Cooling to Facilitate Metabolic Suppression in Healthy Individuals

Jon C. Rittenberger; Kathryn L. Flickinger; Alexandra Weissman; Melissa Repine; Jonathan Elmer; Francis X. Guyette; Clifton W. Callaway

BACKGROUND: Carbon dioxide (CO_2) toxicity could be catastrophic for astronauts. Suppressing metabolism by lowering body temperature decreases CO_2 production and may facilitate rescue in the event of a crippled ship. Lowering body temperature requires shivering suppression. We evaluated dexmedetomidine to facilitate cooling of healthy individuals.

METHODS: Following consent, we administered a 1 mcg · kg^{-1} bolus of dexmedetomidine followed by continuous infusion (0.5–1.4 mcg · kg^{-1} · h^{-1}) for 3 h of cooling. We cooled subjects using a bolus of 30 cc · kg^{-1} of 4°C saline followed by surface cooling. We measured vital signs, thermal and comfort scales, sedation, and shivering for 3 h and during recovery. ANOVA evaluated changes in measures over time.

RESULTS: Nine subjects completed the study. Mean age was 31 (SD 8) yr, mean mass was 71 (SD 14) kg, height of 168 (SD 9) cm, and body mass index of 25 (SD 3). Median time to 1°C drop in core temperature was 16 (IQR 15, 32) min. Temperature changed over time with median lowest temperature being 33.1°C (IQR 32.8°C, 34.1°C). Neither heart rate nor diastolic blood pressures changed over time. Systolic blood pressure decreased over time. Subjects responded to verbal stimuli and completed tasks throughout the protocol. During cooling and maintenance, subjects reported discomfort and the sensation of being cold.

CONCLUSION: Dexmedetomidine facilitates shivering suppression during prolonged cooling in healthy individuals. Subjects are easily roused, have mild decreases in systolic blood pressure, and note sensations of discomfort and cold. Cooling to suppress metabolism is a feasible countermeasure to prolong astronaut endurance.

KEYWORDS: hypothermia, cognition, metabolism, dexmedetomidine.

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One potential threat to astronaut safety is a carbon dioxide (CO_2) scrubbing module failure. At baseline, astronauts in the International Space Station breathe atmosphere containing approximately 4 mmHg CO_2, compared to terrestrial CO_2 of approximately 0.3 mmHg. CO_2 levels greater than 5 mmHg cause poor concentration, fatigue, dizziness, headaches, and difficulty sleeping.[7] Thus, a malfunctioning CO_2 scrubber could rapidly result in impairment and eventually threaten survival. Suppressing astronaut metabolism and CO_2 production could slow CO_2 accumulation and prolong survival time while correcting or rescuing from such a malfunction. Similarly, metabolic suppression could extend time available for rescue, facilitating additional options in situations like the Apollo 13 or STS-107 missions. Preclinical data suggest that metabolic rate decreases 7–8% for each 1°C decrease in core temperature.[8] Thus, a small change in core temperature could significantly reduce energy needs and CO_2 production by the crew.

Forced reductions of core body temperature below about 36.5°C in normal humans triggers shivering, which increases metabolism and prevents further reductions in core temperature unless extraordinary measures are applied. Lowering core body temperature as a strategy to reduce metabolism requires reliable and safe shivering suppression. A number of anesthetic

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medications can suppress shivering, but these medications also cause sedation or respiratory depression.

We have tested the ability of several drugs to suppress shivering during forced cooling of healthy humans.[6,10] Dexmedetomidine is an alpha-2-adrenergic agonist that reduces shivering without impairing breathing and also allows rapid awakening.[4] Dexmedetomidine induces a drowsy state that resembles physiological sleep rather than the anesthetic or intoxicated state created by other drugs.[1] Whether dexmedetomidine is safe and effective for maintaining lower body temperature in spontaneously breathing humans over prolonged periods is unknown. We hypothesized that a bolus of dexmedetomidine followed by infusion will suppress shivering during forced cooling of healthy individuals for 3 h with mild side effects.

METHODS

Subjects

The University of Pittsburgh Human Research Protection Organization (formerly IRB) approved this study. All subjects provided written informed consent prior to participation. We recruited healthy individuals between the ages of 18–49 yr old. Subject screening included a physical examination to confirm and an electrocardiogram to exclude the presence of conduction abnormalities. Each subject self-reported they were free from heart disease, vascular disease, renal or hepatic impairment, or any allergy to dexmedetomidine. Women could not be pregnant or currently breastfeeding and provided a negative urine pregnancy test on each protocol day.

