

Suppression of Shivering during Hypothermia Using a Novel Drug Combination in Healthy Volunteers

Rainer Lenhardt, M.D.,* Mukadder Orhan-Sungur, M.D.,† Ryu Komatsu, M.D.,† Raghavendra Govinda, M.D.,‡ Yusuke Kasuya, M.D.,‡ Daniel I. Sessler, M.D.,§ Anupama Wadhwa, M.D.||

Background: Hypothermia may be beneficial in stroke victims; however, it provokes vigorous shivering. Buspirone and dexmedetomidine each linearly reduce the shivering threshold with minimal sedation and no respiratory depression. This study tested the hypotheses that the combination of buspirone and dexmedetomidine would (1) synergistically reduce the shivering threshold, (2) synergistically reduce the gain and maximum intensity of shivering, and (3) produce sufficient inhibition to permit cooling to 34°C without excessive hypotension or sedation.

Methods: Eight healthy men were randomly assigned on 4 days to (1) no drug, (2) buspirone (60 mg orally), (3) dexmedetomidine (intravenous infusion to target plasma concentration of 0.6 ng/ml), or (4) combination of buspirone and dexmedetomidine at same doses. Lactated Ringer's solution (approximately 3°C) was infused intravenously to decrease tympanic membrane temperature by 1.5°C/h. Shivering threshold was defined as an increase in oxygen consumption greater than 20%. Sedation was evaluated using the Observer's Assessment of Sedation/Alertness scale.

Results: Mean arterial pressure and heart rate were slightly lower on dexmedetomidine and combination days. Likewise, the level of sedation was statistically different on these 2 days but clinically unimportant. Buspirone reduced the shivering threshold from 36.6°C ± 0.4°C to 35.9°C ± 0.4°C, dexmedetomidine reduced it to 34.7°C ± 0.5°C, and the combination to 34.1 ± 0.4°C. The interaction effect of 0.04°C was not significant. The gain of shivering and maximum shivering intensity were similar on each day.

Conclusions: The combination of buspirone and dexmedetomidine additively reduced the shivering threshold. Thus, sup-

plementing dexmedetomidine with buspirone blocks shivering and causes only minimal sedation.

BRAIN hypoxia and ischemia lead to stroke, the third most common cause of death in the Western world and the most important source of adult disability. Any reduction in stroke-related morbidity would thus benefit an enormous number of people and markedly reduce overall healthcare costs. Induced hypothermia has been proposed as a treatment for acute stroke and has been shown to be effective in animal trials alone or in combination with other measures.^{1,2} A recent meta-analysis of hypothermia in animal models of acute ischemic stroke indicates that hypothermia reduces infarct size significantly and improves neurobehavioral outcomes.³ Consequently, various clinical trials have been initiated to test the feasibility and efficacy of hypothermia in stroke and brain injury patients.[#] Studies on therapeutic hypothermia continue to be of intense interest despite conflicting and negative results from studies applying therapeutic hypothermia to adults⁴ and neonates⁵ with traumatic brain injury, during neonatal asphyxia resuscitation,^{6,7} and during cerebral aneurysm clipping.⁸

To effectively cool patients and to avoid thermal discomfort, shivering must be avoided. A drug regimen should be developed that induces thermoregulatory tolerance (defined as reducing the core body temperature that triggers shivering); agents that reduce the intensity of shivering would be especially welcome. There are many drugs known to inhibit normal thermoregulatory responses; however, they are all anesthetics or major sedatives that produce an amount of respiratory depression that may render stroke patients ventilator-dependent and should, therefore, be avoided.⁹⁻¹²

