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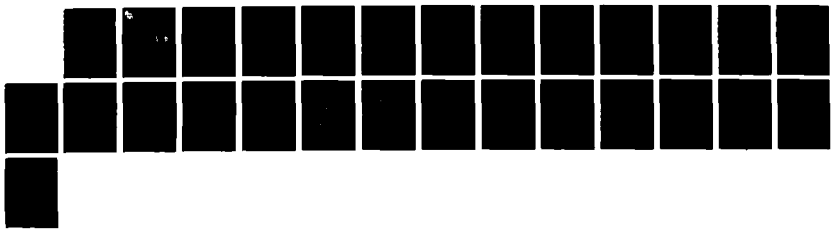

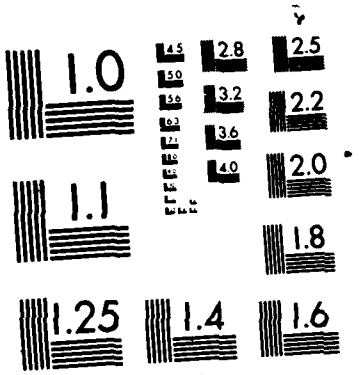

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EFFECTS OF ATROPINE, 2-PAM, OR PYRIDOSTIGMINE IN EUVOLEMIC OR HEMORRHAGIC CONSCIOUS SWINE

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Effects of atropine, 2-PAM, or pyridostigmine in euvolemic or hemorrhagic conscious swine--Wade et al.

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We investigated the effects of atropine, pralidoxime chloride (2-PAM), or pyridostigmine on the physiological and metabolic responses to hemorrhagic hypotension in conscious swine. All treatments were evaluated in euvolemic and hemorrhaged animals (36 ml of blood/kg/over one hour). Hemorrhage reduced blood pressure by 58 mmHg and decreased plamsa acetylcholinesterase (AChE) activity by 18% in the control animals (n=6). Atropine injection increased heart rate similarly in hemorrhaged (n=6) and euvolemic (n=6) animals. Blood pressure was also transiently elevated following atropine administration. Injection of 2-PAM acutely elevated the levels of plasma lactate and plasma AChE, but values were similar to those in the untreated animals within 15 min in both euvolemic (n=7) and hemorrhaged (n=7) animals. Treatment with pyridostigmine for 3 days reduced plasma AChE by 37% and red blood cell AChE by 35% (n=12). Pretreatment with pyridostigmine had no effect on any of the responses to hemorrhage. Posthemorrhage treatment with atropine or 2-PAM or pretreatment with pyridostigmine had no detrimental effects on the physiological or metabolic responses to

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moderate hemorrhage in conscious swine.

Abstract

We investigated the effects of atropine, pralidoxime chloride (2-PAM), or pyridostigmine on the physiological and metabolic responses to hemorrhagic hypotension in conscious swine. All treatments were evaluated in euvolemic and hemorrhaged animals (36 ml of blood/kg/over one hour). Hemorrhage reduced blood pressure by 58 mmHg and decreased plasma acetylcholinesterase (AChE) activity by 18% in the control animals (n=6). Atropine injection increased heart rate similarly in hemorrhaged (n=6) and euvolemic (n=6) animals. Blood pressure was also transiently elevated following atropine administration. Injection of 2-PAM acutely elevated the levels of plasma lactate and plasma AChE, but values were similar to those in the untreated animals within 15 min in both euvolemic (n=7) and hemorrhaged (n=7) animals. Treatment with pyridostigmine for 3 days reduced plasma AChE by 37% and red blood cell AChE by 35% (n=12). Pretreatment with pyridostigmine had no effect on any of the responses to hemorrhage. Posthemorrhage treatment with atropine or 2-PAM or pretreatment with pyridostigmine had no detrimental effects on the physiological or metabolic responses to moderate hemorrhage in conscious swine.

Keywords: Wounds and injuries; Trauma

INTRODUCTION

Military personnel are to be issued a nerve agent antidote kit (NAAK), which consists of atropine and pralidoxime chloride (2-PAM) (1,2), for treatment of nerve agent poisoning. Pretreatment with pyridostigmine to be taken in anticipation of nerve agent attack may also be used (2,3). It is assumed that individuals pretreated with pyridostigmine may incur conventional battlefield injuries (4) and that casualties will receive postexposure therapies (5). The effects of these pharmacological pretreatments and antidotes on the care and outcome of the casualty with conventional injuries are unknown. Of concern are the nerve agent antidote's pharmacological effects on the physiological and metabolic responses to injury, interference with the triage of casualties, interaction with analgesics and anesthetics, and patient variability in the response to and recovery from surgery. The present studies were undertaken to investigate the effects of atropine, 2-PAM, or pyridostigmine administration on the physiological and metabolic responses to hemorrhagic hypotension in conscious swine.

METHODS

Immature (2- to 3-month-old) Yorkshire swine (gilts and barrows) weighing 20 to 25 kg were studied. The animals were purchased from a commercial supplier and housed in the Institute for at least ten days prior to surgery. They were fed a commercial ration (Purina) and allowed water ad lib.

After fasting overnight, each animal was given a preanesthetic intramuscular injection of 0.08 mg/kg atropine sulfate, 2.2 mg/kg ketamine HCl and 2.2 mg/kg xylazine. Halothane anesthesia was induced using a face mask and maintained with an endotracheal tube. The posterior aorta and jugular vein were catheterized using sterile procedures (6). The catheters were tunneled under the skin; the arterial catheter exited on the dorsal surface of the back, and the venous catheter via the neck. The animal was observed until fully recovered and returned to a holding cage. Catheter patency was maintained by flushing at 3- to 4-day intervals with heparin (1000 u/ml) in normal saline.

