

High-dose diazepam facilitates core cooling during cold saline infusion in healthy volunteers

David Hostler, William E. Northington, and Clifton W. Callaway

Abstract: Studies have suggested that inducing mild hypothermia improves neurologic outcomes after traumatic brain injury, major stroke, cardiac arrest, or exertional heat illness. While infusion of cold normal saline is a simple and inexpensive method for reducing core temperature, human cold-defense mechanisms potentially make this route stressful or ineffective. We hypothesized that intravenous administration of diazepam during a rapid infusion of 30 mL·kg⁻¹ of cold (4 °C) 0.9% saline to healthy subjects would be more comfortable and reduce core body temperature more than the administration of cold saline alone. Fifteen subjects received rapidly infused cold (4 °C) 0.9% saline. Subjects were randomly assigned to receive, intravenously, 20 mg diazepam (HIGH), 10 mg diazepam (LOW), or placebo (CON). Main outcomes were core temperature, skin temperature, and oxygen consumption. Data for the main outcomes were analyzed with generalized estimating equations to identify differences in group, time, or a group × time interaction. Core temperature decreased in all groups (CON, 1.0 ± 0.2 °C; LOW, 1.4 ± 0.2 °C; HIGH, 1.5 ± 0.2 °C), while skin temperature was unchanged. Mean (95% CI) oxygen consumption was 315.3 (253.8, 376.9) mL·kg⁻¹·min⁻¹ in the CON group, 317.9 (275.5, 360.3) in the LOW group, and 226.1 (216.4, 235.9) in the HIGH group. Significant time and group × time interaction was observed for core temperature and oxygen consumption ($p < 0.001$). Administration of high-dose diazepam resulted in decreased oxygen consumption during cold saline infusion, suggesting that 20 mg of intravenous diazepam may reduce the shivering threshold without compromising respiratory or cardiovascular function.

Key words: therapeutic hypothermia, diazepam, shivering, oxygen consumption.

Résumé : D'après certaines études, une légère hypothermie améliore le bilan neurologique consécutif à un traumatisme crânien, à un accident cérébrovasculaire grave, à un arrêt cardiaque et au coup de chaleur à l'effort. L'injection d'une solution saline froide est une méthode simple et peu coûteuse pour diminuer la température interne, mais les mécanismes de défense de l'organisme contre le froid rendent cette approche stressante et peu efficace. Nous avançons l'hypothèse selon laquelle l'ajout de diazépam à l'injection intraveineuse rapide de 30 mL de solution saline (0,9 %) à une température de 4 °C chez des sujets en bonne santé est plus tolérable et contribue à une plus grande diminution de la température interne que l'injection seule d'une solution saline froide. On injecte rapidement à 15 sujets une solution saline (0,9 %) à une température de 4 °C. On divise au hasard les sujets en trois groupes : un groupe recevant par voie intraveineuse une concentration de 20 mg de diazépam (HIGH), un autre, une concentration de 10 mg de diazépam (LOW) et un autre, un placebo (CON). Les variables dépendantes sont la température interne, la température cutanée et la consommation d'oxygène. On analyse les résultats au moyen d'équations d'estimation généralisées pour identifier les différences entre les groupes, dans le temps et l'interaction groupe × temps. La température interne diminue chez tous les groupes (1,0 ± 0,2 °C CON, 1,4 ± 0,2 °C LOW, 1,5 ± 0,2 °C HIGH) et la température cutanée ne varie pas. La consommation d'oxygène moyenne (intervalle de confiance à 95 %) est de 315,3 (253,8; 376,9) mL·kg⁻¹·min⁻¹ chez le groupe de contrôle, de 317,9 (275,5; 360,3) mL·kg⁻¹·min⁻¹ chez le groupe LOW et de 226,1 (216,4; 235,9) mL·kg⁻¹·min⁻¹ chez le groupe HIGH. On observe une interaction significative de la température interne et du consommation d'oxygène avec le temps et le groupe × temps ($p < 0,001$). L'administration d'une forte dose de diazépam diminue la consommation d'oxygène pendant l'injection d'une solution saline froide, ce qui signifie que l'injection intraveineuse de 20 mg de diazépam abaisse le seuil de frisson sans interférer avec les fonctions respiratoires et cardiovasculaires.

Mots-clés : hypothermie thérapeutique, diazépam, frisson, consommation d'oxygène.