Two nonanesthesia drugs, buspirone, a serotonin 1A partial antagonist, and dexmedetomidine, a central alpha agonist, produce substantial thermoregulatory inhibition.^{11,13} Both drugs reduce the thermoregulatory thresholds for shivering. They have also been tested in combination with meperidine, an opioid with special antishivering action, and found to act synergistically (buspirone¹⁴) or additively (dexmedetomidine¹⁵). However, there is some concern about both these drug combinations. If there is a need to suppress shivering for an extended period of time, such as in intensive care unit-patients, meperidine is suboptimal because it has the potential to depress respiration. In addition, its metabolite normeperidine, which accumulates in the patient's blood, can cause respiratory depression¹⁶ and seizures.^{16,17} In contrast, a combination of buspirone and

This article has an accompanying Editorial View. Please see: Talke P: It's hot to be cool. ANESTHESIOLOGY 2009; 111:10-1.

* Associate Professor, || Assistant Professor, Department of Anesthesiology and Perioperative Medicine, University of Louisville, Louisville, Kentucky, and the Outcomes Research Consortium; † Research Fellow, Outcomes Research Institute, University of Louisville; ‡ Research Fellow, Department of Anesthesiology and Perioperative Medicine, University of Louisville, Louisville, Kentucky; § Chair, Department of Outcomes Research, The Cleveland Clinic, Cleveland, Ohio.

Received from the Department of Anesthesiology and Perioperative Medicine, University of Louisville, Louisville, Kentucky, and the Department of Outcomes Research, The Cleveland Clinic, Cleveland, Ohio. Submitted for publication July 9, 2008. Accepted for publication December 17, 2008. Dr. Orhan-Sungur's current position: Attending Physician, Department of Anesthesia, Istanbul University, Istanbul, Turkey; Dr. Komatsu's current position: Clinical Instructor, Department of Anesthesiology, Tokyo Women's Medical University, Tokyo, Japan. Funded by GM 061655 from the National Institutes of Health, Bethesda, Maryland (to Dr. Sessler), the Joseph Drown Foundation, Los Angeles, California, and the Gheen's Foundation, Louisville, Kentucky. Mallinckrodt Anesthesiology Products, Inc., St. Louis, Missouri, donated the thermocouples we used.

Address correspondence to Dr. Lenhardt: Department of Anesthesiology, University Hospital, 530 S. Jackson St., Louisville, Kentucky 40202. rainer.lenhardt@louisville.edu. Information on purchasing reprints may be found at www.anesthesiology.org or on the masthead page at the beginning of this issue. ANESTHESIOLOGY's articles are made freely accessible to all readers, for personal use only, 6 months from the cover date of the issue.

<http://www.clinicaltrials.gov> Identifier: NCT00283088, NCT00299416, NCT00178711, and NCT00222742; accessed June 26, 2008.

dexmedetomidine would lack side effects such as respiratory depression and drug-related risk of seizures and can be used for extended periods (for example, more than 24 h).

Accordingly, we evaluated the effects of buspirone and dexmedetomidine on thermoregulatory function in humans. Specifically, we tested the hypotheses that the combination (1) synergistically reduces the shivering threshold, (2) synergistically reduces the gain and maximum intensity of shivering, and (3) produces sufficient inhibition to permit endovascular cooling to 34°C without excessive hypotension, autonomic nervous system activation, sedation, or respiratory compromise.

Materials and Methods

With approval of the Human Studies Committee at the University of Louisville (Louisville, Kentucky) and written informed consent according to the Declaration of Helsinki, we studied eight healthy, male volunteers aged 18 to 40 yr. None of the volunteers was obese (body mass index [BMI] greater 35 kg/m²), taking any drugs, or had a history of thyroid disease, dysautonomia, or Raynaud syndrome.

Protocol

The volunteers fasted and refrained from smoking for 8 h. They also abstained from consuming alcohol for 24 h before each study day. They were minimally clothed and rested supine on a standard operating room table. Ambient temperature was maintained near 23°C. Volunteers lay on a circulating-water mattress (Cincinnati Sub-Zero, Cincinnati, OH) while covered with a forced-air warmer (Arizant Medical, Inc., Eden Prairie, MN). They each participated on 4 days in a random order: (1) control (no drug), (2) Buspirone (60 mg orally), (3) Dexmedetomidine (delivered by a computer-controlled intravenous infusion to target a plasma concentration of 0.6 ng/ml), and (4) the combination of 60 mg of buspirone and dexmedetomidine (target plasma concentration of 0.6 ng/ml). Study days were separated by at least 24 h.

