = 0.008$) 15 and 30 minutes after medetomidine administration. Although PCWP increased, differences from the baseline value were not significant. The RPP decreased significantly ($P < 0.001$) to 55% of baseline 15 minutes after medetominde adminsitration and remained decreased at 30 minutes. Left ventricular stroke work index decreased significantly ($P < 0.001$) to 61% of baseline at 15 minutes and 71% of baseline at 30 minutes. Right ventricular stroke work index also decreased significantly ($P < 0.002$) to 43% of baseline at 15 minutes and 62% of baseline at 30 minutes. Pulmonary vascular resistance increased, but the difference was significant ($P = 0.007$) only at 15 minutes after medetomidine administration.

There was no significant change in pH 15 or 30 minutes after medetomidine injection, although pH did increase in all cats (**Table 2**). Although Pa_{O_2}, increased and Pa_{CO_2} decreased, these differences were

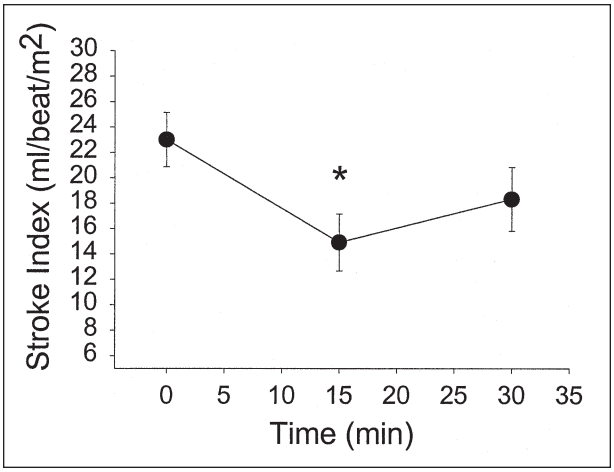

Figure 3—Mean (± SEM) stroke index in 7 cats before and after medetomidine (20 µg/kg, IM) administration. *See* Figure 1 for key.

Table 2—Effects of medetomidine administration (20 µg/kg, IM) on arterial blood gas variables in 6 clinically normal cats

	Time		
Variables	**Baseline**	**15 min**	**30 min**
pH	7.291 ± 0.022	7.326 ± 0.02	2 7.336 ± 0.023
$Paco_2$ (mm Hg)	38.98 ± 2.20	34.90 ± 0.97	34.78 ± 0.72
Pao_2 (mm Hg)	112.53 ± 4.93	111.27 ± 4.24	120.52 ± 7.84
HCO_3 (mmol/L)	18.55 ± 1.05	18.58 ± 1.26	18.85 ± 1.13

Data are reported as mean ± SEM.
See Table 1 for key.

not significant, compared with baseline values. Arterial HCO_3 concentrations increased slightly; however, differences were not significant. Blood gas data were only recorded for 6 of the 7 cats, because results for 1 cat were obviously in error. The reasons for this outlier are unknown, but sample mishandling or measurement errors are possibilities.

Discussion

Medetomidine is commonly used in clinical practice as a sedative-analgesic agent in dogs and cats, and although there are several studies documenting its hemodynamic effects in dogs,[16,19,23] to our knowledge there are no reports of the cardiovascular effects of medetomidine used alone in conscious clinically normal cats instrumented with indwelling cardiac catheters. Although lower than the recommended label dose of 40 to 150 µg/kg, we chose to administer medetomidine at 20 µg/kg, IM. This decision was made on the basis of our extensive clinical experience with the drug at the University of Illinois Small Animal Teaching Hospital over the past several years. This dose of medetomidine reliably induces sedation, analgesia, and muscle relaxation that lasts for approximately 30 to 60 minutes.

Values for baseline HR, MAP, CO, and SV were in line with those reported elsewhere in conscious cats.[24,25] Presumably our cats were under some degree of stress during initial baseline data collection, because although they were all accustomed to being handled, they were not specifically trained to lie in right lateral

recumbency for extended periods. This protocol was designed to mimic the clinical situation in which medetomidine is most often used; that is, in patients requiring chemical restraint to facilitate completion of various diagnostic or noninvasive therapeutic procedures. The mean baseline HR of 194 beats/min and mean MAP of 139 mm Hg likely reflect a moderate amount of stress comparable to that observed in many cats undergoing restraint for diagnostic evaluation.

