CHEST

Original Research

CRITICAL CARE MEDICINE

Effects of Hypercapnia on BP in Hypoalbuminemic and Nagase Analbuminemic Rats*

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Study objective: **To determine if animals with abnormally low albumin levels are more susceptible to the effects of hypercapnia on BP compared to normal animals.**
Design: **Prospective, controlled laboratory experiment.**
Setting: **University research laboratory.**
Animals: **Eighteen male Sprague-Dawley rats: 6 rats 10 to 12 weeks old (young Sprague-Dawley [YSD]), 6 rats 6 to 9 months old (old Sprague-Dawley [OSD]), and 6 rats 10 to 12 weeks old (Nagase analbuminemic mutant Sprague-Dawley [NAR]).**
Methods: **Under general anesthesia and paralysis, we varied the $Paco_2$ by changing the respiratory rate on mechanical ventilation. Mean arterial pressure (MAP) was monitored in a continuous fashion. We obtained arterial blood for blood gas and electrolyte analysis, and nitric oxide (NO) production.**
Results: **OSD rats had reduced serum albumin, while NAR rats were analbuminemic. Although NAR animals had a decreased buffer capacity compared to age-matched control animals (0.010 vs 0.013, $p < 0.05$), the MAP decreased in an identical fashion in all three groups. NO production increased with hypercapnia but was similar in all three groups. However, NAR rats had consistently higher plasma strong ion gap (2.8 to 4.1 mEq/L greater) compared to either YSD or OSD rats ($p < 0.01$), and baseline strong ion difference (mean ± SD) was significantly lower in NAR rats (28.7 ± 2.1 mEq/L) compared to either YSD rats (33.0 ± 5.1 mEq/L) or OSD rats (31.2 ± 5.1 mEq/L) [$p < 0.05$].**
Conclusions: **These findings suggest that analbuminemic or hypoalbuminemic rats are not more susceptible to hypercapnia-induced hemodynamic instability. Baseline values for apparent strong ion difference are lower in NA rats consistent with a reduced buffer base resulting from analbuminemia.** ***(CHEST 2007; 131:1295–1300)***

Key words: acid-base balance; analbuminemia; BP; hypercapnia; hypoalbuminemia; pH

Abbreviations: MAP = mean arterial pressure; NAR = Nagase analbuminemic mutant Sprague-Dawley; NO = nitric oxide; NS = not significant; OSD = old Sprague-Dawley; SBE = standard base excess; SIDa = apparent strong ion difference; SIDe = effective strong ion difference; SIG = strong ion gap; V_E = minute ventilation; YSD = young Sprague-Dawley

Hypoalbuminemia is common among critically ill patients, both adult and pediatric.[1–3] Among its many physiologic functions, albumin plays an important role in the maintenance of intravascular colloid osmotic pressure[4] and, as a weak acid, regulation of blood pH.[5,6] Hypercapnia has known effects on the vasomotor tone of blood vessels, and it also affects cardiac performance, leading to hypotension. These effects are at least partially offset by an acidosis-induced increases in endogenous catecholamines. However, acidosis also increases nitric oxide (NO) release,[7,8] which further reduces arterial tone.

Hypoalbuminemia in critically ill patients is explained in part by pathophysiologic events in acute diseases such as decreased synthesis due to the effects of inflammatory cytokines on the liver, increased losses in burns, or decreased levels due to fluid shifts in the setting of sepsis. Poor nutritional status and a catabolic state seen with many critically ill patients further reduce protein synthesis. Loss of

albumin invariably results in decreased plasma buffer capacity, and as such would be expected to result in poorer tolerance of hypercapnia.

Hypercapnia is frequently observed in the critically ill, either as a consequence of the underlying pulmonary or neurologic disease, or as a result of

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intentional reductions in minute ventilation to reduce airway pressure—so-called *permissive hypercapnia*. Increased $PaCO_2$ is expected to cause a decrease in BP.[9,10] Whether hypoalbuminemic (or analbuminemic) subjects are more susceptible to this effect is currently unknown. Thus, the current study was conducted to determine if hypoalbuminemic animals were at increased risk of hypercapnia-induced hypotension.

Materials and Methods

Animals

Following approval by the Animal Care and Use Committee of the University of Pittsburgh, standard Sprague-Dawley rats (Hilltop Farms; Pittsburgh, PA) and Nagase analbuminemic mutant Sprague-Dawley (NAR) rats (University of California at Davis; Davis, CA) were studied. We studied 18 animals: 6 rats 10 to 12 weeks old (young Sprague-Dawley [YSD]), 6 rats 6 to 9 months old (old Sprague-Dawley [OSD]), and 6 rats 10 to 12 weeks old (NAR).

