Effects of Almitrine Bismesylate in a Microswine Model of Hypoxemic Hypothermia

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We have developed an anesthetized microswine model of hypoxemic hypothermia and rewarming for testing prophylaxes and treatments. The respiratory stimulant almitrine bismesylate (ALM) was considered as a potential field expedient therapy for hypoxemic hypothermia. Preliminary experiments demonstrated that five consecutive 100 $\mu g \cdot kg^{-1}$ ALM intravenous (iv) doses given to normothermic microswine 3-4 min apart increased minute ventilation from an average of 3.4 $L \cdot min-1$ to 4.5 $L \cdot min^{-1}$ (n = 2). However, when either a single iv ALM dose of 150 $\mu g \cdot kg^{-1}$ (n = 1) or three consecutive 100 $\mu g \cdot kg^{-1}$ iv doses given 15 min apart (n = 1) to hypoxemic hypothermic microswine with a mean esophageal temperature (Tes) = 28.8°C, and a mean arterial O_2 partial pressure (PaO_2) = 49 mmHg, the hypoxemia was potentiated (mean PaO_2 = 32 mmHg) and respiratory arrest ensued. Other experiments using continuous ALM iv infusion (1.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$) in hypoxemic hypothermic microswine (n = 6, Tes = 30.6 ± 0.5, PaO_2 = 55.4 ± 12.9) did not demonstrate significant ($p \leq 0.05$) cardiorespiratory differences (ventilation, heart rate, blood pressure, blood gases) when compared to hypoxemic hypothermic controls (n = 6, Tes = 30.7 ± 0.5, PaO_2 = 53.3 ± 13.6). These results suggest that high dose iv bolus administration of ALM is not indicated as a potential field expedient therapy for hypoxemic hypothermia, while further work is required to assess the potential efficacy of other continuous low dose iv infusion regimens.

THROUGHOUT HISTORY, hypothermia has been a major threat to military operations (6,14). This threat is magnified at altitude since ambient temperature decreases an average of 2.0°C for every 300 m of elevation (5); thus, soldiers deployed to mountainous terrain are subjected not only to hypoxia, but also the threat of hypothermia. At high altitude, the combination of hypoxemia and hypothermia presents a serious hazard to individual and unit effectiveness.

Some of the physiologic effects of hypoxia include peripheral vasoconstriction, dehydration, and hemoconcentration (5), all of which are also induced by hypothermia (22). Thus, a higher incidence and greater severity of hypothermia-related injuries can be expected when altitude and cold are combined, and their effects are generally additive (12). Ultimately, death may occur consequent to hypoxemia, hypothermia and/or subsequent resuscitation.

When a severely hypothermic mountain casualty (core temperature < 30°C) is found, the potential for life-threatening cardiac arrhythmias is a primary concern because of the hyperirritability of the compromised myocardium. Both hypoxia and hypothermia are noncardiogenic causes of ventricular arrhythmias, and ventricular fibrillation may be precipitated simply by the physical agitation of transport over rugged terrain to an evacuation helicopter (18,21). While supplemental oxygen can reduce this propensity for fibrillation (21), the logistical problems of transporting oxygen cylinders over mountainous terrain would render it, at best, an inconvenient field treatment, especially with multiple casualties. The advantages of a drug such as almitrine bismesylate (ALM, Vectarion®, Servier Laboratories, Orleans, France) are that it does not require sophisticated equipment for use, and can be rapidly administered to multiple casualties.

ALM is a rapidly-acting and persistent respiratory stimulant which increases pulmonary ventilation by specifically stimulating the carotid body (15,17), irrespective of the level of oxygenation (10). It has also been suggested that ALM improves the pulmonary ventilation/perfusion ratio by redistributing blood from poorly ventilated to better ventilated areas via finely regulated hypoxic pulmonary vasoconstriction (HPV) (16,20).