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Introduction

Background

Induced hypothermia has been proposed as a potential therapeutic intervention for several clinical conditions. Two

clinical trials have demonstrated improved outcome after cardiac arrest, and other trials are exploring the use of hypothermia for the treatment of stroke (Aronowski et al. 2003; Bernard et al. 2002; Hypothermia After Cardiac Arrest Study Group 2002; Lyden et al. 2005). It has been suggested

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that rapid infusion of cold saline may be a useful therapy for heat stroke, especially in cases where immersion cooling is not possible or not tolerated by the patient (Bouchama et al. 2007; Hsiao et al. 2007). Cold saline infusion has been used to reduce core temperature in both awake and anesthetized human subjects (Frank et al. 1997; Rajek et al. 2000). However, these studies employed routes and anesthetics that may not be available in all clinical settings or at the site of a sporting event. Additionally, therapies requiring the patient to be unconscious may be inappropriate if they suffer from an evolving neurologic injury that requires continued assessment.

Rapid infusion of 30 mL·kg⁻¹ of cold (4 °C) normal saline has previously been shown to reduce core body temperature by 1 °C or more in healthy volunteers (Moore et al. 2008). However, the procedure causes significant discomfort and shivering, which prevents further reductions in temperature. We hypothesized that the administration of intravenous diazepam during the infusion would reduce subject discomfort and allow for greater cooling.

Materials and methods

Study design

We conducted a prospective laboratory study of cold saline infusion in healthy volunteers. This study was approved by the University of Pittsburgh Institutional Review Board and the Montefiore University Hospital General Clinical Research Center Scientific Review Committee.

Selection of participants

A convenience sample of male and nonpregnant female subjects ($n = 15$) between the ages of 18 and 35 years was recruited from the university population. Subjects received \$100 compensation if they passed the screening and the protocol was initiated. The randomization order was preset, and subjects were enrolled in the order in which they volunteered. Subjects were not informed of their assignment, but blinding was not possible after initiating the infusion.

Twenty-three subjects provided informed consent. Each subject underwent a standard history, a physical examination, lab studies (electrolytes, renal and liver function, thyroid-stimulating hormone, hemoglobin, and hematocrit), and a 12-lead electrocardiogram to screen for the presence of cardiac or any other underlying disease. Subjects were excluded if they had an abnormal lab value, any known medical problems, or if they were taking any medications, with the exception of seasonal allergy medication, over-the-counter nonsteroidal anti-inflammatory drugs, acetaminophen, or contraceptives. Other exclusion criteria included a history of cardiac disease in a family member under the age of 40, allergy to diazepam or other benzodiazepine or narcotic medication, smoking, recreational drug use, or a body mass index > 35 mg·kg⁻².

Testing protocol

Testing was performed in the Clinical and Translational Research Center at the University of Pittsburgh Montefiore Hospital (Pittsburgh, Penn.). During the test, male subjects wore short pants with exposed torso and female subjects wore short pants and a sports bra.

An 18-gauge peripheral intravenous catheter was placed in the antecubital vein of each subject. Subjects were monitored with a standard 3-lead electrocardiogram, blood pressure cuff, and pulse oximetry probe (placed on the arm opposite to the peripheral intravenous catheter). Oxygen consumption was measured by indirect calorimetry, using a Deltatrac II respiratory gas analyzer (Datex Ohmeda Inc., Helsinki, Finland). While in a fasting state, a respiratory gas exchange hood was placed over the individual's head and the resting metabolic rate was measured for 15 min prior to infusion.

Subjects received a total infusion of 30 mL·kg⁻¹ of cold (4 °C) normal saline over a 30-min interval. A 30-min infusion represented the fastest rate that could be achieved in most subjects with a peripheral catheter and pressure infuser (Moore et al. 2008). Subjects randomized to the high-dose diazepam group (HIGH) received 10 mg intravenously at the beginning of the infusion, and an additional 5 mg bolus was given at minute 10 and minute 20 (20 mg total) of the 30-min infusion. Subjects randomized to the low-dose diazepam group (LOW) received 5 mg, 2.5 mg, and 2.5 mg (10 mg total) on the same schedule as the high-dose group. Subjects in the placebo group (CON) received 2 mL of sterile saline in place of diazepam. Heart rate was recorded at baseline and at 2-min intervals during the infusion. Blood pressure and subject discomfort were measured at 5-min intervals.