Surgical Preparation

For anesthesia, we used pentobarbital sodium, 50 mg/kg intraperitoneally, for induction and then maintained anesthesia with 10 mg/kg intraperitoneally when needed. Each animal was intubated with a beveled 16-gauge angiocatheter and ventilated with room air using a rodent ventilator (Harvard; Holliston, MA) at a tidal volume of 6 mL/kg and a frequency sufficient to maintain the pH between 7.35 and 7.45. We isolated the right carotid artery by dissection and cannulated with 1.27-mm PE-90 tubing. This tubing was formed into a catheter by inserting a beveled 20-gauge needle. We placed a three-way stopcock to allow BP monitoring using a monitor (Hewlett Packard 78342A; Hewlett Packard; Andover, MA), blood sampling, drug administration, and fluid resuscitation. The whole system was flushed with 0.5 mL of heparinized (3,000 U/L) hetastarch in a buffered electrolyte solution (Hextend; Hospira; Lake Forest, IL).

Neuromuscular blockade was achieved by the use of pancuronium bromide (Elkins-Sinn; Cherry Hill, NJ). At time = 30 min, 0.1 mg/kg was administered; at time = 110 min, a second dose of 0.02 mg/Kg was administered. If there was spontaneous breathing or resistance to ventilation, another 0.02 mg/kg dose was administered. Pancuronium was selected based on its pharmacologic properties, nondepolarizing, long half-life (90 to 120 min), and low protein binding (94%).

Experimental Protocol

After the instrumentation, we drew 150 μL of blood into a heparinized syringe for arterial blood gas analysis and hemoglobin, lactate, and electrolyte concentrations (ABL-725; Radiometer; Copenhagen, Denmark). The animals were then maintained at a steady state as defined by stable BP for at least 10 min. After this period, 3 mL of whole blood were collected in a heparinized syringe over a 6-min period to avoid hypotension, and BP determinations were obtained at 0 min, 3 min, and 6 min. This sample was used for blood gas analysis and for measurement of electrolytes, albumin, total protein, magnesium, and phosphate. We administered 3 mL of heparinized Hextend as fluid replacement and allowed 10 min for stabilization.

In order to define the $pH/PaCO_2$ relationship across the entire physiologic range, we began by altering minute ventilation ($\dot{V}E$) from baseline determined by pH of 7.35 to 7.45, to 125%, 150%, 175%, and 200% of $\dot{V}E$ in the hyperventilation arm. We next obtained a second baseline, and the hypoventilation arm of the study was performed by decreasing the $\dot{V}E$ to 80%, 60%, 40%, and 30% of that baseline. These changes were made every 20 min. Blood samples were obtained at the end of each period, from time = 0 min to time = 200 min. A total of 11 samples of 125 μL were obtained corresponding to prebaseline, baseline $\dot{V}E$, 125% $\dot{V}E$, 150% $\dot{V}E$, 175% $\dot{V}E$, 200% $\dot{V}E$, second baseline, 80% $\dot{V}E$, 60% $\dot{V}E$, 40% $\dot{V}E$, and 30% $\dot{V}E$.

At time = 200 min, prior to killing the animals, blood was obtained for blood gas analysis and for albumin, total protein, electrolyte, magnesium, and phosphate determinations. For all six NAR rats, this sample was also used to measure total nitrite as a means of determining NO production. The NO results were then compared to pooled data from three OSD rats and three YSD rats.

NO Production Assay

Total nitrite was measured using cadmium-mediated reduction of NO_3^- to NO_2^- followed by the Griess reagent.[11] To reduce NO_3^- to NO_2^- in plasma, cadmium filings (0.4 to 0.7 g per tube) [Fluka Chemicals; Milwaukee, WI] were loaded into 1.5-mL microcentrifuge tubes. The filings were washed twice with 1.0 mL of deionized water, twice with 1.0 mL of 0.1 mol/L HCl, and twice with 0.1 mol/L NH_4OH. Ten microliters of 30% (weight/volume) $ZnSO_4$ were added to 200 μL of plasma, vortexed, incubated at room temperature for 15 min, and centrifuged at 14,000*g* for 5 min. The resulting supernatants were added to the cadmium-containing microcentrifuge tube and incubated at room temperature overnight with constant mixing. The samples were transferred to fresh microcentrifuge tubes and centrifuged

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