We hypothesized that ALM would increase arterial oxygenation in hypoxemic hypothermic microswine by mechanisms related to peripheral chemoreceptor stimulation and/or HPV. If ALM has the potential to be a practical and effective field expedient treatment for hypoxemic hypothermia allowing for safe patient transport, it would be a valuable countermeasure with immediate impact for treating altitude and cold illness and injury.

METHODS

Animals

The Institutional Animal Care and Use Committee approved the experimental protocol describing this study

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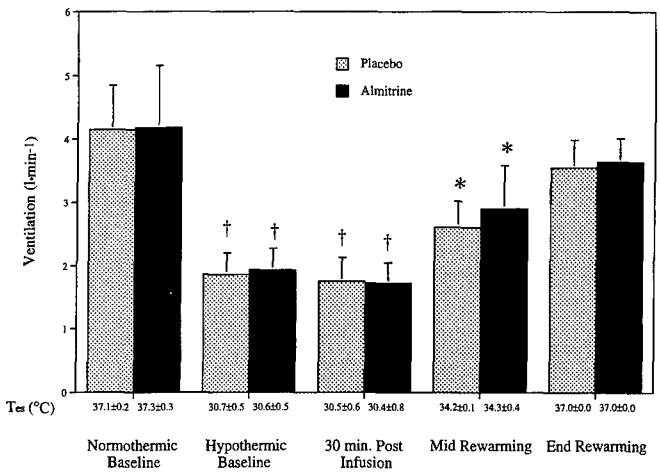

Fig. 1. Minute ventilation responses to hypoxemic hypothermia and rewarming comparing effects of continuous ALM infusion (1.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$) and PCB groups (n = 6). There were no differences between ALM and PCB groups. Values are means ± SD; Tes = mean esophageal temperature; * indicates significance from normothermic baseline, † indicates significance from both normothermic baseline and end rewarming ($p \leq 0.05$).

prior to initiation. The animals were maintained under the surveillance of a veterinarian in a facility fully accredited by the American Association for Accreditation of Laboratory Animal Care.

Microswine (Charles River Laboratories, Wilmington, MA) were used in this study for several reasons. The pathophysiology and biochemistry of swine have been well-documented (2,3,19). Unlike rats and rabbits, they have sufficient blood volume to allow the requisite consecutive samples. They were preferred over dogs because their physiology has been reportedly "closer" to humans (2,3), and are usually regarded as a non-pet species.

Eight barrows, 7-8 mo old, weighing 33.3 ± 2.2 kg were used. The animals were socially housed in fiberglass pens with slatted floors with ad lib access to water via an automatic watering system. Miniswine laboratory chow was given in two daily feedings.

Since splenic contraction is the primary cause of hemoconcentration in hypothermic pigs (11), the microswine were first splenectomized under isoflurane anesthesia for the experimental model preparation. The pig, unlike the human, has a large and contractile spleen capable of storing 20-25% of the total red cell volume (13). Thus, release of splenic-sequestered erythrocytes into the circulation during hypothermia and/or rewarming may result in effects that do not occur in humans because of their comparatively small (1-2%) splenic red cell reserve (1,4,8).

At 3-4 weeks following the splenectomy, 18 gauge Tygon (Norton Performance Plastics, Akron, OH) jugular venous and carotid arterial catheters were aseptically implanted from a neck incision under isoflurance anesthesia for blood sampling, and ALM or malic acid placebo (PCB) intravenous (iv) infusion. These catheters were flushed with sterile saline (0.9%), filled with heparin (1000 units · ml^{-1}), exteriorized at the back of the neck, then the incision was routinely closed. Catheter patency was maintained by flushing with sterile saline and filling with heparin every 2-3 d.

Postoperative analgesia for both surgical procedures was provided by butorphanol tartrate (0.5 $mg \cdot kg^{-1}$, im) or nalbuphine HCl (1.0 $mg \cdot kg^{-1}$, im) for at least the first two postoperative days. Nafcillin sodium (8 $mg \cdot kg^{-1}$, iv) was administered intraoperatively, and once postoperatively as a prophylactic measure to offset the risk of infection from surgery. After catheterization and a 5- to 7-d recovery period, the experimental portion of the protocol was performed.