After five to seven days of postoperative recovery, the animals were fasted overnight. The following morning

the animals were transported to the laboratory in a portable holding cage. The pigs remained in the holding cage throughout the experiment. The animals were connected to a 12-inch pressure-monitoring injection line fitted with a three-way stopcock and filled with heparinized saline. The system was then flushed with heparinized saline and connected to a pressure transducer and monitoring system (Gould, Model 24005, Cleveland, OH). Following a 30-minute equilibration period, the animals remained euvolemic or were bled at a rate of 36 ml/kg over a 60-minute period for an estimated 50% loss of blood volume. The one-hour bleeding period was selected arbitrarily to simulate a hemorrhage that might be seen in a combat casualty. The rate of blood loss was based again arbitrarily on an exponential scale such that 10% increments of the total estimated blood volume were removed uniformly over successive intervals of 9, 10, 11.5, 13.5, and 16 minutes. Upon completion of the hemorrhage the animals were studied for an additional three hours. Hemodynamic measurements and blood samples (20 ml) were obtained throughout the 60-min hemorrhage period and for three hours during recovery (see Fig. 1 for sample times). Animals underwent one of the following treatments:

1. Saline Control: Upon completion of the hemorrhage period, animals (n=6) were injected intra-arterially with 0.1 ml/kg of normal saline (0.9% NaCl). This infusion volume was selected because it was similar to the carrier volume infused in previous studies.

2. Atropine: Animals were injected intra-arterially with atropine sulfate 0.08 mg/kg (Sigma Chemical Co., St Louis, MO) taken up in 0.1 ml/kg of normal saline just after the 60-min sample was taken at the end of the hemorrhage period. Euvolemic animals (n=6) and hypovolemic animals (n=6) were evaluated. The dose of atropine selected is the total dose recommended for treating exposure to nerve agents, i.e., three Mark II autoinjectors (1).

3. 2-PAM: After the blood samples were taken during the 60-min hemorrhage, the animals were injected intra-arterially with 20 mg/kg of pralidoxime methochloride (2-PAM) (Aldrich Chemical Co., Milwaukee, WI) taken up in a 0.1 ml/kg of normal saline. Euvolemic (n=7) and hemorrhaged (n=7) animals were injected with 2-PAM after 60 minutes, at the completion of the hemorrhage. The dose

(20 mg/kg) is similar by weight to the recommended total dose, i.e. 3 Mark II autoinjectors (1).

4. Pyridostigmine: Pyridostigmine bromide (Mestinon®, Roche Laboratories, Nutley, NJ) was administered orally at 1500, 2300, and 0700 hours at 60 mg per dose for three days. The pyridostigmine was administered in the liquid form by a syringe from which the animal voluntarily licked the contents. Prior to administration of pyridostigmine a blood sample was obtained on day 0 to measure basal plasma and red blood cell acetylcholinesterase activity. On the day of the experiment, procedures were begun at 0900 hours, two hours after the last dosing. Seven animals underwent hemorrhage, while five animals served as euvolemic controls. The dose of pyridostigmine, approximately 9 mg/kg/day, was selected because it had produced the desired reduction (30% to 50%) in plasma and red blood cell acetylcholinesterase activity (2, 3, 7-10).

Blood pressure and heart rate were measured for one minute during each sampling period from the blood pressure tracing and an average obtained. Blood lactate (Sigma Chemical Co, St. Louis, MO) and glucose (Beckman Instruments, Anaheim, CA) levels were measured by standard assay techniques. Hematocrit was measured by the microcapillary method. Blood gases were measured on a System 1303 (Instrumentation Laboratory, Lexington, MA). Plasma and red blood cell acetylcholinesterase activities (AChE) were measured using a Technicon Auto Analyzer II system with modification of the method of Ellman et al (11), that had been adapted by Levine et al (12) and using acetylthiocholine as the substrate (see Letterman Army Institute of Research standard operating procedure OP-ACH-38, 1982 and update). The method of Groff and Ellin (13) was used to measure the levels of 2-PAM in plasma.

Data were analyzed using a two-way analysis of variance with comparisons made between groups (a hemorrhage control versus hemorrhage drug treatment) and over time. Differences between means were assessed using a Newman-Keuls test. When appropriate, a t-test was used. A probability less than or equal to 0.05 was accepted as being significant. Values in the text are mean plus or minus the standard error of the mean.

RESULTS

Control: Hemorrhage produced a significant fall in mean arterial pressure (MAP) of 58 mm Hg (Figure 1, Table 1). MAP rose over the recovery period, but was still reduced in comparison to initial values. Heart rate was not significantly altered. Arterial Pco_2 was significantly reduced from 37 mm Hg at time 0 to 28 mm Hg at the end of hemorrhage and returned to basal values, 35 mm Hg, during the recovery period (Fig. 2, Table 2). Plasma glucose and blood lactate levels were increased over the course of hemorrhage and remained elevated throughout the recovery period (Figure 2, Table 3). Plasma acetylcholinesterase activity (AChE) decreased during the hemorrhage by 18% and remained reduced during the 3 hours of recovery (Figure 3, Table 4). Red blood cell AChE activity expressed per unit of packed cell volume was unchanged, but over the course of the experiment hematocrit was reduced from 27 to 21% (Table 3).

