Cardiopulmonary Effects of a Ketamine/Acepromazine Combination in Hypovolemic Cats

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ABSTRACT

The cardiopulmonary effects of a ketamine/acepromazine combination was studied in ten cats subjected to a 25% whole blood volume loss. Test parameters included cardiac output, measured via thermodilution, heart rate, respiratory rate, arterial blood pressure (systolic, diastolic and mean) and blood gas analysis. Values for cardiac index, stroke volume and systemic vascular resistance were calculated from these data. Posthemorrhage, cardiac output, cardiac index, stroke volume, heart rate and measurements of arterial blood pressure were significantly decreased ($p < 0.05$). Following the induction of ketamine/acepromazine anesthesia, cardiac output, cardiac index, stroke volume and heart rate showed mild but statistically insignificant declines and were above their respective posthemorrhage values 120 min into ketamine/acepromazine anesthesia. Measurements of arterial blood pressure showed further declines from their respective posthemorrhage values that were statistically significant ($p < 0.05$).

Following hemorrhage, respiratory rate increased significantly ($p < 0.05$), associated with a fall in arterial CO_2 tension. During ketamine/acepromazine anesthesia, respiratory rate showed a dramatic and significant decline ($p < 0.05$) with arterial CO_2 tension rising to prehemorrhage values. Systemic vascular resistance, arterial O_2 tension and pH remained essentially unchanged throughout the experimental period.

RÉSUMÉ

Cette expérience consistait à étudier l'effet d'une combinaison de kétamine et d'acépromazine sur la fonction cardio-pulmonaire de dix chats auxquels on avait enlevé 25% de leur volume sanguin. Les paramètres expérimentaux incluaient: le débit cardiaque, tel que mesuré par la thermodilution, la fréquence cardiaque, le rythme respiratoire, les pressions artérielles systolique, diastolique et moyenne, ainsi que l'analyse des gaz sanguins. Les auteurs calculèrent les valeurs relatives à l'index cardiaque, au débit systolique et à la résistance vasculaire systémique, à partir des paramètres précités. Après l'hémorragie, le débit et l'index cardiaques, le débit systolique, la fréquence cardiaque et la mesure des pressions artérielles précitées subirent une baisse appréciable ($p < 0,05$). Après l'induction de l'anesthésie, avec la combinaison de kétamine et d'acépromazine, le débit et l'index cardiaques, le débit systolique et la fréquence cardiaque affichèrent une chute discrète, sans signification statistique; après 120 minutes d'anesthésie, leurs valeurs respectives dépassaient celles d'après l'hémorragie; la mesure des pressions artérielles précitées démontra par ailleurs une chute additionnelle et significative du point de vue statistique ($p < 0,05$), par rapport à leurs valeurs respectives d'après l'hémorragie.

À la suite de l'hémorragie, le rythme respiratoire augmenta de façon significative ($p < 0,05$) et s'accompagna d'une chute de la tension artérielle en CO_2. Au cours de l'anesthésie à la kétamine et à l'acépromazine, le rythme respiratoire afficha une baisse dramatique et significative ($p < 0,05$), alors que la tension artérielle en CO_2 remonta à sa valeur d'avant l'hémorragie. La résistance vasculaire systémique, la tension artérielle en O_2 et le pH demeurèrent essentiellement inchangés, tout au long de la période expérimentale.

INTRODUCTION

The presentation of blood volume depleted animals is a relatively common occurrence in veterinary practice. The reduction in blood volume may be secondary to a loss of whole blood, plasma, or of water and electrolytes, but the underlying pathophysiology revolves around the hypvolemic state. The loss of circulating volume decreases venous return followed by decreases in stroke volume (SV), cardiac output (CO), and arterial blood pressure (ABP) (1-5). This initiates a reflex systemic

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response mediated by the sympathoadrenal system which attempts to maintain ABP and increase vascular volume (4,5). Heart rate (HR) often rises in an attempt to compensate for the CO decline (4,5). Systemic vascular resistance (SVR) increases with regional differences directing blood flow away from the nonvital organs in an attempt to maintain perfusion pressure to the heart and brain (2-4). Increased sympathetic tone decreases the reservoir capacity of the veins directing blood back to the heart to augment venous return and subsequently SV and CO (1,3,4). Other effects of increased sympathetic tone include a differential pressure response favouring the pre- versus postcapillary sphincter as well as a rise in serum osmolality secondary to catecholamine induced hyperglycemia (7-10). The subsequent alteration in Starling forces favors the absorption of interstitial fluid and a subsequent increase in blood volume (3,4,8,10).