Outcome measures

Core body temperature was monitored using a precalibrated ingestible thermometer pill that continuously measures temperatures in the range of 0 to 50 °C (HQ Technologies, Palmetto, Fla.). This mode of core temperature monitoring has been previously validated (O'Brien et al. 1998). The temperatures measured with this system are between rectal and esophageal temperature, and this probe responds to rapid heating and cooling. The capsule was administered to the subjects 60 min prior to beginning the protocol with approximately 30 mL of water. Subjects arrived to the protocol after a 12-h fast to minimize the effect of food and fluid in the gastrointestinal tract (Wilkinson et al. 2008). The protocol was initiated after 3 consecutive measurements indicated a stable core temperature.

Skin-surface thermistors were placed over the clavicular head of pectoralis major, the supraspinatus, the triceps brachii, and the quadriceps femoris muscles. Core and skin surface temperatures were documented every 2 min during the infusion. Mean skin temperature (T_{sk}) was calculated with the following formula:

$$T_{sk} = T_{chest}(0.25) + T_{back}(0.25) + T_{thigh}(0.3) + T_{arm}(0.2)$$

(Ayling 1986).

To assess the effects of the interaction of diazepam and cold intravenous fluids on comfort, participants rated their thermal sensation on a 9-point scale (Gagge et al. 1969). Subjects were instructed to rate discomfort based on whole-body sensation, not to rate pain or discomfort at the infusion site.

Following the 30-min infusion, subjects were monitored for a minimum of 60 min prior to being discharged into the care of another adult. In all cases, subjects exceeded a core temperature of 36.5 °C prior to discharge.

Table 1. Demographic and morphometric data. Data are shown as means \pm SD.

Group	Males (n)	Age (y)	Height (cm)	Mass (kg)	Body mass index (kg·m ⁻²)
CON (n = 5)	2	24.6 \pm 5.1	168.0 \pm 7.8	72.4 \pm 12.8	25.5 \pm 3.5
LOW (n = 5)	4	24.4 \pm 3.4	178.8 \pm 6.0	84.6 \pm 11.4	26.4 \pm 2.5
HIGH (n = 5)	3	24.8 \pm 3.7	177.2 \pm 12.5	77.4 \pm 8.8	24.7 \pm 2.7

Note: CON, placebo; LOW, 10 mg diazepam; HIGH, 20 mg diazepam.

Primary data analysis

Demographics and morphometrics were analyzed between groups with analysis of variance (ANOVA). Repeated temperature measurements, oxygen consumption ($\dot{V}O_2$), and heart rate data were compared with repeated-measures ANOVA. Thermal sensation was compared, with a theoretical mean value of 5 (neutral), using a Wilcoxon rank sum test. Changes over time were examined with a Friedman test, with a Dunn's post hoc test for multiple comparisons. Statistical significance was set at $p \leq 0.05$. Analyses were performed with Stata for Mac, release 8.0, and Prism, release 4.0c. Data are presented as means \pm SD.

Results

Twenty-three subjects were screened for the study, and 8 were excluded during the initial screening. By protocol, 7 subjects had been excluded because they had lab values outside the normal range, although these deviations were clinically insignificant. One subject was excluded and referred to a primary physician after an abnormal 12-lead electrocardiogram. The remaining 15 subjects entered and completed the protocol. All subjects received the prescribed volume of saline. The demographics and morphometrics for each group were not different (Table 1).

Main results

Core temperature decreased in all groups (CON, 1.0 ± 0.2 °C; LOW, 1.4 ± 0.2 °C; HIGH, 1.5 ± 0.2 °C), while mean skin temperature was unchanged over time. There was an effect of time ($F_{15,180} = 104.6$, $p < 0.001$) and a group \times time interaction ($F_{30,180} = 2.23$, $p = 0.007$) for core temperature (Fig. 1A). There was no effect of group. However, the group \times time interaction for core temperature suggests that the change across time differed between groups. Since all groups received cold saline, a decrease in core temperature over time is expected. The significant interaction effect reflects the fact that the change across time differed between groups. Mean skin temperature did not differ by group or time.