Atropine: Atropine administration resulted in a significant increase in heart rate which was similar in hemorrhaged and euvolemic animals (Fig. 4, Table 1). Blood pressure was also acutely elevated following atropine administration in hemorrhaged and euvolemic animals (Fig. 4, Table 1). Arterial Pco_2 levels of plasma glucose and blood lactate, and plasma and red blood cell AChE were not altered following atropine administration in euvolemic animals and were not significantly different following hemorrhage in comparison to untreated hemorrhaged animals (Tables 3, 4).

2-PAM: The administration of 2-PAM did not significantly alter blood pressure or heart rate in euvolemic animals and did not change the response to hemorrhage (Table 1). Blood glucose levels, red blood cell AChE activity, and arterial Pco_2 also were not changed (Tables 2, 3, 4). However, in euvolemic animals the administration of 2-PAM caused an acute increase in lactate from 4.5 to 10.1 mg/dl at two minutes but the level returned to basal values within 15 minutes, and a similar trend was noted in plasma AChE activity (0.46 ± 0.05 to 0.50 ± 0.05 u/ml in two minutes) (Tables 2, 4). Following hemorrhage the lactate levels changed from 31.8 ± 3.4 mg/dl to 52.9 ± 3.6 mg/dl and the plasma AChE activity from 0.40 ± 0.04 U/ml to 0.47 ± 0.04 U/ml at two minutes with both parameters returning to pretreatment levels within 15 minutes. The plasma levels of 2-PAM were not significantly different during the recovery period in

treated euvolemic and hemorrhaged animals (Figure 5). The half-life of 2-PAM, 65 to 75 min, was therefore not altered by this degree of hemorrhage.

Pyridostigmine: Beyond the expected reduction in the AChE activities of red blood cells (to 65 $\pm$ 5% of initial values) and of plasma (to 63 $\pm$ 4% of initial values) following the three days of treatment, none of the measured variables showed significant changes in euvolemic animals over time or varied in the response to hemorrhage in comparison to untreated animals (Tables 1, 2, 3, and 4). The decrease in plasma AChE activity during hemorrhage, 17%, was similar to that observed in euvolemic animals, 20% (Table 4), following administration of pyridostigmine (Table 4).

DISCUSSION

In the investigation of atropine, 2-PAM, or pyridostigmine administration on the physiological and metabolic responses to hemorrhage, possible detrimental effects leading to a decrease in survival were of concern. However, the moderate hemorrhage in this study of conscious swine caused no severe adverse effects with any of the therapies investigated.

A change in heart rate was shown with atropine injection in both euvolemic and hypovolemic animals. The increase in heart rate did not attain maximal values for pigs (14). In humans the dose of atropine used in our study produces only a moderate increase in heart rate (15, 16). The slight but significant increase in blood pressure of about 10 mm Hg observed with atropine may be beneficial and may in fact possibly influence survival in severe hemorrhage. In humans, however, a slight decrease in systolic blood pressure has been reported (15, 16). Though no negative effects were found, we are still concerned about the responses to atropine (tachycardia, mydriasis, dizziness, lassitude and increased body temperature in some instances) which would interfere with the triage of the battlefield casualty. This problem has yet to be resolved.

The administration of 2-PAM produced acute increases in blood lactate and plasma AChE activity. The increase in lactate during hemorrhage may be detrimental if adequate buffering capabilities are not available. Plasma lactate concentration is indicative of outcome (survival)

in a variety of traumatic conditions (17, 18, 19). The rise in plasma AChE activity due to 2-PAM may be beneficial by partly rectifying the reduction in activity incurred during hemorrhage. However, both the increases in blood lactate and plasma AChE activity in response to 2-PAM administration were acute, lasting 5 minutes, and would appear to have no influence on the care or outcome of the combat casualty.

The clearance of 2-PAM from the plasma was not altered by hemorrhage in the present study, though a reduction due to a decrease in metabolism and excretion associated with falls in renal and hepatic blood flow during hemorrhage was postulated (20, 21). The observed half life of 2-PAM in pigs is 65 to 75 min, similar to that in man (22).

Although the reduction in AChE activity achieved in the swine chronically administered pyridostigmine was similar to that in man with the pretreatment dose, i.e. 20-40%, a larger dose per kilogram was required. Furthermore, the measured metabolic and physiologic responses to hemorrhage in the swine were not altered by pyridostigmine. It thus appears that pretreatment with pyridostigmine will not be of immediate concern in the outcome of the combat casualty. However, the interaction of pyridostigmine with anesthetics and analgesics, specifically morphine (23, 24), is still of concern.

In untreated animals, plasma AChE activity was reduced with hemorrhage and remained decreased over the course of the experiment. Others have reported a similar fall in total blood AChE activity with hemorrhage and in burn victims (25-29). The 18% reduction in plasma AChE activity in the present study could have been caused primarily by transcapillary refill, which may account for as much as 30% of the plasma volume following this degree of hemorrhage (30, 31). Frawley et al (27) reported that AChE activity may remain at a reduced level for days after a battlefield injury. In the present study, while no change in red blood cell AChE activity per milliliter of packed cell volume was found, there was a reduction in red cell volume due to hemorrhage, resulting in a decrease in total vascular red blood cell AChE activity. The combined reduction of AChE associated with red blood cells and plasma represents a 57% decrease in vascular AChE activity.

A fall in vascular AChE activity does not indicate associated changes in autonomic nervous system function, as changes in plasma levels may not reflect changes in AChE at the synaptic cleft. The decrease in available AChE in the vascular compartment is possibly of little consequence since inhibition of up to 90% of activity is necessary to produce abnormal function, due to AChE being present in most tissues in quantities in excess of that normally required to degrade acetylcholine (32). However, the decrease in AChE due to hemorrhage may explain the findings of Piscevic et al (33) that simultaneous hemorrhage and chemical agent trauma resulted in the death of animals exposed to normally nonlethal doses of the nerve agent sarin. Thus, the reduction in AChE activity that occurs during traumatic hemorrhage may potentiate the responsiveness to acetylcholine (nerve agents).

