Effects of glycopyrrolate on cardiorespiratory function in horses anesthetized with halothane and xylazine

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Objective—To evaluate cardiopulmonary effects of glycopyrrolate in horses anesthetized with halothane and xylazine.

Animals—6 horses.

Procedure—Horses were allocated to 2 treatment groups in a randomized complete block design. Anesthesia was maintained in mechanically ventilated horses by administration of halothane (1% end-tidal concentration) combined with a constant-rate infusion of xylazine hydrochloride (1 mg/kg/h, IV). Hemodynamic variables were monitored after induction of anesthesia and for 120 minutes after administration of glycopyrrolate or saline (0.9% NaCl) solution. Glycopyrrolate (2.5 µg/kg, IV) was administered at 10-minute intervals until heart rate (HR) increased at least 30% above baseline or a maximum cumulative dose of 7.5 µg/kg had been injected. Recovery characteristics and intestinal auscultation scores were evaluated for 24 hours after the end of anesthesia.

Results—Cumulative dose of glycopyrrolate administered to 5 horses was 5 µg/kg, whereas 1 horse received 7.5 µg/kg. The positive chronotropic effects of glycopyrrolate were accompanied by an increase in cardiac output, arterial blood pressure, and tissue oxygen delivery. Whereas HR increased by 53% above baseline values at 20 minutes after the last glycopyrrolate injection, cardiac output and mean arterial pressure increased by 38% and 31%, respectively. Glycopyrrolate administration was associated with impaction of the large colon in 1 horse and low intestinal auscultation scores lasting 24 hours in 3 horses.

Conclusions and Clinical Relevance—The positive chronotropic effects of glycopyrrolate resulted in improvement of hemodynamic function in horses anesthetized with halothane and xylazine. However, prolonged intestinal stasis and colic may limit its use during anesthesia. (*Am J Vet Res* 2004;65:456–463)

Heart rate (HR) is 1 of the major determinants of **cardiac output (CO)**.[1,2] During anesthesia in horses, it is recommended that clinically important bradycardia should be treated by administration of an anticholinergic agent, especially when the bradycardia is associated with hypotension and other signs of poor tissue perfusion.[3] In small animals, anticholinergics, such as atropine and glycopyrrolate, are commonly used to treat bradycardia associated with the use of opioids during inhalant anesthesia.[4,5] Glycopyrrolate is a muscarinic receptor antagonist that has the advantage of not crossing the blood-brain and placental barriers, resulting in decreased likelihood of CNS and fetal effects.[6] In anesthetized dogs, glycopyrrolate (5 to 10 µg/kg, IV) effectively reverses bradycardia (HR < 65 beats/min) and increases **arterial blood pressure (ABP)**.[5] Because of its nonspecific selectivity for muscarinic cholinergic receptors, glycopyrrolate results in positive chronotropism that is accompanied by effects on other organ systems, including decreased salivation, decreased airway secretions, bronchodilation, and transient decreased gastrointestinal motility.[7] The decrease in gastrointestinal motility is a major limitation for the use of glycopyrrolate and other nonselective muscarinic antagonists in anesthetized horses.[8-11] Consequently, limited information is available regarding the use of glycopyrrolate for treating horses with intraoperative bradycardia. Evidence exists that relatively low doses of glycopyrrolate (2.5 to 5.0 µg/kg) are effective for the treatment of bradycardia in horses (defined as an HR < 30 beats/min), causing a substantial increase in HR and ABP.[12] However, it has not been determined whether this positive chronotropic effect is associated with an improvement in CO and tissue oxygen delivery.

The α_2-agonist agents, such as xylazine, are commonly administered before general anesthesia in horses. Concomitant use of α_2-agonists with inhalant anesthetics may be advantageous because of their analgesic, sedative, and muscle-relaxant effects, which decrease the concentration of inhalants required for maintaining anesthesia.[13] Although use of α_2-agonists before induction of general anesthesia has become a routine practice, the use of α_2-agonists by continuous infusion in conjunction with inhalant anesthetics has not been fully investigated and may lead to undesired adverse effects, such as vagally mediated bradycardia and

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decreases in CO and tissue oxygen delivery.[14-16] In horses, HRs as low as 20 beats/min have been recorded following IV injection of an α_2-agonist, and there is evidence that the associated decrease in CO is primarily attributable to the decrease in HR.[14] Bradycardia induced by the administration of α_2-agonists can be prevented by the administration of a low dose of glycopyrrolate (2.5 µg/kg), which results in improved CO and tissue oxygen delivery when the α_2-agonist (ie, xylazine) is used alone as a sedative[16] or is combined with ketamine and administered IV to induce anesthesia.[15] However, it is not known whether this improvement in cardiopulmonary function would still be evident during anesthesia with an inhalant or whether the anticholinergic would induce a clinically detectable delay in the return to normal intestinal motility during the postanesthetic period.

Our hypothesis for the study reported here was that a dose of glycopyrrolate capable of increasing HR by at least 30% during a clinical situation usually associated with bradycardia (defined as HR ≤ 30 beats/min) would result in an improvement of cardiopulmonary function (ie, HR, CO, and tissue oxygen delivery). It was also hypothesized that the use of relatively low doses of glycopyrrolate (up to 7.5 µg/kg) would not cause prolonged postanesthetic ileus or colic.

Materials and Methods

Animals—Six healthy adult horses (5 females and 1 male) that weighed (mean ± SD) 449.5 ± 28.8 kg were used in the study. Before starting the study, health status of each horse was assessed by means of a CBC count, serum biochemical analysis, and physical examination.

Food but not water was withheld for 12 hours before each experiment. The study was conducted in compliance with the guidelines of the Canadian Council on Animal Care, and the study was approved by the University of Guelph Animal Care Committee.