Physiological Measurements

Arterial blood pressure (P_a) was measured using a P23 ID transducer (Gould Electronics, Valley View, OH), and ventilation was measured using a 21072A pneumotach and 47304A flow transducer (Hewlett-Packard, Boise, ID). Tidal volume (V_T) and respiratory rate (RR) were integrated for determination of minute ventilation (V_E), corrected for body temperature and water vapor saturation (BTPS). Both P_a and V_E were recorded on a 2400S 4-channel physiological recorder (Gould Electronics, Valley View, OH). Esophageal temperature (T_{es}) was moni-

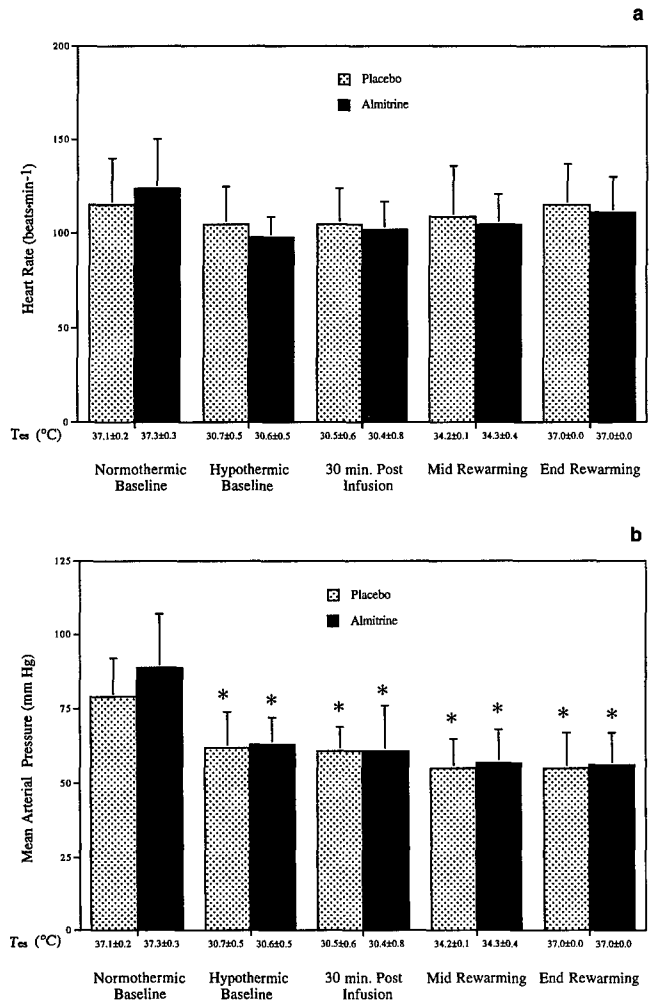

Fig. 2. a: Heart rate; and b: mean arterial pressure responses to hypoxemic hypothermia and rewarming comparing the effects of continuous ALM infusion (1.0 $\mu g \cdot kg^{-1} min^{-1}$) to equivalent PCB infusion. There were no differences between ALM and PCB groups (n = 6). Values are means ± SD; Tes = mean esophageat temperature; * indicates significance from normothermic baseline ($p \leq 0.05$).

TABLE I. ARTERIAL BLOOD GASES.