In conclusion, pharmacological pretreatment with pyridostigmine or the administration of the antidotes atropine or 2-PAM does not appear to affect the physiological and metabolic responses to hemorrhagic hypotension as investigated in conscious swine not exposed to nerve agent poisoning. Of concern still are the possibilities that these agents may interfere with analgesics and anesthetics, and may vary the response to and recovery from surgery. These issues remain to be investigated.

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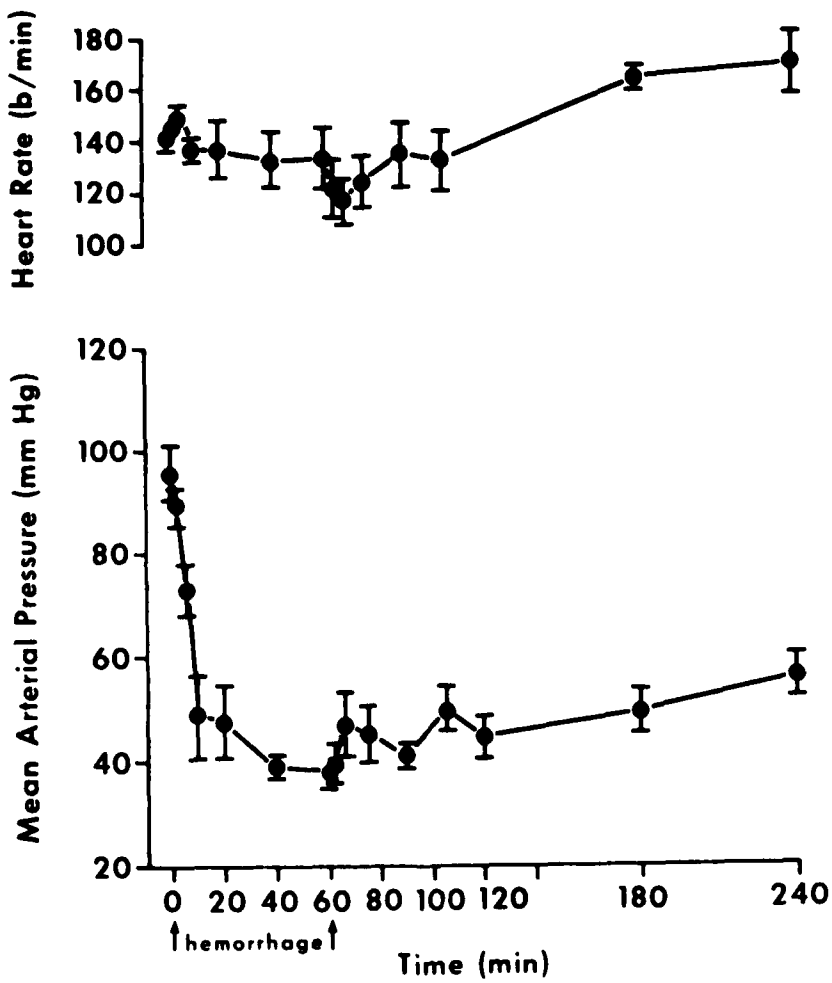

Figure 1: Heart rate and mean arterial pressure in response to hemorrhage in six conscious swine.