The decrease in HR induced by medetomidine was pronounced. Two of the 7 cats had a HR < 100 beats/min. α_2–Agonist-induced bradycardia is typically attributed to a baroreceptor-mediated response to an increase in SVR and to diminished CNS sympathetic outflow.[1,13,15,16,26,27] This is supported by our data, as SVR was significantly increased at 15 minutes, compared with the baseline value, and remained greater than the baseline value 30 minutes after medetomidine administration. However, the difference at 30 minutes was not significant. This increase was most likely related to the α_2-mediated vasoconstrictive effects of medetomidine.[13,28]

In dogs, arterial blood pressure has a biphasic response after α_2-agonist administration, with an initial increase followed by a gradual decrease.[5,19] Similar results have been seen in cats given medetomidine systemically or epidurally during general anesthesia with isoflurane.[20,21] In our study, we did not find significant increases in SAP, MAP, and DAP after medetomidine administration, compared with baseline values. In fact, in 4 of the 7 cats, SAP and MAP were decreased 15 minutes after medetomidine administration. We chose to record measurements on the basis of data reported previously indicating that peak decreases in HR and peak increases in MAP develop approximately 15 minutes after IM injection of medetomidine.[21] One possible explanation for this apparent discrepancy is that in stressed cats with high concentrations of circulating endogenous catecholamines, relatively high baseline arterial pressures prevented substantial increases in pressure values from being recognized. A second explanation could be that in the absence of inhalant anesthetic-induced decreases in vascular tone and baseline blood pressure, the central sympatholytic effects of medetomidine predominate, resulting in equivocal alterations in blood pressure. Clearly, another possibility is that potential early and transient changes in pressure were not recorded because of the timing of data collection. Although the differences were not significant, we did observe an increase in diastolic arterial pressure and a decrease in systolic arterial pressure. Diminished pulse pressure is likely a result of an increase in SVR secondary to peripheral vasoconstriction.

Cardiac output and CI decreased significantly following medetomidine administration, with the reductions comparable to results reported elsewhere.[21] A decrease in CO has been attributed by other investigators to bradycardia rather than reduced SV.[29,30] However, our cats had a concurrent reduction in SI that also contributed to a reduced CI. This reduction in SV may be the result of diminished central sympathetic outflow, or it may be a direct myocardial depressant effect. Although we did not measure any index of ventricular contractility, other studies.[13,27] evaluating dexmedetomidine in autonomically blocked dogs, using load-insensitive indices of contractility and isolated ventricular myocardial cell preparations, suggest that this effect is likely related to increased SVR affecting cardiac loading conditions in combination with CNS depression rather than direct changes in contractilityCentral venous pressure increased significantly 15 and 30 minutes following medetomidine administration, which may be attributed to α_2–adrenergic-mediated reductions in venous capacitance in combination with bradycardia and diminished SV.[16] Mean pulmonary arterial pressure did not significantly change from baseline after medetomidine administration, and medetomidine-induced alterations in PAP have not been reported previously in dogs or cats.[16] This may be the result of the low density of α_2-receptors in the pulmonary vasculature relative to systemic vessels and the minor role of neuronal regulation in the pulmonary circulation.[29-31]

Pulmonary capillary wedge pressure is an approximation of left ventricular preload.[5] Although PCWP increased in our study, these differences were not significant. Pypendop et al[16] reported a transient increase in PCWP in dogs after IV administration of medetomidine that appeared to be dose dependent.

Rate-pressure product is an estimate of myocardial oxygen consumption. In our study, RPP decreased significantly after medetomidine administration, likely because the reduction in HR caused decreased myocardial oxygen demand and myocardial work.[5] Decreases in LVSWI and RVSWI were related to a decreased SI and, to a lesser degree, increases in CVP and PCWP. These changes are comparable to those described elsewhere for dogs.[16]

Analysis of blood gas tensions for the 6 cats indicated that our cats were mildly acidotic prior to medetomidine administration, with a mean arterial pH of 7.291 (reference range, 7.31 to 7.46).[32] This could have been the result of mild hypercapnia, with a mean Pa_{CO_2} of 38.98 mm Hg at baseline (reference range, 25.2 to 36.8 mm Hg).[32] However, HCO_3 concentrations at baseline were within reference range (mean, 18.55 mEq/L; reference range, 14.4 to 21.6 mEq/L).[32] Although not significant, pH increased slightly 15 and 30 minutes after medetomidine injection. This change can be accounted for by an accompanying decrease in Pa_{CO_2}.[33] Interestingly, other authors have reported a decrease in arterial pH and an increase in Pa_{CO_2} after medetomidine administration in dogs and cats anesthetized with isoflurane.[20,23,34] The reason for this discrepancy likely involves the compounding respiratory depressant effects that develop when medetomidine is combined with a potent inhalant anesthetic such as isoflurane.[35]