Insertion of instruments prior to induction of anesthesia—A local anesthetic solution (0.5 to 1.0 mL of 2% lidocaine) was injected SC over the jugular veins before catheters were inserted. A 14-gauge catheter[a] was inserted into the left jugular vein of each horse for use in administration of drugs and fluids during anesthesia. Two 8.5-F catheter introducers[b] were inserted approximately 30 cm apart in the right jugular vein. A 160-cm-long, balloon-tipped, flow-directed thermodilution catheter[c] was advanced through the first introducer until the catheter tip was positioned in the pulmonary artery; this catheter was used for intermittent assessment of CO by a thermodilution technique and measurement of **mean pulmonary artery pressure (MPAP)**. A polyethylene catheter (110 cm long, 2.9-mm outer diameter) was advanced through the second introducer until it was positioned in the cranial vena cava; this catheter was used for the measurement of **central venous pressure (CVP)** and the injection for thermodilution CO measurements. Catheter placement was verified by observing characteristic pressure waveforms on the screen of a monitor.[d]

Induction and maintenance of anesthesia—Xylazine hydrochloride[e] was administered as a preanesthetic medication (1.1 mg/kg, IV). Five minutes after administration of xylazine, anesthesia was induced by injection of ketamine hydrochloride[f] (2.2 mg/kg, IV). Horses were positioned in left lateral recumbency, intubated with a cuffed endotracheal tube, and connected to a circle breathing circuit.[g] Anesthesia was maintained by administration of halothane[h] in oxygen and by a constant-rate infusion of xylazine (1 mg/kg/h, IV), which was controlled by an infusion pump.[i] End-tidal halothane was maintained at 1.0% throughout the experiment by adjusting the vaporizer settings. Controlled mechanical ventilation was used to maintain eucapnia ($PaCO_2$ between 40 and 50 mm Hg), and lactated Ringer's solution was administered throughout the experiment (3 mL/kg/h, IV).

Insertion of instruments and general procedures after induction of anesthesia—A 20-gauge, over-the-needle catheter[j] was inserted into the facial or transverse facial artery to measure **systolic arterial pressure (SAP)**, **diastolic arterial pressure (DAP)**, and **mean arterial pressure (MAP)**.

After anesthesia was induced, all catheters were connected to pressure transducers[k] calibrated to a value of 0 at the level of the sternum. The pressure transducers were also calibrated against a mercury manometer before each experiment. A base-apex lead attachment was used for electrocardiographic monitoring. Arterial blood samples were collected for blood gas analysis[l] and determination of **hemoglobin (Hb)** concentration.[m] Blood gas samples were stored on ice and analyzed within 60 minutes after collection. Arterial blood gas values were adjusted on the basis of body temperature (ie, pulmonary artery temperature).

Measurements of CO were obtained by rapid (during a 3-second period) injection of 35 mL of cold (0° to 4°C) 5% dextrose solution into the catheter positioned in the cranial vena cava; these injections were accomplished by use of a specially built manual injector. To minimize the effects of increased intrapleural pressure on venous return and CO, mechanical ventilation of the anesthetized horses was interrupted briefly (< 20 seconds) during the determination of each thermodilution curve. At each recording period, data were analyzed by use of a CO computer,[n] and CO was calculated as the mean value for 3 thermodilution curves that yielded CO values within 10% of each other.

Derived hemodynamic and respiratory variables were calculated by use of standard equations. **Stroke volume (SV)** was calculated as follows: SV = CO/HR. **Systemic vascular resistance (SVR)** was calculated as follows: SVR = (MAP – CVP)/(CO × 79.9). **Arterial oxygen content (Ca_{O_2})** was calculated as follows: Ca_{O_2} = (1.39 × Hb concentration × arterial Hb saturation) + (0.0031 × Pa_{O_2}). **Oxygen delivery (DO_2)** was calculated as follows: DO_2 = CO × Ca_{O_2}.

Airway gas was continuously sampled from the proximal end of the endotracheal tube into an infrared gas analyz-

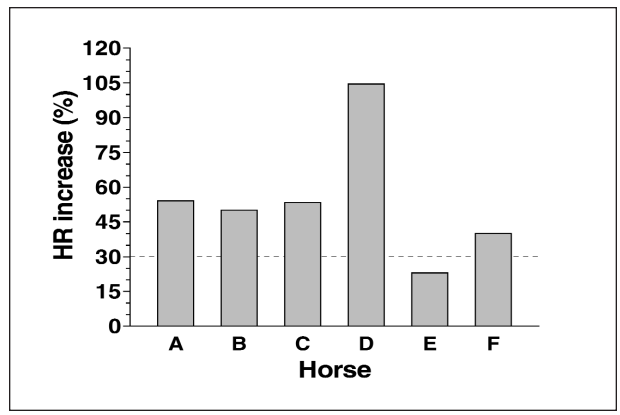

Figure 1—Percentage of heart rate (HR) increase above baseline values observed 10 minutes after IV administration of the last glycopyrrolate bolus in 6 horses anesthetized by administration of halothane and a constant-rate infusion of xylazine hydrochloride. Notice that 1 horse did not achieve the targeted HR (30% increase above baseline value; horizontal line) after receiving the maximum cumulative dose of glycopyrrolate (7.5 µg/kg).

er[d] at a sampling rate of 150 mL/min to monitor end-tidal halothane and end-tidal carbon dioxide concentrations. The gas analyzer was calibrated by use of a standard gas mixture[o] before each experiment.

Experimental design and treatments—The study was conducted by use of a randomized complete block design. Each horse received saline (0.9% NaCl) solution or glycopyrrolate,[p] with a minimum washout period of 14 days between treatments.