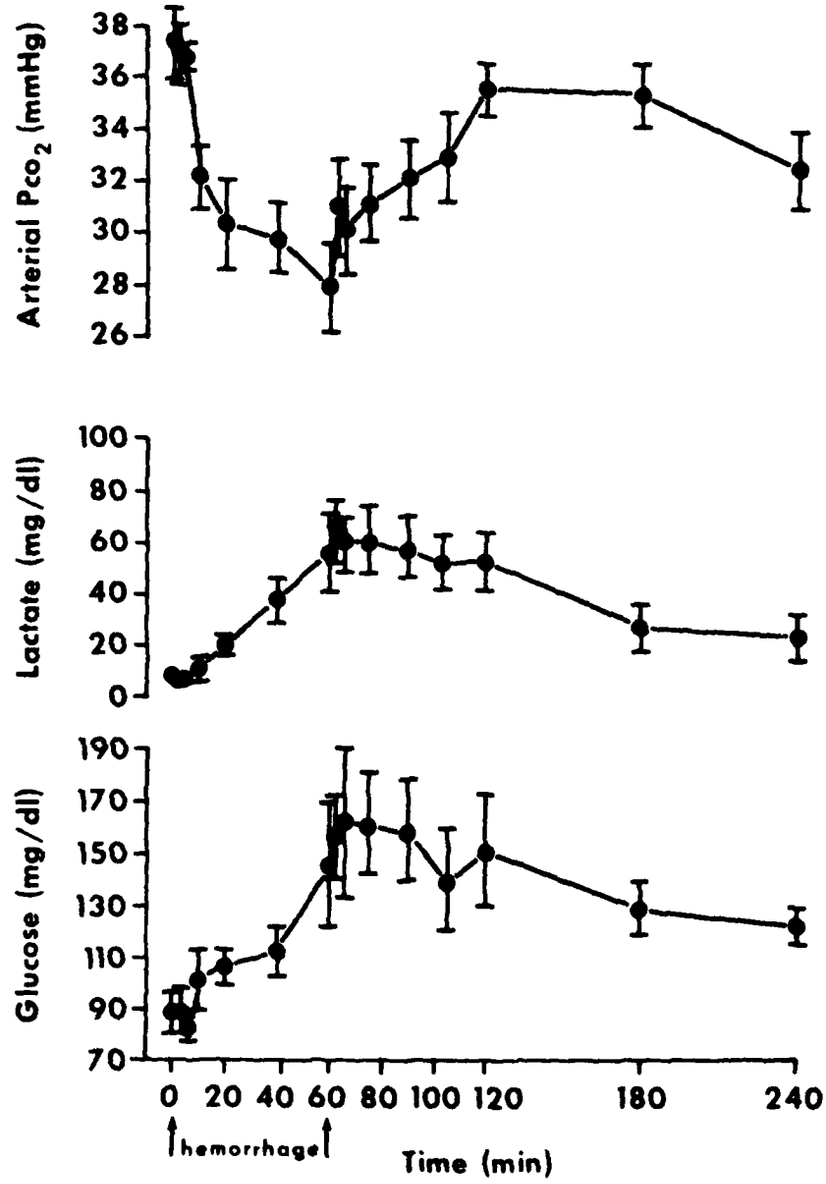

Figure 2: Arterial CO_2 pressure, blood lactate and blood glucose levels in response to hemorrhage in six conscious swine.

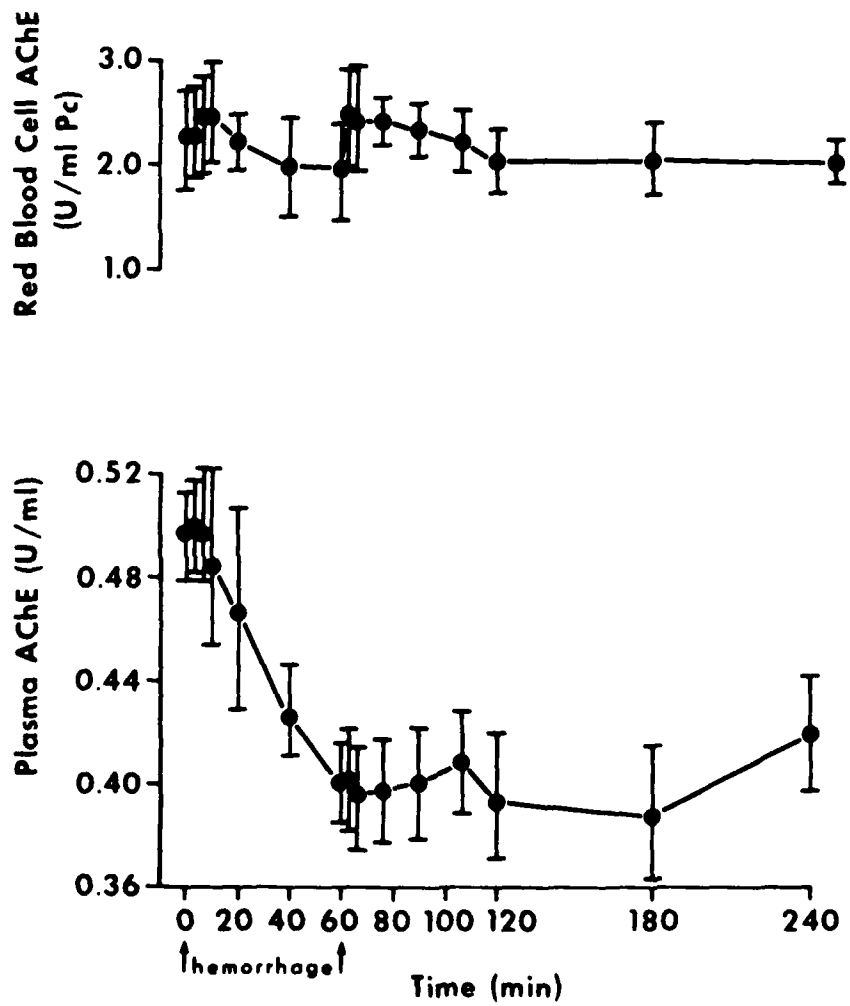

Figure 3: Plasma and red blood cell acetylcholinesterase activity (AChE) in response to hemorrhage in six conscious swine.

