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Original Contribution

Effects of ethanol on systemic hemodynamics in a porcine model of accidental hypothermia☆,☆☆

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ABSTRACT

Objectives: Accidental hypothermia is frequently associated with ethanol intoxication. Each has independent effects on systemic hemodynamics, but their combined effects are poorly understood. We aimed to describe the hemodynamic effects of ethanol intoxication in a model of severe hypothermia and rewarming.
Methods: Anesthetized pigs was assigned to control (n = 8) or ethanol groups (ETOH) (n = 7, 3 mg/kg of ethanol via an orogastric tube). Subjects were cooled to 25°C using ice packs and then warmed to baseline core temperature with passive external and active core rewarming.
Results: In the ETOH group, peak serum ethanol concentration was 202 mg/dL at 25°C. Ethanol had no effect on time of cooling or rewarming. In both the control and ETOH, there were similar maximal decreases in mean arterial pressure (from 94 ± 24 to 50 ± 15 mm Hg and 100 ± 27 to 31 ± 12 mm Hg, respectively), ventricular contractility (rate of maximal left ventricular pressure rise from 5731 ± 1462 to 2610 ± 596 mm Hg/s and 6832 ± 1384 to 1937 ± 437 mm Hg/s, respectively), and cardiac output (from 2.14 ± 0.8 to 0.53 ± 0.3 L/min and 2.93 ± 0.9, to 0.44 ± 0.2 L/min, respectively; all $P < .001$). After rewarming, only in the ETOH group were persistent decreases in mean arterial pressure (59 ± 14 mm Hg), contractility (3982 ± 1573 mm Hg/s), and cardiac output (1.6 ± 0.9 L/min, all $P < .03$) observed.
Conclusions: Hypothermia caused significant adverse effects on cardiac function and systemic hemodynamics, which returned to baseline with rewarming. Ethanol intoxication had no additional effects on systemic hemodynamics during cooling; however, it caused more prolonged depression of cardiac function and adverse effects on systemic hemodynamics during rewarming. These data may have implications for resuscitation of ethanol-intoxicated victims of accidental hypothermia.

1. Introduction

Accidental hypothermia is frequently observed in urban settings, especially among the elderly, isolated, substance abusers, and the homeless [1,2]. The most common drug associated with accidental hypothermia is ethanol [3-5], and, in alcoholics, ethanol is associated with up to 80% of hypothermia cases [6]. Acute ethanol intoxication predisposes to accidental hypothermia through multiple mechanisms. It decreases judgment and increases risk-taking behavior; causes cutaneous vasodilation, which promotes heat loss; impairs shivering; promotes hypoglycemia as well as directly effecting the hypothalamus, all resulting in a fall in core temperature [7]. In addition, hypothermia may slow the metabolism of ethanol [8], potentially increasing its deleterious effects. However, several noncontrolled studies and anecdotal reports have actually found increased survival both experimentally and in patients during hypothermia with concomitant ethanol intoxication [9-11].

Both ethanol and hypothermia have independent effects on the circulatory system. Hypothermia decreases left ventricular systolic pressure, aortic pressure, heart rate, cardiac output, myocardial blood flow, and myocardial oxygen consumption while significantly increasing peripheral vascular resistance [12]. At lower concentrations, ethanol has been found to increase cardiac output, systolic blood pressure, and myocardial oxygen consumption and has a vasodilatory effect, especially in cutaneous blood vessels, thus decreasing peripheral vascular resistance. At higher doses, ethanol depresses myocardial function [13]. Although the independent effects of ethanol intoxication and hypothermia on systemic hemodynamics have been well studied, how ethanol modifies systemic hemodynamics during severe hypothermia and rewarming is

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poorly understood. The aim of this study was to describe the systemic hemodynamic effects of ethanol intoxication in a model of severe hypothermia and rewarming.

2. Methods

Eighteen pigs were assigned to 1 of 2 groups using alternating blocks of 4 per group. We planned to assign a total of 8 subjects per group based on prior experiments in a similar model examining the systemic hemodynamic effects of ethanol in a model of drug toxicity. One animal in the control group had ventricular fibrillation after accidental manipulation of the Swan-Ganz catheter during hypothermia and died. One animal in the ethanol group (ETOH) died during induction of anesthesia, and another had an asystolic arrest at 28°C. These animals were all excluded from subsequent analysis. Data are reported for experiments performed on the remaining 15 pigs, with a mean body weight of 15.3 ± 1.8 kg in the control (n = 8) and 15.4 kg in the hypothermia (n = 7) groups, respectively. Pigs were chosen because of the similarity of their response to hypothermia and similar thermoregulatory mechanisms to humans [14]. The experiment complied with the guidelines established by the National Institutes of Health for Animal Care and were approved by the Medical Center's Animal Care and Use Committee.

2.1. Instrumentation and measurements

Pigs were premedicated with an intramuscular injection of ketamine hydrochloride (3 mg/kg), and anesthesia was induced with pentobarbital 25 mg/kg via ear vein and was maintained with α-chloralose (100 mg/kg) dissolved in polyethylene glycol. α-Chloralose was chosen to preserve autonomic reflex control of the cardiovascular system [15,16] and avoid persistent myocardial depression observed with pentobarbital anesthesia [12]. Supplemental doses of α-chloralose were given at fixed intervals throughout the experiment to maintain surgical anesthesia.