Procedure

Experiments took place in the Applied Physiology Laboratory at the University of Pittsburgh.[4] Intervention days were separated by at least 1 wk. Subjects refrained from food, alcohol, and tobacco for 6 h prior to the study protocol. We allowed subjects to drink water. After obtaining baseline postvoid weight and body anthropomorphic measurements, we placed 18-gauge or 20-gauge intravenous catheters bilaterally in veins proximal to the wrist. We monitored subjects using three-lead electrocardiogram, continuous pulse oximetry, nasal cannula continuous waveform capnography, and noninvasive blood pressure. A naso-esophageal temperature probe was placed to monitor core (esophageal) body temperature. Surface cooling consisted of water circulating pads with a gel adherent to the skin (Arctic Sun, Medivance, Inc., Louisville, CO, United States), which were placed on the torso and legs. All experiments occurred between 08:00 and 14:00, with subjects lightly clothed in a lab with ambient temperature between 20–22°C.

We recorded thermal sensation, comfort, sedation, and shivering scales every 5 min. Subjects reported comfort and thermal sensation scores verbally or by pointing to a score on a placard with each scale. The general (overall) comfort scale (1–4) had anchors of 1, "comfortable" and 4 "very uncomfortable." The thermal sensation scale (1–5) had anchors of 1 "comfortable" and 5 "very cold." An investigator rated sedation using the Richmond Agitation-Sedation Scale (RASS).[5,11] The RASS is a 10-point scale ranging from −5 (unresponsive to voice or painful stimulation) to 4 (combative and danger to self or staff). An investigator visually and manually assessed intensity of shivering using the Bedside Shivering Assessment Scale (BSAS).[2] The BSAS (0–3) ranges from 0 (no shivering) to 3 (severe shivering: generalized or sustained upper/lower extremity shivering).

After placement of all monitors and baseline measurements, we administered a 1 mcg $\cdot$ kg^{-1} bolus of dexmedetomidine (Hospira, Lake Forest, IL, United States) over 10 min followed by an infusion starting at 0.5 mg $\cdot$ kg^{-1} $\cdot$ h^{-1}. The infusion was increased by 0.2 mg $\cdot$ kg^{-1} $\cdot$ h^{-1} every 5 min until the patient was shivering (BSAS $\geq$ 1) or had an increase in core temperature to a maximum dose of 1.4 mg $\cdot$ kg^{-1} $\cdot$ h^{-1}.

To induce cooling, we infused 30 ml $\cdot$ kg^{-1} cold (4°C) normal saline intravenously via a pressure bag (approximately 10 min $\cdot$ L^{-1}) through an 18-gauge or 20-gauge IV in the antecubital fossa. Maximum bolus volume was 2 L. Following the cold saline bolus, we activated the surface cooling pads at their maximal cooling rate (water circulating at 4°C).

In the first two experiments, the cold saline bolus started contemporaneously with the bolus of dexmedetomidine. One subject experienced vagal symptoms of malaise and nausea, with profound bradycardia during the infusions, which rapidly resolved with stopping both infusions. This subject did not complete the protocol and is not included in the final data. After this subject, we changed the protocol to administer the cold saline bolus after completion of the initial dexmedetomidine bolus.

Investigators stopped drug administration or cooling if heart rate declined to less than 45 bpm for 2 consecutive minutes, systolic blood pressure (SBP) declined to $<$ 90 mmHg for 5 consecutive minutes, tissue pulse oximetry (S_pO_2) declined to $<$ 90% for 1 min, or the subject became deeply sedated (RASS −4). Dexmedetomidine infusion continued for up to 3 h. After 3 h, surface cooling stopped, and the subjects were allowed blankets to promote passive warming. After stopping dexmedetomidine, we monitored the subjects for a minimum of 120 min or until RASS was 0 and they were able to eat, void, and ambulate without difficulty.

Statistical Analysis

Data were analyzed using descriptive statistics. Time-course analyses were completed using analysis of variance (ANOVA) STATA 14.0 (College Station, TX, United States).