There is no doubt that the immediacy of the sympathoadrenal response is a vital survival reflex.

However, animals are often subject to emergency surgical procedures in an effort to identify and treat the precipitating cause of the hypovolemic state. Some of the commonly used anesthetic agents are known to interfere with normal cardiovascular reflexes and the sympathetic nervous system (11-13) which is of some concern as it has been demonstrated that sympathectomized animals do not tolerate hemorrhage as well as animals with an intact sympathetic nervous system (4).

Both ketamine hydrochloride and acepromazine alter sympathetic nervous system related homeostasis, and the two agents are often used in combination in feline practice. Ketamine has long been advocated for use in high risk cardiac, critical and hypotensive patients (14,15). Although ketamine causes a direct depression of myocardial contractility, its net effect is one of cardiovascular stimulation, an indirect result of its sympathomimetic properties (16,17). Acepromazine (ACP) is an alpha antagonist which produces arterial hypotension as well as tranquilization (18,19). Therefore its use is cautioned in animals that are hypotensive (18,19). Since ketamine alone induces a cataleptic state it is often used concurrently with acepromazine, the combination benefiting from acepromazine's muscle relaxing properties. In the healthy normovolemic cat the combination results in a significant depression of CO, SV and ABP (20,21). Heart rate and SVR are not significantly altered (20,21). These responses (except for a rise in HR) were also identified in the dog (22).

It was the purpose of this experiment to determine the cardiopulmonary effects of a ketamine/acepromazine (K/A) combination in healthy cats subjected to a hemorrhagic insult.

MATERIALS AND METHODS

The following experimental protocol was designed in accordance with CCAC guidelines. Ten mature cats of either sex and mixed breed were used. They had a mean weight of 4.2 kg (± 0.63 SD) and were judged to be healthy on the basis of history, physical examination, thoracic radiographs and electrocardiogram (ECG). The cats were brought into the hospital facility and allowed a 24 h acclimatization period. Anesthesia was induced with 5% halothane (Somnothane, Hoechst, Montreal) in oxygen (O_2) at a flow rate of 5 L/min administered to the cats in a 22 L (5 gallon) aquarium or cat box. Following induction the cats were intubated and maintained on the least inspired concentration of halothane allowing surgical cut down and exposure of the left jugular vein and carotid artery. The thermodilution (Edwards Laboratories, Santa Ana, California), injectate (Edwards Laboratories, Santa Ana, California), and arterial catheters were then surgically placed in the pulmonary artery, right atrium and left carotid artery respectively. The technique of catheter insertion and location verification has been described in previous reports (23-25).

Following a minimal 24 h recovery period, the cats were subjected to the hemorrhagic protocol. The blood volume in the healthy, nonsplenectomized cat is defined as 55.0 mL/kg (27,28) and 13.5 mL/kg were subsequently removed. This constituted approximately 25% of the blood volume. The blood volume was slowly removed via the arterial catheter in three equal aliquots over 15-20 min. Arterial blood pressure was constantly monitored via a VR-6 Simultrace Recorder (Electronics for Medicine Inc., White Plains, New York) and once stable, for at least a 5 min period, K/A anesthesia was induced. Following bleeding it generally took 10-15 min for this stabilization to occur so that the period from the start of bleeding to the start of anesthesia was approximately 30-35 min.

The ketamine (Ketaset, rogar/STB, Montreal)/acepromazine (Atravet, Hoechst, Montreal) combination was administered intramuscularly, in the same syringe, at a dose of 20 mg/kg and 0.11 mg/kg respectively. In their clinical application the aforementioned dosages and route of administration would be a commonly used method of induction (16,21) and it was the intent of this study to mimic the clinical setting as closely as possible. Depth of anesthesia was assessed via a lack of response to deep pain (flexor reflex using a hemostat). A lack of response was judged not only by the lack of gross motor movement, but also by the absence of changes in the HR and ABP monitored on the VR-6 Simultrace Recorder. The CO, HR, ABP (systolic, diastolic and mean), respiratory rate (RR) and arterial blood gas values were recorded prior to bleeding, immediately prior to anesthesia and at 10, 20, 30, 45, 90 and 120 min postinduction.