Mean (95% CI) $\dot{V}O_2$ was 315.3 (253.8, 376.9) mL·min⁻¹ in the CON group, 317.9 (275.5, 360.3) mL·min⁻¹ in the LOW group, and 226.1 (216.4, 235.9) mL·min⁻¹ in the HIGH group. There was an effect of time ($F_{6,72} = 6.91$, $p < 0.001$) and group ($F_{2,72} = 7.9$, $p = 0.006$), and a group \times time interaction ($F_{12,72} = 3.54$, $p = 0.004$) for $\dot{V}O_2$ (Fig. 1B). Heart rate changed over time ($F_{15,180} = 2.75$, $p = 0.008$) and displayed a group \times time interaction ($F_{30,180} = 3.65$, $p < 0.001$), with changes approximating the change in $\dot{V}O_2$ (Fig. 2). Respiratory rate and end tidal CO₂ did not differ by group or time (Fig. 3).

Thermal sensation decreased from the theoretical mean of 5 (neutral) in the CON ($p = 0.004$) and LOW ($p = 0.002$)

Fig. 1. Core temperature (A) and oxygen consumption ($\dot{V}O_2$) (B) during a 30-min infusion of cold saline. Data presented as means \pm SD. *, CON (placebo) different from HIGH (20 mg diazepam) group. †, LOW (10 mg diazepam) different from HIGH group. CON data points have been moved 0.5 units along the x axis for clarity.

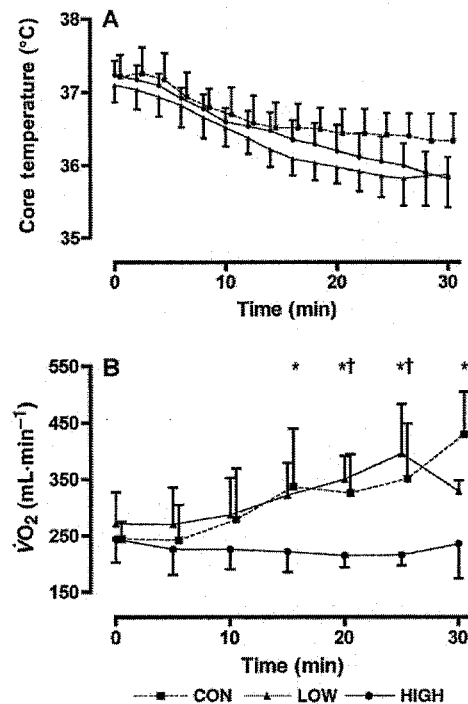


Fig. 2. Heart rate during a 30-min infusion of cold saline. Data presented as means \pm SD. CON data points have been moved 0.5 units along the x axis for clarity.

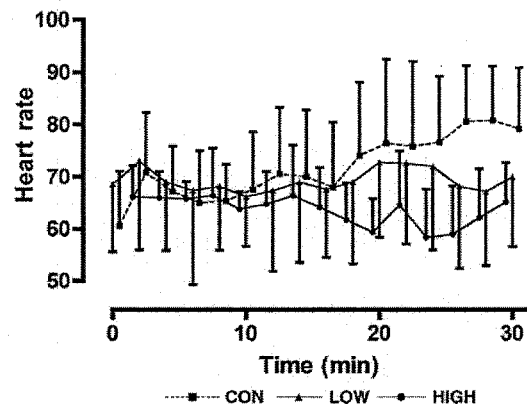
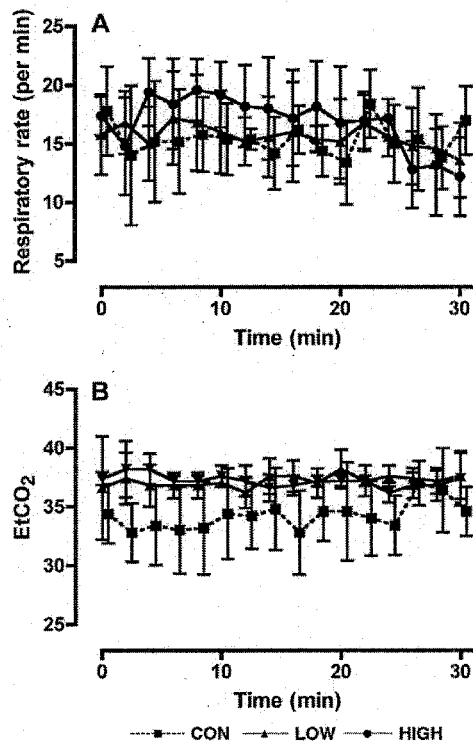


Fig. 3. Respiratory rate (A) and end tidal (Et) CO₂ (B) during a 30-min infusion of cold saline. Data presented as means \pm SD. CON data points have been moved 0.5 units along the x axis for clarity.



groups, but not in the HIGH group ($p = 0.02$). Thermal sensation values decreased over time ($p = 0.02$), indicating that the subjects reported feeling colder (Fig. 4). On average, the LOW group reported colder sensation than the HIGH group.