Before induction of anesthesia on the morning of each experiment, intestinal sounds were assessed by auscultation. Briefly, each of the 4 abdominal quadrants (ie, upper and lower on the left and right side) was auscultated. Two sites within each quadrant were auscultated (at least 2 min/site). There was a minimal delay (< 1 minute) between assessments at the various sites. A subjective score was assigned to each quadrant in accordance with a scoring system described eleswhere[11] (0, no bowel sounds; 1, mild, low-pitched crepitation-like sounds audible once per minute at both sites within a quadrant; 2, low-pitched crepitation-like sounds audible more than once per minute at both sites within a quadrant; 3, long and loud gurgling sounds audible once per minute at both sites within a quadrant; and 4, long and loud gurgling sounds audible more than once per minute at both sites within a quadrant. Scores were totaled for all 4 quadrants; thus, the possible scores ranged from 0 (total lack of motility) to 16.

Baseline cardiopulmonary variables were recorded between 30 and 45 minutes after induction (mean ± SD, 38.3 ± 4.5 minutes). Subsequently, each horse received 10 mL of saline solution IV (control treatment) or glycopyrrolate, which was administered IV as a bolus (2.5 µg/kg), at 10-minute intervals. Glycopyrrolate was administered until HR

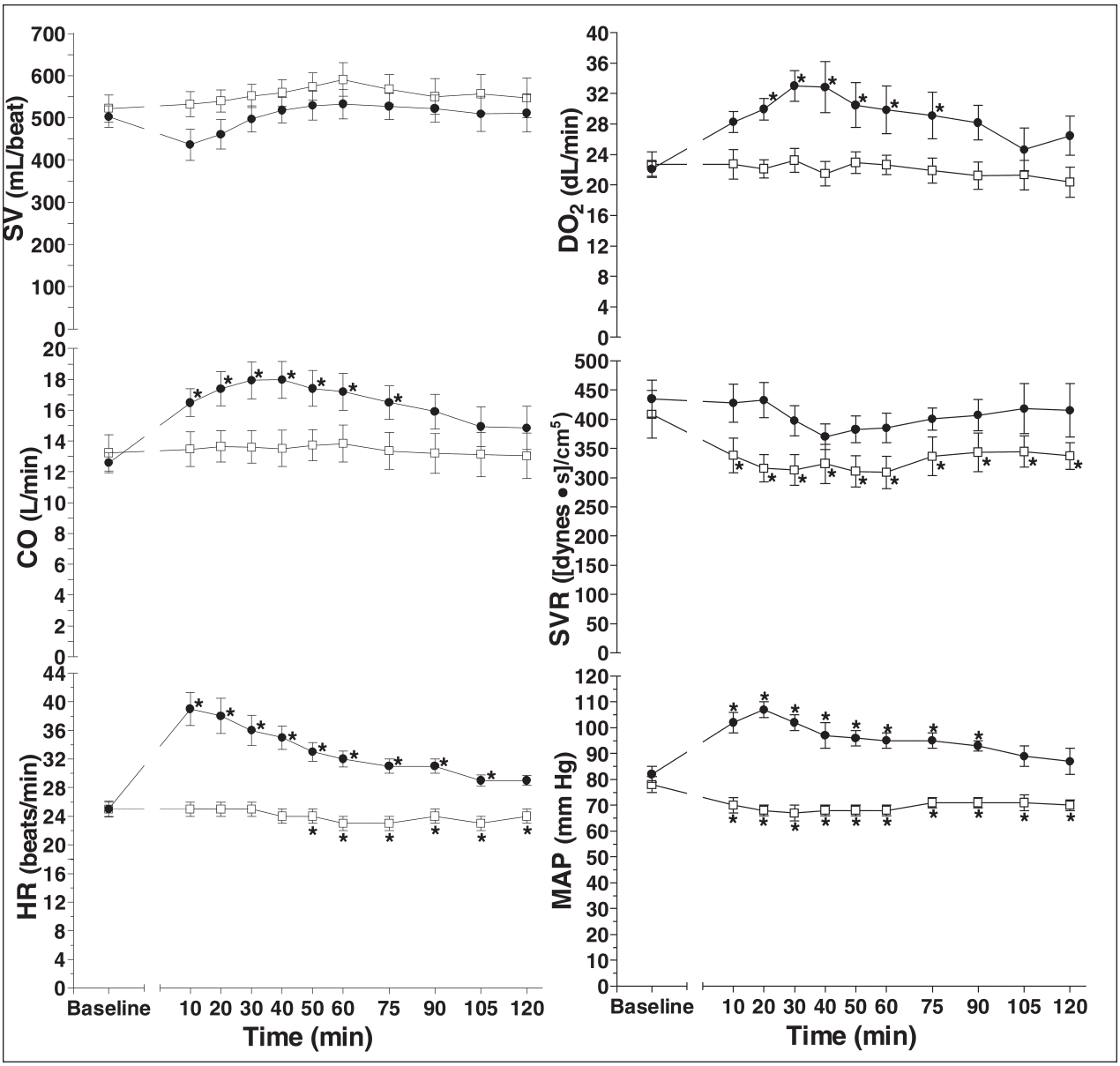

Figure 2—Effects of administration of saline (0.9% NaCl) solution (control treatment; open square) or glycopyrrolate (solid circle) on HR, cardiac output (CO), stroke volume (SV), mean arterial pressure (MAP), systemic vascular resistance (SVR), and oxygen delivery (DO_2) in 6 horses anesthetized with halothane (1% end-tidal concentration) and a constant-rate infusion of xylazine (1 mg/kg/h). Values reported are mean ± SEM. Baseline was recorded after induction of anesthesia. For all variables, values differed significantly ($P < 0.05$; 2-way ANOVA) between treatment groups. *Within each treatment group, value differs significantly ($P < 0.05$; Dunnett test) from the baseline value. Time 0 = Time of the last injection of glycopyrrolate or saline solution.