To measure CO, the thermodilution catheter was connected to a cardiac output computer (Edwards Laboratories, Santa Ana, California) and 2 mL of 5% dextrose at room temperature was used as the thermodilution tracer, being injected in to the right atrium via the injectate catheter. The cardiac output was displayed by digital readout with duplicate readings taken and averaged. A VR-6 Simultrace Recorder was used to follow ABP (systolic, diastolic and mean) as well as displaying a continual ECG to monitor HR and rhythm. Respiratory rate was monitored visually. The SV (CO/HR), CI (CO/kg) and SVR (mean ABP x 80/CO) were calculated from the above data. Central venous pressure (CVP) was monitored ran-

TABLE I. Cardiac Output, Cardiac Index, Stroke Volume and Heart Rate in Ten Cats Subjected to a 25% Blood Volume Loss Followed by Ketamine/ACP Anesthesia

Time (min)	Cardiac Output (mL/min) Mean	± SEM	Cardiac Index (mL/min/kg) Mean	± SEM	Stroke Volume (mL/beat) Mean	± SEM	Heart Rate (beats min) Mean	± SEM
Prehemorrhage	760.00	43.17	185.02	11.79	4.06	0.18	186	5.03
Immediately posthemorrhage							165	7.32
Preanesthetic (0 time)	420.00	27.23	102.13	6.97	2.65	0.20	161	6.26
10	415.56	28.82	101.80	8.44	2.36	0.16	169	3.56
20	405.56	34.04	99.23	9.15	2.59	0.18	159	5.21
30	391.11	25.25	95.86	7.75	2.51	0.15	154	3.97
45	383.33	30.91	93.86	8.34	2.58	0.21	148	6.02
60	400.00	31.27	97.74	8.29	2.66	0.19	150	5.09
90	410.00	31.40	99.94	8.05	2.66	0.14	154	6.38
120	452.22	36.09	111.33	11.32	2.76	0.11	161	7.91

domly and hematocrit (PCV) and total protein (TP) were measured in five of the ten cats. The results were statistically analyzed using a Dunnett's analytical technique allowing each animal to act as its own control. A significance level of $p < 0.05$ was chosen. During the data collection, body temperature was monitored via the thermodilution catheter and all cats maintained at normothermia (37.5-38.5° C) using a water heating pad.

RESULTS

Cardiac output (mL/min), CI (mL/min/kg), ABP (systolic, diastolic and mean), HR (beats/min) and SV (mL/beat) were all significantly decreased posthemorrhage (Tables I and II). At zero time (preanesthetic) CO was 55%, CI 55%, HR 88%, SV 65% and systolic, diastolic and mean ABP approximately 65% of their prehemorrhage values. Following the induction of K/A anesthesia only measurements of ABP were significantly decreased from their preanesthetic values. Systolic, diastolic and mean ABP reached a maximum depression at the 10 and 20 min readings being approximately 75% of preanesthetic or zero time values. This depression was significant from the 10 to 90 min readings for systolic and diastolic ABP and at the 10 and 20 min readings for mean ABP. The values gradually rose to remain depressed but near their preanesthetic measurements. Cardiac output, CI and SV declined following K/A administration but the depressions were not statistically significant when compared to their preanesthetic (0 time) values. The decline in SV was maximum at 10 min. For CO and CI this occurred at 45 min. These values were approximately 90% of their preanesthetic measurements. At 120 min, values for CO, CI and SV had risen above their preanesthetic values but were still only 60 to 70% of their prehemorrhage indices. Heart rate was not significantly different throughout anesthesia when compared to its preanesthetic values. Immediately posthemorrhage RR showed an increase that corresponded with a decline in the arterial CO_2 tension ($PaCO_2$) (Table III). Respiratory rate showed a significant decline from its preanesthetic values that persisted through to the 120 min reading being 30% of its preanesthetic measurements. Systemic vascular resistance, arterial O_2 tension (PaO_2), $PaCO_2$ and pH were not statistically different from their prehemorrhage values throughout the anesthetic time period (Tables II and III). Although changes in CVP, PCV and TP lacked statistical significance, trends were noted. Packed cell volume and TP measured prehemorrhage and again at the 120 min reading, dropped from an average of 39.5% and 69.5 gm/dL to 28.5% and 51.5 gm/dL respectively. Posthemorrhage CVP measurements were consistently in the low normal range (0-1 mmHg).