Pigs were endotracheally intubated and ventilated with a volume cycled respirator (Harvard Apparatus) on room air. The left femoral vein and artery were isolated by surgical dissection. The femoral vein was cannulated for administration of anesthesia. The femoral artery of each pig was cannulated; the catheter advanced into the aorta to both measure central arterial pressure via a pressure transducer (Gould, Cleveland, OH) and obtain arterial blood gas samples. The external jugular vein and carotid artery were isolated, and a catheter with a microtip pressure transducer (Millar) was advanced from the carotid artery into the left ventricle to measure left ventricular systolic and diastolic pressures. The entire left ventricular pressure waveform of each of the left ventricular beats recorded by the Millar catheter was sampled every 2 millisecond by an analog-to-digital converter (Labview), and the digital information was stored on the hard disk of a computer (Gateway). In each experiment, the rate of left ventricular pressure rise and fall was determined as an index of left ventricular contractile function ([rate of maximal left ventricular pressure rise] max) and relaxation ([rate of maximal left ventricular pressure rise] min), determined from the average of 10 left ventricular waveforms that were recorded at each time interval.

A fiberoptic balloon-tipped catheter (Oximetric) was inserted into the external jugular vein of each pig and advanced into the main pulmonary artery. This catheter was connected to pressure transducer for measurements of pulmonary artery and pulmonary capillary wedge pressures and connected to a S02/CO computer (Oximetric) for continuous measurements of mixed venous blood oxygen saturation, core temperature, and cardiac output by thermodilution technique. [17,18] An average of at least 3 measurements of cardiac output that agreed within 10% was used. An electrocardiogram (ECG) for heart rate monitoring was obtained by attaching electrodes to the anterior chest wall of each pig.

Aortic pressure, left ventricular pressure, pulmonary artery pressure, and a surface ECG were continuously recorded and displayed on a PC4886 computer (Gateway). After completion of instrumentation, each pig was allowed 30 minutes for the monitored variables to achieve a steady state.

2.2. Study design and protocol

Each pig was assigned into 1 of 2 groups: in the ETOH (n = 7), subjects received ethanol, 3 g/kg bolus by orogastric tube, and then underwent hypothermia. In the control group (n = 8), animals received an equal volume of normal saline by orogastric bolus before undergoing hypothermia. This dose of ethanol was chosen to achieve serum concentrations in the study animals that would be comparable with the serum ethanol concentrations observed in individuals who experience moderate intoxication while using ethanol recreationally.

When each pig was allowed to achieve a steady state after surgery, maintenance fluids were stopped; and baseline hemodynamic, electrocardiographic, and temperature measurements were obtained. At the initiation of each experiment and every sampling interval thereafter, 0.5-mL samples of arterial and venous blood were collected for blood gas and co-oximetric analysis (Instrumentation Laboratories). In each pig, 1- to 2-mL blood samples for serum ethanol concentration were obtained at 30 minutes postbolus and every sampling interval thereafter. Blood gas values were not normalized for temperature.

After baseline measurements, ethanol or placebo bolus was given. Thirty minutes after the bolus, another set of measurements was obtained, and hypothermia was initiated. Animals were cooled via ice packs in the axilla, groin, and abdomen in a standardized fashion for each animal. This method of external cooling was chosen to simulate clinical hypothermia seen in accidental environmental exposure [8]. Data were recorded and analyzed from 10 consecutive pressure waveforms from each pig at baseline, 30 minutes postbolus, 34°C, 31°C, 28°C, and 25°C. Rate of cooling was recorded. A goal of 25°C was chosen, as this temperature represents severe hypothermia in humans but is still above the temperature at which ventricular fibrillation is likely to occur [12,19]. Pigs were observed at 25°C for 15 minutes at which time rewarming was initiated.

Rewarming was achieved by active core rewarming, using a bolus of 20 mL/kg of warmed normal saline. All intravenous and intracavitary fluids used were warmed in a standard microwave to a temperature of 39°C to 42°C. Stomach contents were aspirated from the orogastric tube, and 2 warmed normal saline orogastric lavages were done 1 hour apart. Thirty minutes after the first lavage, warm peritoneal lavage was done using 15 mL/kg of warm normal saline. Peritoneal lavage was then repeated once more 1 hour after the initial peritoneal lavage. Continuous external rewarming was done using bags of warmed saline placed in the axilla, groin, and abdomen in combination with use of a warming blanket. We used this combination of active core rewarming and active external rewarming without cardiopulmonary bypass, as this method is frequently used clinically and a protocol is readily available in most emergency departments and importantly does not interfere with normal hemodynamic autoregulation [1,19]. During rewarming, data from each pig at 25°C, 28°C, 31°C, 34°C, and at return to baseline temperature were recorded. Goal of rewarming was return to baseline postinstrumentation temperature for each animal.

2.3. Data analysis

Mean arterial, left ventricular pressure, pulmonary capillary wedge pressure, pulmonary artery pressure, heart rate, and arrhythmias were determined from direct analysis of 10 consecutive recorded pressure waveforms at each measurement interval. Core body temperature was directly recorded from the Swan-Ganz catheter. Stroke volume and systemic vascular resistance (SVR) were calculated from standard formulas:

$$\text{SV} = \text{Cardiac output (CO)}/\text{heart rate}$$

$$\text{SVR} = [(\text{MAP-CVP}) \times 79.98]/\text{CO}$$