increased at least 30% above the baseline value or until each horse had received a maximum of 3 boluses (maximum cumulative dose of 7.5 µg/kg). This dose was determined as the end point because higher doses (10 µg/kg) have been associated with an increased risk of colic.[11]

After the last injection of glycopyrrolate or saline solution (time 0), cardiopulmonary data were recorded at 10-minute intervals for 60 minutes, followed by recording at 15-minute intervals for the next 60 minutes. At the end of the anesthetic procedure, each horse was moved to a padded stall and received 100% oxygen (15 L/min) insufflated via the endotracheal tube until they were able to stand. Time until a horse was able to stand and a recovery score were used to assess quality of the recovery. Recovery score was determined by 1 of the investigators (SD) who was aware of the treatments administered to each horse. Scores were assigned as follows: 0, horse died or was unable to stand after anesthesia as a result of major trauma or myopathy; 1, violent recovery with several attempts to stand, severe ataxia, or self-inflicted injuries; 2, > 3 attempts to stand, moderate degree of ataxia, and minor injuries; 3, 2 or 3 strong efforts in an attempt to stand; 4, able to stand in a single attempt.

After the end of the anesthetic procedure, personnel who were not aware of the treatment administered to each horse monitored all horses at hourly intervals until 48 hours after anesthesia for signs of abdominal discomfort (eg, pawing, rolling, looking at the flank, or sweating). Investigators recorded intestinal auscultation scores, pulse rate, and attitude at 2-hour intervals until 12 hours after discontinuation of the anesthetic and then at 6-hour intervals until 24 hours after discontinuation of the anesthetic. In a preliminary study, data for 3 conscious horses without motility disturbances revealed that the auscultation scoring system was repeatable and the total score could range from 12 (75% of the maximum score) to 16 (maximum score). On the basis of these preliminary observations, the return to normal intestinal sounds during the postanesthetic period was calculated as the time elapsed until an auscultation score of ≥ 12 was achieved.

Data analysis—Statistical analysis was performed by use of a statistical software package.[q] To study temporal changes during anesthesia, a 1-way ANOVA for repeated measures was performed for each treatment group. When a significant ($P < 0.05$) effect of time was detected, values for each time point were compared with baseline values by use of the Dunnett test. To determine whether conditions before treatment were similar between groups, baseline cardiopulmonary variables obtained before injection of saline solution or glycopyrrolate were compared by use of a paired Student *t* test. Posttreatment comparisons between the saline solution and glycopyrrolate treatments were performed by use of a 2-way ANOVA, with time and treatment as main factors. A Mann-Whitney *U* test was used to compare recovery time and intestinal auscultation scores. Parametric data were reported as mean ± SEM, and nonparametric data (ie, auscultation scores) were reported as box plots (median, 25th percentile, 75th percentile, maximum value, and minimum value). For all statistical analyses, values of $P < 0.05$ were considered significant.

Results

Baseline values for cardiopulmonary variables did not differ between glycopyrrolate and saline (control) treatments. In 5 horses, the targeted HR (minimum of 30% increase above baseline HR) was achieved with a total cumulative dose of glycopyrrolate of 5.0 µg/kg. One horse did not achieve the targeted HR (increase of only 23% above baseline) 10 minutes after the third dose was given, despite the fact this horse received the maximum cumulative dose of 7.5 µg/kg (**Fig 1**).

Comparisons between treatments revealed that glycopyrrolate resulted in significantly higher HR and CO values and significantly lower SV values (**Fig 2**). After glycopyrrolate administration, HR and CO values increased significantly from baseline values until 105

Table 1—Effects of administration of saline (0.9% NaCl) solution (control treatment) or glycopyrrolate (Glyco) on heart rate (HR), systolic arterial pressure (SAP), diastolic arterial pressure (DAP), mean pulmonary artery pressure (MPAP), concentration of arterial hemoglobin (Hb), and arterial oxygen concentration (Cao_2) in 6 horses anesthetized by use of halothane (1% end-tidal concentration) and a constant-rate infusion of xylazine hydrochloride (1 mg/kg/h)