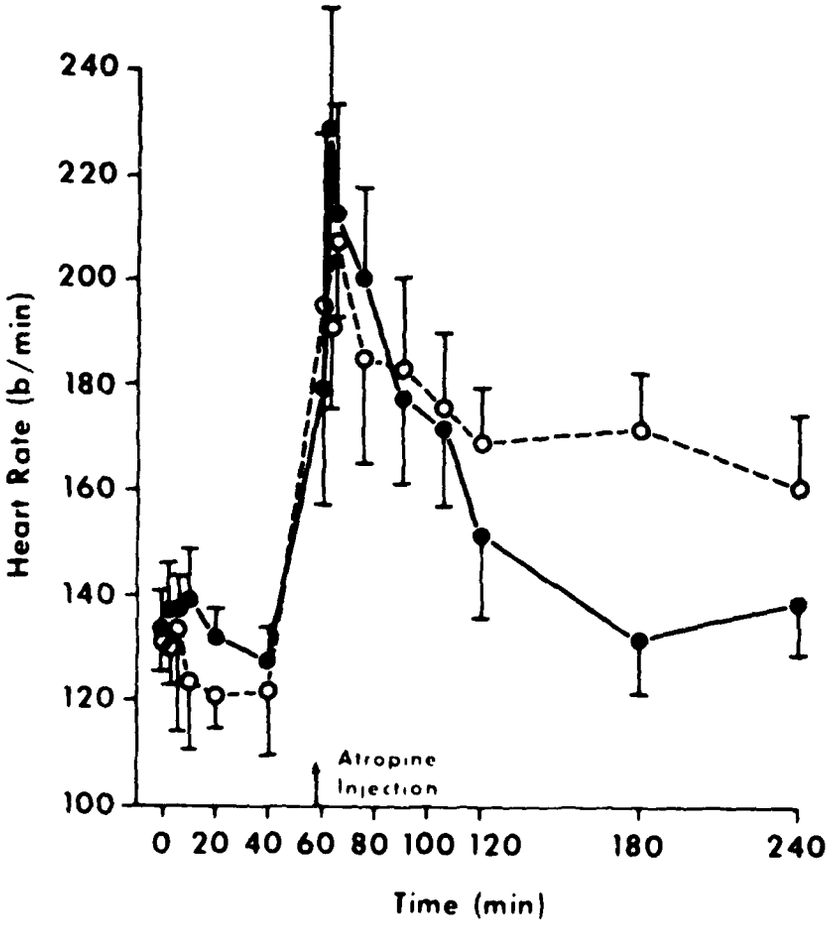

Figure 4: Heart rate response to intra-arterial atropine administered at 60 min in euvolemic (●——●) and hypovolemic (O----O) conscious swine.

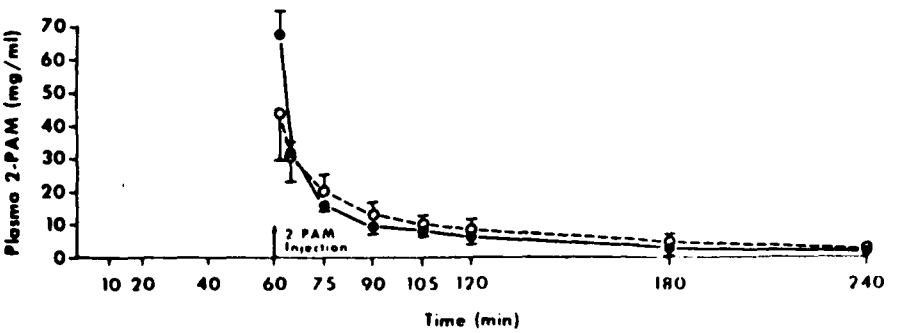

Figure 5: Plasma 2-PAM levels in response to intra-arterial administration in euvolemic (●——●) and hypovolemic (O----O) conscious swine.

Table 1: Mean arterial pressure, pulse pressure, and heart rate of swine with euvolemia (E) or hemorrhage (H) (0-60 min) with treatment of control (C), atropine (A), 2-PAM (2P), or pyridostigmine (P).

	Time (min)									
	0	60	62	65	75	90	105	120	180	240
Mean Arterial Pressure (mmHg)										
H-C	96±5	38±3	39±4	48±6	45±5	41±2	58±4	44±4	49±4	58±4
E-A	97±3	106±5	107±6	101±6	105±6	112±14	111±8	100±9	96±10	93±8
H-A	95±4	45±4	52±5	57±4	48±4	55±3	56±2	55±3	54±5	66±6
E-2P	97±5	88±6	91±4	89±6	84±6	86±8	92±8	96±6	100±8	95±8
H-2P	101±5	38±4	65±7	52±6	44±3	48±7	48±5	50±4	54±4	64±5
E-P	99±5	105±3	[a]	103±5	104±3	99±3	102±6	104±3	102±5	[a]
H-P	102±4	33±2	[a]	41±3	42±3	47±5	54±6	48±5	50±6	[a]
Pulse Pressure (mmHg)										
H-C	53±7	39±7	45±8	34±3	44±10	42±8	49±13	52±12	49±14	59±19
E-A	50±2	41±4	38±5	36±4	42±4	35±5	40±4	38±6	38±5	37±5
H-A	58±3	34±5	28±3	26±3	36±11	36±3	34±5	35±1	41±7	48±7
E-2P	46±6	45±6	43±5	44±5	43±5	44±6	42±6	42±5	38±5	39±5
H-2P	62±6	35±6	41±11	38±9	39±3	42±1	43±3	43±3	42±4	45±6
E-P	54±7	50±7	[a]	53±3	51±8	50±8	46±8	48±7	44±7	[a]
H-P	61±9	28±5	[a]	23±4	33±5	38±5	34±3	28±3	32±4	[a]
Heart Rate (beats/min)										
H-C	141±5	132±12	121±10	116±9	123±11	136±13	132±11	141±12	162±5	167±11
E-A	134±7	139±24	229±24*	213±20*	200±18*	178±17*	172±15*	151±16*	132±10	138±10
H-A	132±6	120±12	192±18+	208±19+	185±17+	183±14+	176±13+	168±10+	172±10	161±13
E-2P	141±9	131±8	123±7	123±6	119±7	121±5	122±4	131±8	130±8	119±8
H-2P	137±8	139±3	125±9	124±10	125±13	131±11	136±13	140±17	142±14	155±15
E-P	131±5	125±7	[a]	126±9	126±5	128±9	125±10	130±10	123±10	[a]
H-P	143±8	128±12	[a]	111±11	112±6	119±9	120±14	125±9	134±13	[a]

[a]Values not obtained; +Significantly different from H-C, P<0.05; *Significantly different from 60 min for euvolemic animals.

Table 2: Arterial blood gas measurements in conscious swine with euvolemia (E) or hemorrhage H (0-60 min) with treatment of control (C), atropine (A), 2-PAM (2P), or pyridostigmine (P).