RESULTS

There were 10 subjects (9 men) who started the protocol and 1 subject failed to complete the experiment after having severe bradycardia during simultaneous infusion of dexmedetomidine and cold saline. After amending the protocol to separate these infusions, 9 subjects (8 men) completed 20 experiments, which comprised the final data for analysis. The mean age was

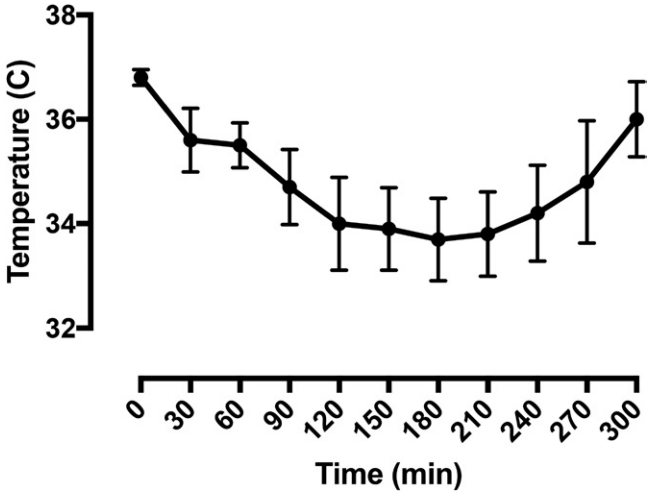

Fig. 1. Core temperature over time. Error bars represent one standard deviation.

31 (SD 8) yr. Mean mass was 71 (SD 14) kg, height 168 (SD 9) cm, and body mass index 25 (SD 3). One subject experienced asymptomatic atrial fibrillation, which resolved when core temperature became > 36°C.

Median time to 1°C drop in core temperature was 16 (IQR 15, 32) min. Temperature changed over time with median lowest temperature of 33.1°C [IQR 32.8°C, 34.1°C; $F(11) = 14.4$, $P < 0.0001$; **Fig. 1**].

The median temperature at the end of the protocol was 33.8°C (IQR 33.1°C, 34.3°C). Neither heart rate [baseline 68 (SD 8) bpm, nadir 47 (SD 15) bpm; $F(11) = 0.73$, $P = 0.71$] nor diastolic blood pressures [baseline 75 (SD 13) mmHg, nadir 59 (SD 8) mmHg; $F(11) = 1.76$, $P = 0.007$] changed over time. Systolic blood pressure decreased from a pre-intervention measurement of 129 (SD 11) mmHg to a nadir of 105 (SD 9) mmHg over time [$F(11) = 2.79$, $P = 0.0035$; **Fig. 2**].

Shivering was mild (BASS −1–2) and increased during induction (BSAS 1; SD 1.3 at 30 min) and maintenance of cooling, and decreased after the cooling pads were removed [BSAS 0; SD 0.3 at 210 min; $F(11) = 3.57$, $P = 0.0003$; **Fig. 3**, left panel].

Most subjects experienced mild (RASS −1 to −2) sedation during induction and maintenance of cooling [$F(11) = 4.38$, $P = 0.0001$; Fig. 3, right panel]. Sedation resolved after dexmedetomidine infusion stopped at minute 180. During cooling and maintenance, subjects experienced discomfort and a sensation of being cold [Thermal: $F(11) = 10.01$, $P = 0.0001$; Comfort: $F(11) = 14.35$, $P = 0.0001$; **Fig. 4**]. These symptoms improved with the cessation of cooling, but required time to abate entirely.

DISCUSSION

Dexmedetomidine facilitates shivering suppression, as measured by BSAS, during prolonged cooling in healthy individuals. A bolus and infusion of dexmedetomidine suppresses shivering adequately to force core body temperature to 33–34°C. Interestingly, the reduction in core body temperature is long-lasting. Core temperature rarely returned to normal before the end of monitoring time. Despite this, subjects were able to eat, ambulate, and void without difficulty.

Subjects were easily roused and had mild decreases in systolic blood pressure. These data suggest that individuals could participate in self-rescue during hypothermia. While subjects appeared grossly returned to baseline within hours after cooling, we did not perform detailed cognitive or psychomotor testing, such as the Cognition Test Battery.[9] Long-lasting effects or hangover from metabolic suppression regimens will be important areas to investigate in the future.