		Time (min)								
Variable	**Treatment**	**Baseline**	**10**	**20**	**30**	**40**	**50**	**60**	**75**	**90**
HR (beats/min)										
	Control	25.2 ± 1.0	25.2 ± 1.1	25.2 ± 1.0	24.5 ± 1.0	24.0 ± 1.2	23.8 ± 0.83	23.3 ± 0.9*	23.3 ± 0.8*	23.8 ± 0.5*
	Glycot	25.2 ± 1.1	38.5 ± 2.3*	38.3 ± 2.5*	36.3 ± 2.1*	34.8 ± 1.6*	3.0 ± 1.3*	32.3 ± 1.1*	31.3 ± 1.0*	30.5 ± 1.0*
SAP (mm Hg)										
	Control	102.0 ± 3.0	93.0 ± 3.0*	92.0 ± 3.0*	92.0 ± 3.0*	92 .0 ± 3.0*	91.0 ± 3.0*	90.0 ± 3.0*	93.0 ± 3.0*	93 .0 ± 3.0*
	Glycot	101.0 ± 3.0	117.0 ± 4.0*	122.0 ± 3.0*	118.0 ± 3.0*	115.0 ± 5.0*	113.0 ± 4.0*	112.0 ± 3.0*	113.0 ± 3.0*	111.0 ± 3.0*
DAP (mm Hg)										
	Control	66.0 ± 3.0	59.0 ± 2.0*	56.0 ± 3.0*	56.0 ± 2.0*	57.0 ± 2.0*	57.0 ± 2.0*	57.0 ± 2.0*	58.0 ± 1.0*	59.0 ± 2.0*
	Glycot	70.0 ± 3.0	92.0 ± 4.0*	96.0 ± 4.0*	91.0 ± 4.0*	86.0 ± 5.0*	87.0 ± 3.0*	85.0 ± 3.0*	84.0 ± 2.0*	81.0 ± 3.0*
MPAP (mm Hg)										
	Control	21.5 ± 1.12	22.5 ± 0.72	22.3 ± 0.82	22.8 ± 0.8	22.7 ± 0.82	23.5 ± 0.8*	23.8 ± 0.7*	23.8 ± 0.8*	23.3 ± 0.6*
	Glyco	21.8 ± 1.5	25.3 ± 2.0*	24.8 ± 1.8*	24.2 ± 1.6	24.0 ± 1.7	23.2 ± 1.5	22.8 ± 1.8	22.2 ± 1.4	22.2 ± 1.1
CVP (mm Hg)										
	Control	13.3 ± 1.4	14.3 ± 0.7	15.2 ± 0.8	15.0 ± 0.7	15.3 ± 1.1*	16.3 ± 0.6*	15.8 ± 0.6*	16.5 ± 0.7*	16.5 ± 0.2*
	Glycot	14.2 ± 1.0	15.0 ± 0.9	14.5 ± 1.2	14.5 ± 1.3	14.8 ± 0.9	14.5 ± 0.9	14.2 ± 0.8	13.7 ± 0.7	13.8 ± 0.7
Hb (g/dL)										
	Control	11.8 ± 0.4	11.6 ± 0.7	11.2 ± 0.8	11.8 ± 0.7	10.9 ± 0.8	11.4 ± 0.5	11.3 ± 0.6	11.3 ± 0.7	11.0 ± 0.5
	Glyco	11.8 ± 0.4	11.7 ± 0.6	11.7 ± 0.6	12.6 ± 0.6	12.2 ± 0.7	11.7 ± 0.6	11.5 ± 0.6	11.8 ± 0.7	11.9 ± 0.3
Cao_2 (mL/dL)										
	Control	17.4 ± 0.8	17.1 ± 1.1	16.5 ± 1.1	17.4 ± 1.1	16.2 ± 1.2	16.9 ± 0.8	16.7 ± 1.0	16.7 ± 1.1	16.2 ± 0.8
	Glyco	17.6 ± 0.6	17.3 ± 0.9	17.4 ± 0.9	18.5 ± 0.9	18.1 ± 0.9	17.3 ± 0.8	17.1 ± 0.7	17.5 ± 0.9	17.7 ± 0.5

Values reported are mean ± SEM. Baseline was recorded after induction of anesthesia. Time of the last injection of glycopyrrolate or saline solution was designated as time 0.

*Within a row, value differs significantly ($P < 0.05$; Dunnet test) from baseline value. †Values differed significantly ($P < 0.05$; 2-way ANOVA) between treatment groups.

Table 2—Effects of administration of saline solution (control treatment) or glycopyrrolate (Glyco) on Pa_{O_2}, Pa_{CO_2}, arterial pH, and arterial base excess (ABE) in 6 horses anesthetized by use of halothane (1% end-tidal concentration) and a constant-rate infusion of xylazine hydrochloride (1 mg/kg/h)

		Time (min)								
Variable	**Treatment**	**Baseline**	**10**	**20**	**30**	**40**	**50**	**60**	**75**	**90**
Pa_{O_2} (mm Hg)	Control	341.0 ± 53.6	329.3 ± 49.9	332.4 ± 45.0	325.2 ± 45.5	343.4 ± 46.6	338.5 ± 44.4	346.9 ± 46.6	327.4 ± 45.0	334.3 ± 46.8
	Glyco	392.2 ± 14.6	359.2 ± 24.9	361.2 ± 27.5	353.4 ± 24.0	356.4 ± 24.2	354.1 ± 30.5	365.0 ± 29.0	337.8 ± 28.2	349.0 ± 28.1
Pa_{CO_2} (mm Hg)	Control	43.7 ± 1.3	48.6 ± 1.1*	47.4 ± 1.1*	47.8 ± 1.0*	47.5 ± 1.3*	46.9 ± 1.4*	47.3 ± 0.9*	44.6 ± 0.5	45.6 ± 0.5
	Glyco†	40.2 ± 0.6	45.8 ± 1.7*	45.5 ± 1.3*	44.5 ± 1.1*	44.2 ± 1.0*	42.7 ± 1.0	45.1 ± 1.6*	43.5 ± 1.1	43.1 ± 0.8
pH										
	Control	7.445 ± 0.009	7.411 ± 0.011*	7.422 ± 0.008	7.421 ± 0.007	7.426 ± 0.008	7.432 ± 0.006	7.431 ± 0.005	7.456 ± 0.005	7.452 ± 0.005
	Glyco†	7.464 ± 0.011	7.428 ± 0.014*	7.432 ± 0.013*	7.443 ± 0.011	7.448 ± 0.010	7.463 ± 0.010	7.449 ± 0.011	7.457 ± 0.011	7.463 ± 0.010
ABE (mmol/L)	Control	5.1 ± 0.7	5.0 ± 0.7	5.3 ± 0.7	5.4 ± 0.7	5.6 ± 0.5	5.8 ± 0.5	5.9 ± 0.5*	6.5 ± 0.6*	6.7 ± 0.5*
	Glyco†	4.8 ± 0.7	4.8 ± 0.8	5.1 ± 0.7	5.4 ± 0.6	5.7 ± 0.7*	5.8 ± 0.8*	5.7 ± 0.6*	6.1 ± 0.6*	6.3 ± 0.6*

See Table 1 for key.

and 75 minutes, respectively. In control horses, HR decreased from baseline values after 60 minutes, whereas CO and SV did not change over time.