Medetomidine has also been reported to cause a decrease in Pa_{O_2} in dogs[23,36,37] and cats.[20] This was not observed in our study. Instead, Pa_{O_2} increased 15 and 30 minutes after medetomidine administration, compared with baseline values, although these differences were not significant. The reasons for these observations are unclear, but one hypothesis would be that tis-

sue oxygen utilization is decreased during peak medetomidine effect. We were interested in evaluating PvO_2 concurrently, and mixed venous sample collection was attempted. Unfortunately, the narrow diameter of the thermodilution catheter prevented us from obtaining samples from the pulmonary artery.

[a]American Edwards Lab Inc, Santa Ana, Calif.
[b]5/6H physiograph, Gilson Medical Electronics, Middleton, Wis.
[c]Cardiac output computer model 9520A, American Edwards Laboratories, Irvine, Calif.
[d]Datascope Passport XG, Datascope Corp, Paramus, NJ.
[e]Model 288 blood gas system, Ciba-Corning, Irvine, Calif.

References

1. Virtanen R. Pharmacological profiles of medetomidine and its antagonist, atipamezole. *Acta Vet Scand Suppl* 1989;85:29–37.
2. Stenberg D, Salven P, Miettinen MV. Sedative actions of the alpha2 agonist medetomidine in cats. *J Vet Pharmacol Ther* 1987;10: 319–323.
3. Thurmon JC, Tranquilli WJ, Benson GJ. Preanesthetics and anesthetic adjuncts. In: Thurmon JC, Tranquilli WJ, Benson GJ, eds. *Lumb and Jones veterinary anesthesia*. 3rd ed. Baltimore: The Williams & Wilkins Co, 1996;183–209.
4. Gleed RD. Tranquilizers and sedatives. In: Short CE, ed. *Principles and practice of veterinary anesthesia*. Baltimore: The Williams & Wilkins Co, 1987;16–27.
5. Hall LW, Clarke KW. Veterinary anesthesia. 2nd ed. London: Bailliere Tindall, 1991;52–64.
6. Maze M, Tranquilli W. Alpha-2 adrenoceptor agonists: defining the role in clinical anesthesia. *Anesthesiology* 1991;74:581–605.
7. Vaha-Vahe T. The clinical efficacy of medetomidine. *Acta Vet Scand Suppl* 1989;85:151–154.
8. Vainio O. Introduction to the clinical pharmacology of medetomidine. *Acta Vet Scand Suppl* 1989;85:85–88.
9. Scheinin M, MacDonald E. An introduction to the pharmacology of alpha 2 adrenoceptors in the central nervous system. *Acta Vet Scand Suppl* 1989;85:11–19.
10. Millan MJ. α_2-adrenergic mechanisms of analgesia: strategies for improving their therapeutic window and identification of a novel, potent α_{2A}-adrenergic receptor agonist, S18616. *Adv Pharmacol* 1998;42:575–579.
11. Vaha-Vahe T. Clinical effectiveness of atipamezole as a medetomidine antagonist in cats. *J Small Anim Pract* 1990;31:193–197.
12. Ruskoaho H. Subtypes and functions of alpha adrenoceptors. *Acta Vet Scand* 1986;82:17-28.
13. de Morais HS, Muir WW. The effects of medetomidine on cardiac contractility in autonomically blocked dogs. *Vet Surg* 1995; 24:356–364.
14. Alibhai HK, Clarke KW, Lee YH, et al. Cardiopulmonary effects of combinations of medetomidine hydrochloride and atropine sulfate in dogs. *Vet Rec* 1996;138:11–13.
15. Vainio O, Palmu L. Cardiovascular and respiratory effects of medetomidine in dogs and influence of anticholinergics. *Acta Vet Scand* 1989;30:401–408.
16. Pypendop BH, Verstegen JP. Hemodynamic effects of medetomidine in the dog: a dose titration study. *Vet Surg* 1998;27:612–622.
17. Verstegen JP, Fargetton X, Ectors F. Medetomidine/ketamine anesthesia in cats. *Acta Vet Scand Suppl* 1989;85:117–123.