The timing of interventions is important. Simultaneous bolus of cold saline and dexmedetomidine caused profound bradycardia in one subject. Our impression from all of these experiments is that cold saline infusion causes a significant vagal response, as most patients report a deep visceral sensation during the infusion. Dexmedetomidine has well-documented direct inhibition on cardiac AV nodal conduction.[3] When administered together, the increased reflex vagal tone and direct AV block profoundly reduce atrial-ventricular conduction, and subjects with slow ventricular escape rhythms will not tolerate the combined infusion. The simplest solution was to

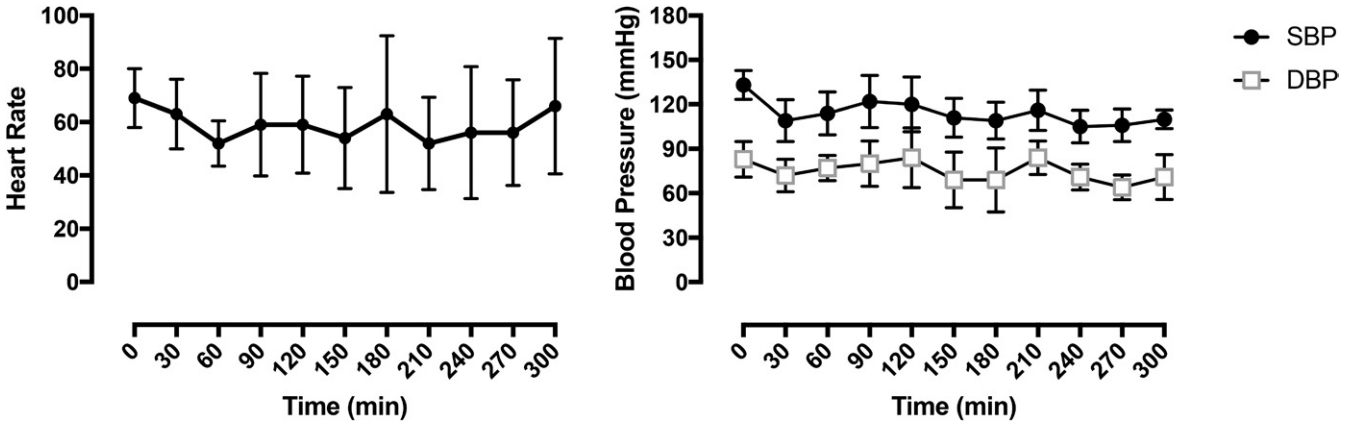

Fig. 2. Left panel: heart rate over time. Right panel: systolic and diastolic blood pressure over time. Error bars represent one standard deviation.

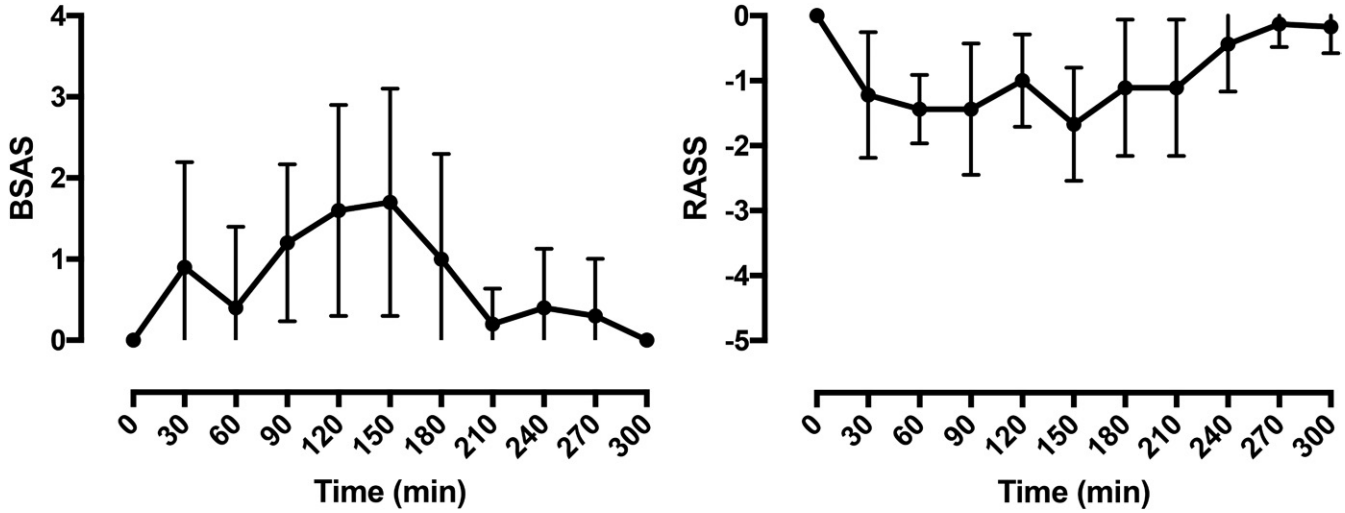

Fig. 3. Left panel: Bedside Shivering Assessment Scale (BSAS) over time. A higher score delineates more shivering. Right panel: Richmond Agitation-Sedation Scale (RASS) over time. A lower score indicates deeper sedation. Error bars represent one standard deviation.

separate these infusions in time and we saw no recurrence after doing so. Future experiments could test whether pharmacological interventions might also reduce this risk.