	Time (min)									
	0	60	62	65	75	90	105	120	180	240
Po_2 (mmHg)										
H-C	99±4	124±5	100±5	95±2	112±5	107±10	117±6	100±6	109±6	121±8
E-A	99±3	86±3	87±3	94±2	86±2.2	92±10	85±9	77±3	83±3	82±2
H-A	88±2	109±6	107±7	99±4	114±3	103±6	112±10	116±7	101±5	100±6
E-2P	87±4	84±3	89±4	83±1	80±1.5	80±2	84±4	81±3	91±7	86±4
H-2P	84±3	99±6	100±3	100±2	107±7	102±9	102±5	101±7	99±6	90±4
C-P	92±3.3	82±4	----[a]	----[a]	83±4	67±4	----[a]	84±4	85±3	----[a]
H-P	94±3	116±2	----	----	111±3	103±2	----	106±2	104±2	----
Pco_2 (mmHg)										
H-C	37.4±1.2	27.8±1.7	31.3±1.9	30.2±1.6	31.2±1.4	32.2±1.5	33.0±1.8	35.6±1.0	35.4±1.4	32.4±1.5
E-A	38.8±1.6	39.9±1.0	37.3±2.6	37.9±3.6	37.6±1.5	39.6±1.7	40.9±2.7	41.4±2.6	39.6±2.3	40.4±1.6
H-A	39.9±0.9	31.8±1.3	35.6±0.5	35.0±0.6	35.6±1.0	35.9±0.6	36.0±0.5	36.4±0.9	38.6±1.0	37.7±1.6
E-2P	37.6±1.6	39.1±1.4	38±1.5	38.3±0.9	38.7±1.5	38.7±1.2	38.8±1.5	38.1±1.0	37.2±1.2	38.6±1.0
H-2P	36.5±0.6	30.5±2.2	35.2±0.7	33.9±1.6	34.8±0.8	34.7±1.5	34.1±0.5	36.0±1.2	36.1±1.0	37.3±0.5
E-P	38.3±0.4	40.6±1.9	----[a]	----[a]	40.2±1.3	37.9±1.5	----[a]	38.4±1.8	39.4±0.9	----[a]
H-P	35.5±0.8	26.4±1.3	----	----	38.4±1.8	32.3±2.2	----	32.3±2.1	33.2±1.7	----
pH										
H-C	7.429±.010	7.458±.022	7.421±.017	7.417±.014	7.466±.009	7.418±.015	7.425±.014	7.419±.012	7.441±.018	7.466±.019
E-A	7.438±.013	7.439±.009	7.458±.025	7.447±.032	7.431±.002	7.426±.012	7.431±.021	7.428±.020	7.442±.021	7.438±.017
H-A	7.427±.010	7.457±.022	7.396±.006	7.409±.012	7.463±.010	7.394±.020	7.432±.009	7.418±.009	7.424±.006	7.447±.011
E-2P	7.444±.014	7.438±.010	7.458±.013	7.438±.012	7.434±.012	7.438±.013	7.439±.012	7.439±.007	7.440±.012	7.436±.006
H-2P	7.477±.018	7.486±.028	7.418±.013	7.414±.010	7.413±.014	7.437±.014	7.454±.020	7.450±.015	7.456±.014	7.449±.012
E-P	7.492±.014	7.483±.012	----[a]	----[a]	7.475±.011	7.486±.016	----[a]	7.486±.016	7.481±.005	----[a]
H-P	7.474±.016	7.504±.033	----	----	7.431±.020	7.426±.019	----	7.451±.017	7.473±.014	----
HCO_3 (mmol/l)										
H-C	25.3±1.2	19.8±0.8	20.6±0.7	19.6±0.4	19.8±0.6	21±0.8	21.9±0.6	23.4±1.0	24.4±1.3	24.2±0.8
E-A	26.2±0.8	27.3±0.6	26.8±0.3	26.4±1.2	25.4±0.8	26.2±1.0	27.4±1.4	27.5±0.8	27.2±1.0	27.6±1.0
H-A	26.7±1.2	22.7±0.9	22.1±1.4	22.5±1.4	22.4±1.1	22.3±1.4	24.2±1.1	23.7±0.9	25.5±1.2	26.2±1.2
E-2P	26.8±1.2	26.6±0.6	26.6±0.6	26.1±0.5	26.1±0.8	26.3±0.4	26.4±0.6	26.1±0.6	25.5±0.3	25.6±0.4
H-2P	27.3±1.0	23.1±1.2	22.4±0.9	21.9±1.2	23.4±0.6	23.6±1.2	24.5±1.0	25.5±1.3	25.8±1.3	26.2±1.0
E-P	29.7±0.9	30.6±1.0	----[a]	----[a]	29.8±1.0	28.8±0.8	----[a]	29.8±0.9	28.7±0.8	----[a]
H-P	26.2±1.2	21.1±1.4	----	----	26.6±1.7	21.6±1.9	----	22.8±1.8	24.8±1.8	----

[a] Values not obtained.

Table 3: Blood lactate, blood glucose, and hematocrit values in swine for euvolemia (E) or hemorrhage (H) (0-60 min) with treatment of control (C), atropine (A), 2-PAM (2P), or pyridostigmine (P).