DISCUSSION

The hemorrhagic hypotension model used involved the removal of a fixed amount, in this case a percentage, of the animal's blood volume. The other experimental model in current use involves predetermining a value of

TABLE II. Arterial Blood Pressure (Systolic, Diastolic and Mean) and Systemic Vascular Resistance in Ten Cats Subjected to a 25% Blood Volume Loss Followed by Ketamine/ACP Anesthesia

Time (min)	Systolic BP (mmHg) Mean	± SEM	Diastolic BP (mmHg) Mean	± SEM	Mean BP (mmHg) Mean	± SEM	Systemic Vascular Resistance (dynes sec cm^{-5}) Mean	± SEM
Prehemorrhage	137.14	6.33	108.86	3.70	122.75	3.99	13047.9	746.7
Immediately posthemorrhage	85.00	11.21	56.71	9.81	72.00	9.71		
Preanesthetic (0 time)	93.29	4.22	65.86	2.14	78.00	2.03	14163.6	1039.0
10	70.57[a]	3.48	48.00[a]	2.00	61.50[a]	4.36	13453.6	1206.3
20	70.29[a]	3.40	48.86[a]	2.53	62.83[a]	4.68	13256.4	1099.8
30	71.14[a]	3.84	50.29[a]	2.61	63.38	4.45	13663.6	1174.2
45	73.43[a]	5.22	51.71[a]	2.49	63.13	4.20	14124.0	1506.0
60	75.00[a]	4.49	53.00[a]	2.41	65.63	3.97	14340.6	1248.4
90	74.43[a]	3.88	54.71[a]	2.24	67.13	3.86	14306.0	1241.5
120	79.57	4.49	59.43	4.52	71.00	4.87	13719.9	1360.8

[a]Values significantly lower ($p < 0.05$) than the preanesthetic values

TABLE III. Respiratory Rate and Arterial Blood Gas Analysis in Ten Cats Subjected to a 25% Blood Volume Loss Followed by Ketamine/ACP Anesthesia

Time (min)	PaO_2 (mmHg) Mean	± SEM	PaO_2 (mmHg) Mean	± SEM	pH Mean	± SEM	Rspiratory Rate (breaths/min) Mean	± SEM
Prehemorrhage	120.43	1.69	25.94	0.70	7.368	0.008	34	2.81
Immediately posthemorrhage							79	13.89
Preanesthetic (0 time)	123.53	4.64	22.34	1.32	7.365	0.014	65	10.95
10	117.34	3.58	24.90	1.15	7.336	0.015	22[a]	2.41
20	121.19	3.54	25.25	1.30	7.354	0.018	19[a]	1.22
30	118.14	2.62	25.75	0.98	7.354	0.017	16[a]	1.09
45	114.19	3.49	25.76	1.25	7.359	0.024	17[a]	0.65
60	112.93	3.24	25.56	0.94	7.363	0.018	19[a]	1.87
90	112.74	3.30	25.64	0.95	7.366	0.018	18[a]	1.47
120	121.66	6.11	24.81	0.88	7.376	0.027	24[a]	3.61

[a]Values significantly lower ($p < 0.05$) than the preanesthetic values

ABP to which the animals are bled and maintained either through the removal of an additional quantity of blood or via the return of a portion of the shed blood volume (4). As it is hypovolemia, secondary to the loss of vascular volume, and not hypotension that is the underlying etiology in hemorrhage, the former model was chosen. This model would therefore most closely minic the true clinical setting and also allow for the resultant sympathoadrenal response to be characterized and studied (4). The blood volume removed from these cats could be classifed as "moderate" hemorrhage and compares favorably with those values used by other investigators (7-9,28).

Cardiac output, CI, SV, HR, CVP, SVR and ABP are cardiovascular parameters that are all related and a focus on one invariably involves a discussion of the others. Cardiac output is the product of HR and SV (1,29). Heart rate is essentially governed via alterations in autonomic nervous system input (i.e. sympathetic vs parasympathetic) and circulating humoral factors (i.e. catecholamines) (1,29). Stroke volume is a composite preload (CVP), afterload (SVR), and the existing state of myocardial contractility (1,29). Arterial BP is a function of blood volume, flow (CO), and the vascular resistance it meets (SVR) (5). Following hemorrhage CO, CI, SV, HR and ABP were all decreased with SVR showing an initial tendency to rise. The CO decline was associated with the reduction in SV secondary to a drop in blood volume and venous return (preload). The effect of SV on CO was compounded by the fall in HR. Although a compensatory rise in HR usually accompanies a hemorrhagic insult, it is not unusual for the rate to drop if the prehemorrhage levels are high (4). There is also marked individual variation (4). The mild (10%) rise in SVR could not offset the CO decline and ABP remained depressed.