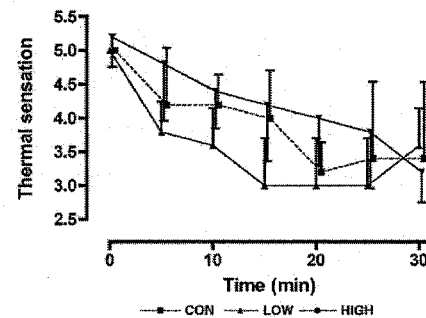
Discussion

High-dose intravenous diazepam delivered during cold saline infusion reduced core body temperature 1.5 ± 0.2 °C without a concomitant rise in $\dot{V}O_2$. In contrast, the temperature reduction noted in the LOW and CON groups was paired with a rise in $\dot{V}O_2$ and noticeable shivering.

In addition to being a putative therapy for heat illness, induced hypothermia may improve patient outcomes after myocardial infarction, major stroke, or traumatic brain injury, making it important to elucidate the physiological responses to rapid intravenous cooling (Dixon et al. 2002; De Georgia et al. 2004; Clifton et al. 2002). Paralytics are not commonly available in the prehospital and sport settings. Furthermore, a patient with an evolving brain injury requires serial neurological assessment, making deep sedation or anesthesia undesirable. The techniques employed in this study are particularly applicable to the prehospital setting, if therapeutic hypothermia is ultimately shown to benefit these acute conditions.

Cooling remains the definitive therapy for heat stroke. Immersion cooling is the treatment of choice for exertional illness, and has been used successfully both in military personnel and athletes (Beller and Boyd 1975; Costrini et al. 1979; Armstrong et al. 1996). However, 1 study reported that patients suffering nonexertional heat stroke did not tol-

Fig. 4. Thermal sensation during a 30-min infusion of cold saline. (5 = neutral, 1 = very cold). Data presented as means \pm SD. CON data points have been moved 0.5 units along the x axis for clarity.



erate immersion cooling well (Hart et al. 1982). Intravenous infusion coupled with diazepam sedation may provide an alternative for treating those patients who cannot tolerate immersion or in situations where immersion cooling is not available. Furthermore, the fluid volume provided by intravenous cooling may correct the distributive shock and hypovolemia seen in both exertional and nonexertional heat stroke (Bouchama et al. 2007; Dahmash et al. 1993; O'Donnell and Clowes 1972; Sprung 1979).

Our study has several important limitations. The study was designed to assess a potential therapy using healthy volunteers. Although our sample size was limited, it was sufficient to demonstrate differences in core temperature and $\dot{V}O_2$. The randomization schedule was preset, and subjects were enrolled in the order they expressed interest and scheduled their screening. Subjects were not informed of their randomization assignment, but it was impossible to adequately blind this study. Although some subjects did not realize they had received diazepam, we cannot be certain that all subjects in the diazepam groups were uninfluenced or whether they correctly identified their assignment.

Second, we did not directly quantify shivering with electromyography. Although some portion of the suppressed $\dot{V}O_2$ response in the HIGH group can be directly attributed to the diazepam sedation, it is likely that the lack of rise in $\dot{V}O_2$ during the infusion resulted from decreased or ablated shivering (Zwischenberger et al. 1987).

Finally, these results must be interpreted cautiously before applying them to the treatment of heat illness in sports. It has been suggested that the use of cold saline might be an effective treatment for exertional heat illness (Bouchama et al. 2007). While this technique has been well-described in postcardiac arrest patients, there are no clinical trials in patients suffering heat illness (Bernard et al. 2002; Hypothermia After Cardiac Arrest Study Group 2002). Subjects in this investigation were normothermic at the onset of the cold saline infusion. With the safety profile of this treatment established, future studies must be conducted in the target population before translation to clinical practice.

Conclusions

A rapid intravenous infusion of 30 mL·kg⁻¹ of cold normal saline coupled with 20 mg of intravenous diazepam results in a 1.5 ± 0.2 °C decrease in core temperature, without a concomitant rise in $\dot{V}O_2$ in conscious, normothermic vol-

unteers. The lack of adverse cardiovascular and respiratory alterations makes this technique immediately applicable to patients suffering acute neurological insults, and warrants further study in subjects suffering heat stroke.

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