		Tes (°C)	P_{aO_2} (mmHg)	P_{aCO_2} (mmHg)	pH	HCO_3 ($mmol \cdot L^{-1}$)
Normothermic	ALM	37.3 ± 0.3	57.9 ± 9.1	47.2 ± 2.2	7.44 ± 0.02	31.6 ± 2.1
Baseline	PCB	37.1 ± 0.2	59.1 ± 5.1	47.6 ± 2.8	7.43 ± 0.01	31.6 ± 2.1
Hypothermic	ALM	30.6 ± 0.5	55.4 ± 12.9	53.9 ± 6.2	7.39 ± 0.04	35.3 ± 2.4
Baseline	PCB	30.7 ± 0.5	53.3 ± 13.6	54.9 ± 9.1	7.39 ± 0.05	35.3 ± 3.2
30 min Post	ALM	30.4 ± 0.8	51.8 ± 15.6	55.6 ± 7.4	7.36 ± 0.02	35.1 ± 2.3
Infusion	PCB	30.5 ± 0.6	50.9 ± 14.5	56.9 ± 8.4	7.37 ± 0.05	35.9 ± 2.4
Mid	ALM	34.3 ± 0.4	56.2 ± 7.9	53.4 ± 5.1	7.42 ± 0.02	35.3 ± 2.2
Rewarming	PCB	34.2 ± 0.1	55.5 ± 5.7	54.3 ± 7.4	7.41 ± 0.04	35.6 ± 2.5
End	ALM	37.0 ± 0.0	52.3 ± 7.2	48.8 ± 6.2	7.46 ± 0.03	34.3 ± 2.8
Rewarming	PCB	37.0 ± 0.0	50.4 ± 3.8	51.3 ± 5.9	7.45 ± 0.04	35.2 ± 1.9

Arterial blood gas responses to hypoxemic hypothermia and rewarming comparing effects of continuous almitrine (ALM) infusion (1.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$) to equivalent placebo (PCB) infusion. There were no significant ($p \leq 0.05$) differences between ALM and PCB groups. Values are means ± SD (n = 6). Esophageal temperature (Tes), arterial O_2 partial pressure (P_{aO_2}), arterial CO_2 partial pressure (P_{aCO_2}), arterial bicarbonate ion concentration (HCO_3^-).

tored using a 450-TH digital thermometer (Doric Scientific, San Diego, CA) with a series 400 rectal thermistor (Yellow Springs Instruments), Yellow Springs, OH).

Arterial and venous blood samples (1 ml) were collected in heparinized syringes at normothermia, then during cooling, hypothermia, and rewarming. Blood gases, corrected for temperature, were quantified using an ABL3 blood gas analyzer (Radiometer, Copenhagen), the microhematocrit technique (in duplicate) was used for hematocrit (Hct) measurements, hemoglobin (Hgb) was measured by the cyanmethemoglobin technique, total protein (TP) was determined by refractometry, osmolality (Osm) was quantified by freezing point depression, and albumin (Alb) was determined using a 550 Express autoanalyzer (Ciba-Corning, Medfield, MA). Percentage changes in plasma volume (%△PV) were derived from Hct and Hgb data using the equations described by Dill and Costill (7).

Hypothermia and Rewarming Procedures

Each animal was used twice, serving as its own control. In random order, either PCB or ALM dissolved in malic acid was administered. A 1-week recovery period was given prior to the second experiment. Feed, but not water, was withheld from the evening (1700 h) prior to the day of the hypoxemia/hypothermia experiments. The animals were sedated with a low dose of sodium pentothal (3 $mg \cdot kg^{-1}$, iv), mask-induced with isoflurane (4-5%)/compressed air mixture, intubated and maintained on 3% isoflurance anesthesia. A semi-closed breathing circuit was used with soda lime for expired CO_2 removal. The microswine were stabilized under normothermic conditions for 20-30 min prior to taking normothermic baseline measurements and blood samples. The animals were then cooled using a temperature controlled water blanket, a hypothermic baseline was established, then either continuous iv infusion of ALM (1.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$) or PCB at an equivalent infusion rate was administered throughout approximately 45 min of hypothermia and 3-4 h of rewarming to normothermia. Arterial hypoxemia was maintained for the entire experimental duration (Table I). After rewarming the pigs were allowed to recover. Post-experimental analgesia was provided by butorphanol tartrate (0.5 $mg \cdot kg^{-1}$, im) to relieve any animal discomfort.

Statistics

Mean values for all experimental and calculated data at the different time intervals between control and experimental groups were compared using a two-way analysis of variance; the null hypothesis was rejected at $p \leq 0.05$ using a post-hoc test (Turkey's critical difference analysis).