	Time (min)									
	0	60	62	65	75	90	105	120	180	240
Blood Lactate (mg/dl)										
H-C	9±1	56±15	67±12	60±10	61±13	59±12	52±11	53±11	27±9	22±9
E-A	8±1	7±1	6±1	11±3	12±3	6±1	8±1	5±1	6±3	5±1
H-A	11±4	40±6	43±7	48±9	46±7	40±6	38±9	32±9	20±7	19±4
E-2P	6±1	4±1	10±1*	7±1*	6±1	5±1	5±1	5±1	5±1	5±1
H-2P	5±1	27±5	48±6	35±5	31±3	26±3	20±2	16±3	9±2	11±2
E-P	4±1	4±1	---[a]	---[a]	4±1	6±3	---[a]	6±3	3±1	---[a]
H-P	15±2	53±12	---	---	67±15	66±17	---	52±13	33±10	---
Blood Glucose (mg/dl)										
H-C	89±7	145±24	157±16	163±29	162±19	159±20	138±21	151±21	129±10	123±8
E-A	75±4	72±5	69±7	75±8	81±9	77±4	75±3	77±2	71±10	85±14
H-A	78±3	113±7	116±15	128±18	118±15	108±8	105±10	100±7	95±16	129±19
E-2P	91±6	88±7	98±12*	97±12	92±5	96±9	99±9	86±5	88±6	93±11
H-2P	88±4	128±9	150±17	129±14	127±13	119±11	115±10	109±12	111±8	120±10
E-P	63±4	67±5	---[a]	---[a]	64±3	66±3	---[a]	64±4	65±6	---[a]
H-P	83±7	124±15	---	---	142±2	140±18	---	127±19	124±18	---
Hematocrit (%)										
H-C	27.2±1.5	22.6±1.6	22.7±1.4	22.5±1.4	22.5±1.5	22.3±1.5	22.7±1.7	21.7±1.8	21.7±1.7	21.0±1.7
E-A	28.5±1.6	27.7±1.4	27.5±1.8	26.3±1.4	26.7±1.5	26.0±1.4	26.2±1.3	25.5±1.5	25.7±1.4	26.0±1.2
H-A	26.8±1.0	22.5±0.9	21.2±1.1	21.3±0.6	20.2±0.9	20.0±1.0	19.8±1.0	19.8±0.8	19.5±0.9	20.2±1.1
C-2P	26.7±0.6	26.7±0.9	26.8±0.7	27.0±0.8	26.4±0.7	26.1±0.6	26.1±0.7	25.8±0.7	25.8±0.9	25.4±1.0
H-2P	26.3±0.8	23.2±0.9	23.1±0.9	22.7±0.7	22.3±0.6	21.9±0.6	21.7±0.5	21.1±0.5	21.1±1.3	21.1±1.0
E-P	28.4±1.8	27.2±1.1	----[a]	----[a]	27.6±1.5	27.6±1.4	----[a]	27.2±0.8	27.2±1.0	----[a]
H-P	29.3±0.4	22.6±0.8	----	----	22.4±0.8	22.1±1.0	----	21.7±1.2	20.1±0.9	----

[a]Values not obtained; *Significantly different for euvolemic animals from 60-min value, P<0.05.

Table 4: Plasma and red blood cell acetylcholinesterase activity (AChE) as a percent of initial value in conscious swine during euvolemia (E) or hemorrhage (H) (0-60 min) with treatment of control (C), atropine (A), 2-PAM (2P), and pyridostigmine (P).

	Time (min)									
	0	30	32	45	75	90	105	120	180	240
Plasma AChE (%)										
H-C	100±3.8[a]	80±3.2	81±4.2	79±4.2	79±4.2	81±4.8	82±4.4	79±6.2	78±5.4	84±4.6
E-A	100±12	105±12.6	105±12.8	100±14.3	107±12.5	101±12.6	106±3.7	101±14.5	104±11.4	98±9.4
H-A	100±12.3	80±8.3	84±13.1	87±14.3	83±10.9	81±12.1	78±8.5	81.9±11.5	79±10.7	88±11.5
E-2P	100±1.1	102±10.5	109±11	105±10	103±9.0	104±11.0	101±11.0	102±10.0	101±9.0	102±9.0
H-2P	100±8.0	88±8.0	103±8.0	92±8.0	87±8.0	81±8.0	84±8.0	88±8.0	87±8.0	91±8.0
E-P	61±10.0	58±10.0	[b]	[b]	57±10.0	59±10.0	[b]	59±8.0	56±10.0	[b]
H-P	65±4.5	48±4.3	[b]	[b]	46±3.6	47±4.0	[b]	44±4.3	44±4.2	[b]
RBCA (%)										
H-C	100±21[c]	85±19	111±22	107±23	106±11	103±15	98±16	90±12	90±16	88±9
E-A	100±16	126±22	100±19	115±16	119±25	104±20	98±12	80±9	79±18	101±12
H-A	100±8	94±15	88±12	84±14	90±13	86±14	92±12	92±11	89±10	165±16
E-2P	100±17	94±22	81±13	80±10	90±15	88±12	97±14	99±16	115±16	101±16
H-2P	100±28	82±18	114±38	124±34	86±13	96±24	86±11	92±16	91±19	85±18
E-P	49±4	52±6	[b]	[b]	52±6	58±5	[b]	[b]	55±6	63±6
H-P	78±7[+]	67±9.4[+]	[b]	[b]	64±9[+]	63±8[+]	[b]	[b]	55±6[+]	51±4[+]

[a] Initial values for plasma (U/ml): H-C = 0.496±0.018; E-A = 0.490±0.061; H-A = 0.504±0.62; E-2P = 0.457±0.048; H-2P = 0.465±0.038; E-P = 0.492±0.064; H-P = 0.447±0.067.

[b] Values not obtained.

[c] Initial values for red blood cell (U/ml P): H-C = 4.11±0.99; E-A = 4.20±0.70; H-A = 4.82±0.40; E-2P = 2.46±0.31; H-2P = 2.68±0.75; E-P = 3.66±0.39; H-P = 3.71±0.21.

[+] Significantly different from H-C, $P<0.05$

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