Glycopyrrolate treatment was associated with significantly higher MAP, SAP, DAP, and DO_2 (Fig 2; **Table 1**). When compared with baseline values, MAP, SAP, and DAP were increased until 90 minutes after glycopyrrolate treatment, whereas MAP, SAP, and DAP decreased from baseline values throughout the observation time for the control treatment. Oxygen delivery increased from 20 until 90 minutes after glycopyrrolate administration. Systemic vascular resistance values were lower for the control treatment. When compared with baseline values, SVR did not change significantly after glycopyrrolate administration, whereas it decreased to below baseline values throughout the observation time for the control treatment.

In horses during the control treatment, CVP increased from baseline values after 40 minutes (Table 1). Analysis revealed that CVP was significantly higher for the control treatment, compared with CVP for the glycopyrrolate treatment. Values for MPAP did not differ between glycopyrrolate and control treatments. When compared with baseline values, MPAP had a transient but significant increase from 10 to 20 minutes after administration of glycopyrrolate, whereas it increased after 50 minutes for the control treatment. Concentration of Hb and Ca_{O_2} values did not differ within or between treatments.

Values for Pa_{O_2} did not differ between or within treatments. The Pa_{CO_2} values were significantly higher for the control treatment and significantly increased from baseline values at several time points for both treatment groups. Values for Pa_{CO_2} ranged from 40.2 to 52.4 mm Hg and 38.3 to 51.9 mm Hg for the control and glycopyrrolate treatments, respectively. Arterial pH values were significantly lower for the control treatment than for the glycopyrrolate treatment. When compared with baseline values, arterial pH was lower from 10 to 20 minutes after treatment with glycopyrrolate and at 10 minutes after administration of saline solution. Values for arterial base excess did not differ between control and glycopyrrolate treatments. When compared with baseline values, arterial base excess was significantly increased after 40 and 60 minutes for the glycopyrrolate and control treatments, respectively (**Table 2**).

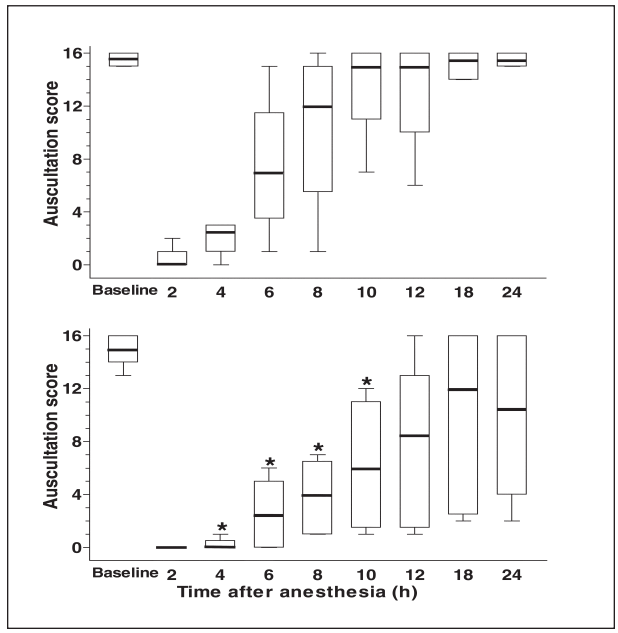

Figure 3—Box-and-whiskers plots of intestinal auscultation scores observed before induction of anesthesia (baseline) and during the postanesthetic period (time after end of anesthesia) in 6 horses anesthetized by use of halothane and xylazine that were treated with saline solution (control treatment; top) or glycopyrrolate (bottom). Each box represents data from the 25th to 75th percentiles. The bold horizontal line within each box represents the median value, and the whiskers represent the range of scores. *Median values differ significantly ($P < 0.05$; Mann-Whitney *U* test) between treatment groups.

All horses had a recovery score of 4 (recovery in a single attempt to stand). Recovery times did not differ between groups, and horses were able to stand a mean of 49.6 ± 5.8 minutes (range, 33 to 68 minutes) after the control treatment, whereas horses were able to stand 53.6 ± 6.3 minutes (range, 27 to 68 minutes) after the glycopyrrolate treatment.

All horses had intestinal auscultation scores within the expected range before induction of anesthesia (≥ 12). During the postanesthetic period, decreased intestinal sounds were observed in both groups, and the time to return to a score of ≥ 12 was 10.0 ± 1.7 hours (range, 6 to 18 hours) for the control treatment **(Fig 3)**. Auscultation

scores were significantly lower for the glycopyrrolate treatment until 10 hours after the end of the anesthetic procedure. Time elapsed to achieve a score ≥ 12 could not be determined in 3 horses when treated with glycopyrrolate because of prolonged postanesthetic ileus (scores ≤ 6) extending beyond the maximum time for auscultation (ie, 24 hours after anesthesia). Two horses achieved a score ≥ 12 at 18 hours after glycopyrrolate treatment, whereas 1 horse achieved a score ≥ 12 at 10 hours after administration of glycopyrrolate and the end of the anesthetic period.

One horse that had low auscultation scores (≤ 6) at 24 hours had received a total cumulative dose of glycopyrrolate of 5 µg/kg; this horse developed signs of abdominal pain (pawing, walking in circles, and becoming recumbent) between 18 and 24 hours after anesthesia, and impaction of the large colon was diagnosed on per rectal palpation at 24 hours. Treatment was initiated at the time of diagnosis, and the horse recovered after receiving fluids (lactated Ringer's solution, 25 L, IV, during a 24-hour period), analgesics (flunixin meglumine, 1 mg/kg), and orally administered cathartics (magnesium sulfate, 300 g).

Discussion

The study reported here documented that there was an improvement of 30% to 40% in CO, DO_2 and MAP when HR increased from a range of 25 to 30 beats/min to a range of 35 to 40 beats/min after the administration of an anticholinergic agent to horses anesthetized by use of halothane and xylazine. Although the continuous infusion of xylazine was used to allow evaluation of glycopyrrolate in a model of sustained bradycardia (HR < 30 beats/min), the concept of the use of a supplemental α_2-agonist during general anesthesia is not new.[17,18] There may be clinical advantages associated with the use of continuous-infusion regimens of α_2-agonists to reduce inhalant requirements, providing that bradycardia induced by α_2-agonists is counteracted.