RESULTS

Preliminary Experiments

A major consideration of this study was that the animals become hypoxemic by spontaneously breathing a hypoxic gas mixture (12.1% O_2, 84.9% N_2, 3.0% isoflurane) in order to simulate hypoxic conditions encountered at an altitude of 4300 m. However, the microswine were unable to tolerate this hypoxic gas mixture under isoflurane anesthesia without undergoing respiratory and cardiovascular arrest. Thus, a compressed air gas mixture (20.3% O_2, 76.7% N_2, 3.0% isoflurane) was adapted and used in order to mimic hypoxic conditions encountered by humans at significant altitude (3000 m), without inducing respiratory collapse or severe respiratory depression.

Additional preliminary experiments designed to determine a normothermic ALM dose for anesthetized microswine (n = 2) demonstrated that five consecutive 100 $\mu g \cdot kg^{-1}$ iv ALM doses given 3–4 min apart increased V_E by approximately 30% (from an average of 3.4 $L \cdot min^{-1}$ to 4.5 $L \cdot min^{-1}$) by a combination of both increased RR and V_T. However, when either a single iv ALM dose of 150 $\mu g \cdot kg^{-1}$ (n = 1) or three consecutive 100 $\mu g \cdot kg^{-1}$ iv doses given 15 min apart (n = 1) were administered to hypoxemic hypothermic microswine (mean T_{es} = 28.8°C, mean P_{aO_2} = 49 mmHg, n = 2), the hypoxemia was potentiated (mean P_{aO_2} = 32 mmHg) and respiratory arrest ensued. These animals were resuscitated using assisted ventilation until initial rewarming, when spontaneous ventilation occurred. Continuous iv infusion of ALM at a relatively low rate (1.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$) was used in subsequent experiments.

TABLE II. HEMATOLOGICAL VARIABLES.

		Tes (°C)	Hct (% rbc)	Hgb ($g \cdot dL^{-1}$)	TP ($g \cdot dL^{-1}$)	Alb ($g \cdot dL^{-1}$)
Normothermic	ALM	37.3 ± 0.3	32.8 ± 2.5	9.9 ± 1.0	6.1 ± 0.4	4.2 ± 0.3
Baseline	PCB	37.1 ± 0.2	32.9 ± 2.2	10.0 ± 0.6	6.0 ± 0.4	4.2 ± 0.3
Hypothermic	ALM	30.6 ± 0.5	34.4 ± 3.0	10.0 ± 0.9	6.0 ± 0.6	3.9 ± 0.2
Baseline	PCB	30.7 ± 0.5	34.1 ± 3.0	10.1 ± 0.6	6.0 ± 0.4	3.9 ± 0.1
30 min Post	ALM	30.4 ± 0.8	34.3 ± 2.8	10.0 ± 0.9	6.0 ± 0.4	3.6 ± 0.3
Infusion	PCB	30.5 ± 0.6	33.7 ± 3.1	10.2 ± 0.7	5.9 ± 0.5	3.8 ± 0.4
Mid	ALM	34.3 ± 0.4	32.3 ± 3.1	10.2 ± 0.7	5.7 ± 0.3	3.7 ± 0.5
Rewarming	PCB	34.2 ± 0.1	33.3 ± 2.6	10.1 ± 0.6	5.7 ± 0.3	3.7 ± 0.3
End	ALM	37.0 ± 0.0	33.0 ± 2.3	10.0 ± 0.8	5.7 ± 0.5	3.8 ± 0.2
Rewarming	PCB	37.0 ± 0.0	33.4 ± 2.1	10.3 ± 0.6	5.8 ± 0.3	3.8 ± 0.3

Hematological responses to hypoxemic hypothermia and rewarming comparing effects of continuous almitrine (ALM) infusion ($1.0\ \mu g \cdot kg^{-1} \cdot min^{-1}$) to equivalent placebo (PCB) infusion. There were no significant ($p \leq 0.05$) differences between ALM and PCB groups. Values are means ± SD (n = 6). Esophageal temperature (Tes), hematocrit (Hct), hemoglobin (Hgb), total protein (TP), albumin (Alb).