Following the induction of K/A anesthesia, CO, CI, SV, HR and SVR remained essentially unchanged, experiencing minor depressions, whereas measurements of ABP showed dramatic and sustained declines. The relative sparing of CO and CI was related to the maintenance of HR and an interplay of those factors governing SV. A decrease in myocardial contractility will decrease SV. Ketamine alone and in combination with ACP is known to depress myocardial contractility (17,30) accounting for the mild postanesthetic reductions in SV and subsequently CO and CI. However, this negative influence on SV was offset, to a large degree, by factors affecting the SVR and vascular volume. Systemic vascular resistance remained essentially unchanged postanesthetic. The initial trend to rise, commonly seen posthemorrhage, failed to develop. Since a rise in vascular resistance is partially mediated through sympathetic alpha adrenergic receptors in peripheral arterioles, the use of ACP, an alpha antagonist, most likely accounted, to a large degree, for the lack of SVR rise. In addition, ketamine causes a dose dependent inhibition of the contractile response of vascular smooth muscle to catecholamines (12,13) which would also interfere with an elevation in SVR. This lack of rise in SVR, or afterload, would favor a maintenance, or decrease, in SV. A decline in blood viscosity, as evidenced in this experiment by the occurrence of hemodilution, would also favor a maintenance, or decrease, in SV.

This has been demonstrated to occur posthemorrhage and is the result of an influx of protein-free interstitial fluid into the intravascular compartment secondary to a lowered capillary hydrostatic pressure and an increase in serum osmolality (6-10). Capillary hydrostatic pressure is influenced by ABP, the relative resistance of pre vs postcapillary sphincter tone and right atrial pressure (6). A decline in ABP and right atrial pressure (i.e. preload) is the direct result of posthemorrhagic vascular volume loss. Acepromazine induced alpha antagonism will further reduce capillary hydrostatic pressure by directly lowering ABP and favoring the relative dominance of beta adrenergic receptors in the capillary beds. The rate and net fluid gain is mainly the result of a beta mediated decrease in capillary hydrostatic pressure and concomitant increase in the capillary surface area available for fluid exchange (6-9). It may be argued that the use of 5% dextrose in water (D5W) as the thermodilution tracer was a factor in the volume expansion. However, D5W is isotonic and the volume used over the experimental period was considerably less than the blood volume removed. On average, approximately 36 mL of D5W was used whereas blood loss averaged 56.5 mL/cat (± 8.54 SD) with an additional 9 mL taken (in 1 mL samples) for blood gas determina-

tions. This expansion of vascular volume was most likely the major reason for the 120 min measurements of CO, CI, and SV being above their respective posthemorrhagic (i.e. preanesthetic) indices.

The early postanesthetic decline in ABP and its persistence throughout anesthesia and into the 120 min reading was primarily due to the effects of the ACP mediated alpha adrenergic blockade. Other factors favoring the ABP decline included the mild drop in CO, the lack of a SVR rise and the inhibitory effect of ketamine on vascular smooth muscle (12,13).

Posthemorrhage, the $PaCO_2$ fell slightly corresponding with the dramatic elevation in RR, most likely a manifestation of the heightened sympathoadrenal state. Subsequently $PaCO_2$ remained within normal limits with the RR showing a dramatic decrease. The statistical significance of the RR decline was influenced by the high posthemorrhage, preanesthetic value but ketamine is known to be depressant to the respiratory system with respiration often being labelled irregular and apneustic (16,31). However, the normal PaO_2 and lack of a $PaCO_2$ rise indicated maintenance of an adequate alveolar ventilation. This relative lack of effect on arterial blood gas parameters has been cited by other investigators (20,32). The maintenance of normal arterial pH is of interest as usually hemorrhagic hypotension is associated with a progressive metabolic acidosis, considered to be secondary to arterial vasoconstriction and the subsequent capillary bed ischemia produced. The most likely explanation involves the ACP induced alpha adrenergic blockade and the resultant maintenance of nutritional blood flow through the capillary network.

Ketamine alone has been advocated for use in high risk patients due to its sympathomimetic effects (14,15). However, when combined with ACP it has been shown to possess potent cardiovascular depressant properties (20,21,30). Although in a clinical setting volume expansion would assuredly precede any anesthetic manipulation in the hypovolemic patient, the studied K/A combination and its effect on ABP would make it a poor anesthetic choice. Not only is K/A an injectable combination, and therefore lacks the potential for rapid reversal, it also depends on renal elimination (primarily ketamine) for patient recovery (33). The attendant decrease in glomerular filtration rate following hemorrhage may therefore allow for inordinately long anesthetic times extending the state of cardiovascular depression.

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