18. Young LE, Jones RS. Clinical observations on medetomidine/ketamine anesthesia and its antagonism by atipamezole in the cat. *J Small Anim Pract* 1990;31:221–224.
19. Savola JM. Cardiovascular actions of medetomidine and their reversal by atipamezole. *Acta Vet Scand* 1989;85:39–47.
20. Duke T, Cox AK, Remedios AM, et al. The cardiopulmonary effects of placing fentanyl or medetomidine in the lumbosacral epidural space of isoflurane-anesthetized cats. *Vet Surg* 1994;23:149–155.
21. Golden AL, Bright JM, Daniel GB, et al. Cardiovascular effects of the α_2-adrenergic receptor agonist medetomidine in clinically normal cats anesthetized with isoflurane. *Am J Vet Res* 1998;59: 509–513.
22. Thomas WP, Sisson D. Cardiac Catheterization and angiocardiography. In: Fox PR, Sisson D, Moise NS, eds. *Textbook of canine and feline cardiology, principles and clinical practice*. 2nd ed. Philadelphia: WB Saunders Co, 1999;173–192.
23. Pypendop B, Serteyn D, Verstegen J. Hemodynamic effects of medetomidine- midazolam-butorphanol combinations and reversibility by atipamezole in dogs. *Am J Vet Res* 1996;57:724–730.
24. Ingwersen W, Allen DG, Dyson DH, et al. Cardiopulmonary effects of a ketamine/acepromazine combination in hypovolemic cats. *Can J Vet Res* 1988;52:423–427.
25. Zsombor Murray E. Noninvasive blood pressure monitoring. In: Wingfield WE, ed. *Veterinary emergency medicine secrets*. Philadelphia: Hanley & Belfus Inc, 1997;422–426.
26. Savola JM, Ruskoahom H, Puurunen J, et al. Evidence for medetomidine as a selective and potent agonist at α_2-adrenoreceptors. *J Auton Pharmacol* 1986;5:275–284.
27. Keegan RD, Greene SA, Bagley RS, et al. Effects of medetomidine administration on intracranial pressure and cardiovascular variables of isoflurane-anesthetized dogs. *Am J Vet Res* 1995;56:193–198.
28. Housmans PR. Effects of dexmedetomidine on contractility, relaxation and intracellular calcium transients of isolated ventricular myocardium. *Anesthesiology* 1990;73:919–922.
29. Serteyn D, Coppens P, Jones R, et al. Circulatory and respiratory effects of combination medetomidine-ketamine in beagles. *J Vet Pharmacol Ther* 1993;16:199–206.
30. Vickery RG, Sheridan BC, Segal IS, et al. Anesthetic and hemodynamic effects of stereoisomers of medetomidine, an α_2-adrenergic agonist, in halothane anesthetized dogs. *Anesth Analg* 1988;67:611–615.
31. Stoelting RK. Pulmonary circulation. In: Stoelting RK, ed. *Pharmacology and physiology in anesthetic practice*. 2nd ed. Philadelphia: JB Lippincott Co, 1991;685–691.
32. Haskins SC. Blood gases and acid-base balance: clinical interpretation and therapeutic implications. In Kirk RW, ed. *Current veterinary therapy VIII*. Philadelphia: WB Saunders Co, 1983;201–215.
33. Muir WW, Hubbell JAE, Skarda RT, et al. Acid base balance and blood gases. In: Muir WW, Hubbell JAE, Skarda RT, et al, eds. *Handbook of veterinary anesthesia*. 3rd ed. St Louis: Mosby Inc, 2000;284–301.
34. Pypendop B, Verstegen J. Cardiorespiratory effects of a combination of medetomidine, midazolam, and butorphanol in dogs. *Am J Vet Res* 1999;60:1148–54.
35. Bloor BC, Abdul-Rasool I, Temp J, et al. The effects of medetomidine, an alpha 2- adrenergic agonist, on ventilatory drive in the dog. *Acta Vet Scand Suppl* 1989;85:65–70.
36. Cullen LK, Reynoldson JA. Xylazine or medetomidine premedication before propofol anaesthesia. *Vet Rec* 1993;132:378–383.
37. Vainio O. Reversal of medetomidine-induced cardiovascular and respiratory changes with atipamezole in dogs. *Vet Rec* 1990;127:447–450.