Hypothermia and Rewarming Experiments

No statistical differences (n = 6) between ALM and PCB were noted for any of the cardiorespiratory variables measured during continuous iv infusion of ALM ($1.0\ \mu g \cdot kg^{-1} \cdot min^{-1}$) or equivalent PCB infusion beginning at hypothermic baseline ($T_{es} \sim 30°C$) and continuing throughout hypothermia and rewarming (**Fig. 1, 2a, 2b, and Tables I and II**). However, significant ($p \leq 0.05$) hypothermia-associated reductions in V_E were apparent for both PCB and ALM groups until end rewarming when V_E returned to normothermic levels (Fig. 1). Consistent with the protocol design, significant hypoxemia was apparent throughout the experiment (Table I). These P_aO_2 levels are comparable with those reported for unacclimatized men acutely exposed to an altitude of approximately 3000 m (9).

During hypothermia and mid-rewarming, arterial blood gas measurements suggested a partially compensated respiratory acidosis (acidemia, hypercapnia, hypercarbia). By end-rewarming, the respiratory acidosis was alleviated as V_E returned toward normothermic baseline levels (Fig. 1) and hypercapnia was reduced (Table I).

Heart rate (HR) and P_a were not significantly altered as the result of ALM or PCB infusion (Fig. 2a and 2b). However, there was a significant ($p \leq 0.05$) hypothermia mediated reduction in P_a which continued throughout rewarming (Fig. 2b). There were no statistically significant differences for Hct, Hgb, TP, and Alb as the result of hypothermia and, ALM or PCB infusion (Table II). Further, %ΔPV calculated from Hct and Hgb data did not change due to either hypothermia, ALM or PCB administration.

DISCUSSION

We have developed an anesthetized microswine model of hypoxemic hypothermia and rewarming for testing prophylaxes, countermeasures, and treatments. The positive ventilatory effect of ALM via activation of peripheral chemoreceptors has been well documented (15,17). We have observed a similar response to iv bolus (high dose) ALM in normothermic anesthetized microswine. However, with iv bolus infusion of ALM during hypoxemic hypothermia, respiration was depressed, hypoxemia intensified, and respiratory arrest ensued. The anticipated positive effects of ALM on ventilation (15), as well as the augmented HPV (16,20) for increasing arterial P_aO_2 may have been blunted by unknown mechanisms related to hypothermia, hypoxemia, and/or anesthesia. Further, the relatively high rates of ALM administration with iv bolus infusion initially used in the present study have been shown to cause generalized pulmonary vasoconstriction, and reduce P_aO_2 (16). However, these investigators (16) also reported that low dose continuous ALM iv infusion ($1.0\ \mu g \cdot kg^{-1} \cdot min^{-1}$) caused HPV thereby shunting blood to better oxygenated alveoli resulting in higher P_aO_2 levels. In theory, our initial results in hypoxemic hypothermic microswine with iv bolus ALM administration suggested that a low dose continuous ALM iv infusion was indicated in order to minimize generalized pulmonary vasoconstriction, stimulate HPV, and potentially alleviate the hypoxemia. Nonetheless, compared to controls, continuous low dose iv infusion of ALM did not improve any measured pathophysiological responses to hypoxemic hypothermia. Higher continuous iv infusion rates may remain efficacious, but these were not attempted.

In conclusion, the results from this study suggest that iv bolus infusion of ALM, in doses that stimulate ventilation under normothermic conditions, is not indicated as a field expedient treatment for hypoxemic hypothermia since rapid administration may increase the incidence and intensity of the related pathophysiological consequences. Further work is required to assess the potential efficacy of different low dose continuous iv infusion regimens.

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The investigations adhered to the "Guide for the Care and Use of Laboratory Animals" prepared by the Committee on Care and Use of Laboratory Animals of the Institute of Laboratory Animal Resources Commission on life Sciences, National Research Council, (NIH Publication 86-23, 1985).

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