Hypercapnia attributable to the respiratory-depressant effects of inhalant anesthetics influences cardiovascular function and may represent a confounding factor in comparative hemodynamic studies.[19-21] In 1 study[21] performed in mechanically ventilated, isoflurane-anesthetized horses, mild increases in $PaCO_2$ (defined as $PaCO_2$ between 55 and 65 mm Hg) were associated with a decrease in HR and cardiac index (ie, CO divided by body weight), whereas moderate to severe hypercapnia ($PaCO_2$ > 75 mm Hg) caused generalized cardiovascular stimulation. Despite the use of mechanical ventilation to maintain $PaCO_2$ values within a narrow range (40 to 50 mm Hg) in the study reported here, $PaCO_2$ was higher for the control treatment than for the glycopyrrolate treatment. However, the range of $PaCO_2$ values was similar between groups (control, 40.2 to 52.4 mm Hg; glycopyrrolate, 38.3 to 51.9 mm Hg), and the mean difference of 1 to 4 mm Hg between treatment groups at each time point probably was not sufficiently large to critically influence hemodynamic variables.

We are not aware of any studies in which investigators have evaluated hemodynamic changes associated with the use of constant-rate infusion of xylazine during inhalant anesthesia in horses. The decreased HR after IV administration of a bolus of xylazine in conscious animals is attributed to an initial baroreceptor-mediated increase in vagal tone, which is triggered by a transient increase in blood pressure caused by vasoconstriction induced by stimulation of extrasynaptic α_2-receptors located in blood vessels.[14-16,22] After the initial increase, blood pressure returns to normal or less than baseline values, and the bradycardia that persists is attributed to stimulation of presynaptic α_2-receptors leading to decreased norepinephrine release from postganglionic sympathetic terminals and CNS-mediated increases in vagal tone.[14-16,22] In the study reported here, it could be hypothesized that the continuous infusion of xylazine caused persistent stimulation of extrasynaptic α_2-receptors (vasoconstriction), leading to sustained decreases in HR through a baroreceptor-mediated mechanism. However, because ABP tended to remain relatively low (SAP < 120 mm Hg) throughout the study for the control treatment, the baroreceptor reflex response may not have played a substantial role in the bradycardia. Even when there is some stimulation of baroreceptors, it should be recognized that halothane reduces the baroreceptor response to increases and decreases of ABP in horses.[23] Despite the transient increase in SVR observed when α_2-agonists are administered IV at relatively high doses, a decrease in SVR may be observed when the CNS-mediated decreases in sympathetic outflow and stimulation of presynaptic α_2-receptors prevail.[2] Indeed, a more specific α_2-agonist, medetomidine, given by continuous infusion in standing ponies tended to decrease SVR below baseline (conscious) values.[24] In our study, it is possible that peripheral vasoconstriction and centrally mediated decreases in sympathetic outflow coexisted throughout the xylazine infusion. However, the relative importance of these factors remains unknown.

Central venous pressure is often used as an index of preload. An increase in CVP may reflect an increase in venous return or decreased ability of the right ventricle to eject blood.[25] In the study reported here, CVP increased toward the end of the observation period in the control horses. This probably did not reflect a true change in venous return and was more likely related to a tendency for lower HRs at that time or, possibly, an impairment of right ventricular function associated with prolonged xylazine infusion.

During inhalant anesthesia, vagally mediated bradycardia may be associated with the use of drugs (ie, α_2-agonists) or surgical stimulation (ie, ocular surgery).[14-16,26] Controversy exists regarding the minimum HR that can be allowed during general anesthesia, and HRs as low as 25 beats/min have been considered acceptable.[3] It is recommended, however, that a low HR should be treated by administration of an anticholinergic, particularly when the decreased HR is associated with hypotension (MAP < 70 mm Hg) and signs of poor tissue perfusion.[3] In the study reported here, an HR < 30 beats/min was associated with relatively lower ABP values, and treatment with glycopyrrolate resulted in an improvement of hemodynamic function as indicated by increases in CO, DO_2, and ABP.

The relationship between HR and CO has been investigated through the use of a pacemaker device in

conscious humans, dogs at rest or during exercise, and anesthetized animals.[27-31] Within a determined range, HR and CO tend to increase in a proportional fashion because SV is maintained (phase 1), whereas at progressively higher HRs, CO tends to plateau (phase 2) and subsequently decrease (phase 3) because of progressive decreases in SV.[27-31] Stroke volume is the difference between left ventricular end-diastolic and end-systolic volumes and is influenced by changes in inotropism, preload, afterload, and diastolic filling time.[1,2] When there is a lack of sympathetic stimulation, higher HRs cause a significant decrease in diastolic filling time, which leads to a decrease in end-diastolic volume and SV.[29,32] In conscious horses in another study,[32] mean ± SEM HR was increased from 36.6 ± 2.8 to 75.7 ± 2.4 beats/min by administration of atropine sulfate (0.04 mg/kg, IV), but CO did not increase because of a decrease in SV. Conversely, during anesthesia achieved by use of halothane and xylazine, as HR increased from 25.2 ± 1 to 38.3 ± 2.5 beats/min by 20 minutes after glycopyrrolate administration, there was a significant improvement in CO. Thus, analysis of results of our study indicates that as HR increases from approximately 25 beats/min to 35 to 40 beats/min in horses anesthetized with halothane combined with xylazine, an increase in CO can be expected when preload, afterload, and contractility remain constant.[2,29-31]