We determined potential side effects to address for practical application of forced cooling, particularly if this is used in remote locations. For example, asymptomatic atrial fibrillation occurred in one subject but resolved during rewarming. This provoked dysrhythmia was likely a result of hypothermia rather than drug infusion and it has little consequence over a few hours. However, a cardiac rhythm change would not be acceptable over days or longer. The decrease in systolic blood pressure and bradycardia did not cause symptoms. These changes in vital signs are consistent with the decreased metabolic rate at a lower core body temperature. These predictable effects define some minimum monitoring that should be in place for safe application.

During induction and maintenance of cooling, subjects experienced the sensation of being cold and rated it as moderate to severe in the level of discomfort. In fact, one subject experienced significant shivering, resulting in tachycardia during cooling. This illustrates the need for adequate shivering suppression to facilitate cooling. Future studies should evaluate methods to mitigate this perception as it may help facilitate temperature modulation. Medications that affect the transient receptor potential cation channel subfamily M member 8 and transient receptor potential cation channel subfamily V member 1 are associated with skin perception of cold and are thus potential targets. For longer cooling durations or frequent cooling bouts to be pursued, this will need to be addressed.

Our study is limited in its duration of cooling. Any application to a mission to space or potential rescue operations would require hours to days of cooling to derive maximal benefit.

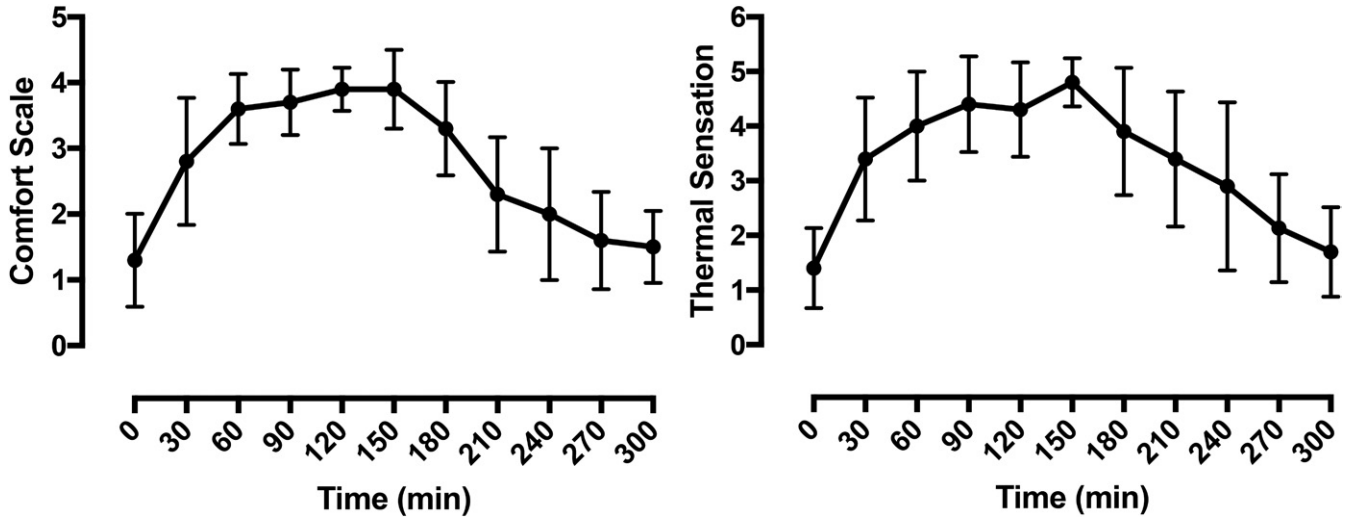

Fig. 4. Left panel: comfort scale over time. A higher score delineates more discomfort. Right panel: thermal sensation over time. A higher score indicates a sensation of more intense cold by the subject. Error bars represent one standard deviation.

Prolonged cooling of nonanesthetized healthy individuals is feasible using intravascular and surface cooling methods. Dexmedetomidine facilitates prolonged cooling by suppressing shivering with tolerable side effects in most subjects. Cooling to suppress metabolism is a feasible countermeasure to prolong astronaut endurance in the event of a failed CO_2 scrubber. It may also be considered in other life support or vehicle failures necessitating prolonged exposure to CO_2.

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