In the study reported here, the increase in arterial pressure observed after glycopyrrolate treatment was attributable to an increase in CO because SVR did not change. On the other hand, ABP and SVR decreased after glycopyrrolate treatment, compared with baseline values for the control treatment. This phenomenon probably contributed to the significant effect we observed for treatment (SVR was significantly lower for the control treatment, compared with SVR for the glycopyrrolate treatment). Sustained decreases in SVR may result when the balance between sympathetic and parasympathetic activity is shifted toward parasympathetic dominance.[2] Studies[33,34] performed in humans have revealed that muscarinic receptors mediate a decrease in vascular resistance, an effect that can be antagonized by the use of muscarinic antagonists, such as atropine. Even though vascular muscarinic receptors may represent an unappreciated mechanism for control of blood pressure in humans, their functional role remains obscure because the peripheral resistance vessels do not receive parasympathetic innervation.[2,33,34]

In horses, a conservative approach for the treatment of bradycardia has been brought about by concerns regarding prolonged gastrointestinal stasis induced by anticholinergics. Atropine and glycopyrrolate inhibit intestinal motility, prolong transit time, and eventually induce colic.[8-11] In 1 study,[11] a dose of glycopyrrolate (2.5 µg/kg) caused only a mild inhibitory effect on intestinal auscultation scores, whereas doses of 5.0 and 10 µg/kg abolished intestinal sounds in a dose-related manner. In that study, signs of abdominal discomfort were observed in 2 of 5 horses in which a dose of glycopyrrolate of 10 µg/kg was administered. It appears that the motility-depressant effect of muscarinic antagonists is dose-dependent, and the common clinical approach is to administer relatively small doses in an attempt to achieve the desired effect on HR without adversely affecting intestinal motility. Even though we attempted to use a low dose of glycopyrrolate (2.5 µg/kg) in the study, higher doses were necessary in all horses (5 µg/kg in 5 horses and 7.5 µg/kg in 1 horse) to achieve the targeted increase in HR. At these doses, glycopyrrolate caused lower scores for intestinal auscultation, and 1 horse that received a dose of 5 µg/kg developed signs of colic. However, care should be taken when interpreting the results of the study reported here because general anesthesia, per se, has also been implicated as a cause of motility disturbances in horses.[35] Furthermore, the concurrent administration of relatively high doses of xylazine, a depressor of intestinal motility, probably contributed to the motility-depressant effects of glycopyrrolate.[9-11,16]

The depressant effects of muscarinic receptor antagonists on intestinal motility have been documented.[8-11] Evidence obtained from other species indicates that nonselective antagonists, such as atropine sulfate, inhibit intestinal motility by blocking type-3 muscarinic receptors located in intestinal smooth muscle cells.[36,37] These receptors are responsible for smooth muscle contraction in response to acetylcholine release from postganglionic neurons located in the myenteric plexus.[36,37] On the other hand, stimulation of α_2-receptors by xylazine may also impair intestinal motility by inhibiting the release of acetylcholine from the neurons of the enteric plexus.[38,39]

The beneficial hemodynamic effects of an increase in HR during use of an inhalant anesthetic and an α_2-agonist were obvious in the study reported here. It is generally assumed that improved cardiovascular function during prolonged inhalant anesthesia would result in better recovery characteristics in horses.[40] Even though 4 of 6 horses recovered slightly faster when treated with glycopyrrolate, recovery time and recovery scores did not differ between the 2 treatment groups. A retrospective study[40] that involved a relatively large sample population revealed that the use of dobutamine to treat hypotension improves the quality of recovery by reducing the severity of complications, such as postanesthetic myopathy. In our study, it is possible that the sample population was too small to reveal a difference between groups in terms of recovery time and recovery score.

On the basis of analysis of results of the study reported here, the positive chronotropic effect of glycopyrrolate was associated with increased CO, DO_2, and ABP. In contrast to situations in which glycopyrrolate was administered before xylazine[16] or before a combination of xylazine and ketamine,[15] the improvement in HR and CO was not associated with excessive hypertension. Although glycopyrrolate causes a beneficial hemodynamic effect during anesthesia achieved by use of halothane and xylazine, prolonged postanesthetic hypomotility and colic may limit its use during inhalant anesthesia, especially in horses prone to motility disturbances or horses that have received high doses of motility-depressant drugs, such as α_2-agonists.

[a]Angiocath, Becton-Dickinson, Sandy, Utah.
[b]Intro-Flex, Baxter Healthcare Corp, Irvine, Calif.
[c]7-F thermodilution catheter, Baxter Healthcare Corp, Irvine, Calif.
[d]Criticare 1100, Criticare Systems Inc, Waukesha, Wis.
[e]Rompun, Agriculture Division, Bayer Inc, Toronto, ON, Canada.
[f]Ketalean, Bimeda-MTC Animal Health Inc, Cambridge, ON, Canada.
[g]Large Animal Control Center, North American Dragger, Telford, Pa.
[h]Halothane BP, Bimeda-MTC Animal Health Inc, Cambridge, ON, Canada.
[i]Flo Gard 6201, Baxter Healthcare Corp, Round Lake, Ill.
[j]Insyte, Becton-Dickinson, Sandy, Utah.
[k]DTX Plus DT-36, Becton-Dickinson, Sandy, Utah.
[l]ABL-3 blood gas analyzer, Radiometer, Copenhagen, Denmark.
[m]Co-oximeter OSM 3, Radiometer, Copenhagen, Denmark.
[n]COM-2 cardiac output computer, Baxter Healthcare Corp, Irvine, Calif.
[o]Anesthesia calibration gas, Criticare Systems Inc, Waukesha, Wis.
[p]Glycopyrrolate, Sabex, Boucherville, QC, Canada.
[q]GraphPad Prism, GraphPad Software Inc, San Diego, Calif.

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