Dexmedetomidine was delivered by a target-controlled infusion system starting 20 min before active cooling. The infusion pump (Harvard Apparatus 22; Harvard Apparatus, South Natick, MA) was controlled using STAN-Pump software**; this software adjusts the infusion rate every 10 s, as necessary, on the basis of the pharmacokinetic data of the study drug.¹⁸⁻²⁰ Buspirone was given orally with a sip of water. The time to peak plasma concentrations after oral administration of buspirone is 60 min; the mean elimination half-life is 150 min.²¹ Buspirone was given in three equally spaced oral doses,

with the first being 90 min before active cooling, the second 45 min before cooling, and the last at the start of cooling.

One investigator prepared the dexmedetomidine infusion and handed the buspirone pill to the volunteer. A second investigator, who was blinded to the assignment, recorded the data and determined shivering thresholds; the second investigator was required to leave the room while the drugs were being administered. The volunteers could not be blinded to buspirone administration as it was given orally. However, volunteers received an intravenous infusion on all study days and were not told if they were receiving dexmedetomidine or vehicle.

A 20-cm-long catheter was inserted into an antecubital vein and subsequently used for infusion of cold fluids. An additional intravenous catheter was inserted into the contralateral arm for drug administration. Throughout the study period, mean-skin temperature was maintained at 31°C by adjusting the temperature of circulating-water garments (Cincinnati Sub-Zero) and forced-air warmers (Augustine Medical, Inc., Eden Prairie, MN). Furthermore, the back, upper body, and lower body were individually maintained at the designated skin temperature.

Lactated Ringer's solution cooled to approximately 3°C was infused *via* the peripheral line at rates sufficient to decrease tympanic membrane temperature approximately 1.5°C/h. Fluid was administered as long as oxygen consumption continued to increase or a total of 5 l was given. We have used this model in numerous previous studies and demonstrated that it markedly reduces core temperature and is well tolerated by young, healthy volunteers.²¹⁻²³

The volunteers used a condom catheter during the study to minimize discomfort of a full bladder that usually otherwise accompanies administration of large fluid volumes. When maximum shivering (or 5 l of fluid) was reached, volunteers were rewarmed with circulating water and forced air.

Measurements

We recorded each volunteer's age, height, and weight. Heart rate was measured continuously during the study using an electrocardiogram; blood pressure was determined oscillometrically at 5-min intervals at the ankle. A pulse oximeter continuously measured arterial oxygen saturation.

Core temperatures were recorded from the tympanic membrane using Mon-a-therm thermocouple (Tyco-Mallinckrodt Anesthesiology Products, Inc., St. Louis, MO). The aural probe was inserted by the volunteers until they felt the thermocouple touch the tympanic membrane; appropriate placement was confirmed when they easily detected gentle rubbing of the attached wire. The aural canal was then occluded with cotton, the probe was securely taped in place, and a gauze bandage was positioned over the external ear. Mean skin-surface tem-

** STANPUMP program. Available at: <http://www.opentci.org>; accessed July 9, 2008.

perature were determined from 15 area-weighted sites, including the right fingertip,²⁴ arms, torso, legs, and feet.

All temperatures were recorded using Mon-a-therm thermocouples connected to calibrated Iso-Thermex 16-channel electronic thermometers having an accuracy of 0.1°C and a precision of 0.01°C (Columbus Instruments International, Corp., Columbus, OH). Individual and mean-skin temperatures were computed by a data-acquisition system, which displayed them at 1-s intervals and recorded them at 1-min intervals.

Oxygen consumption, as measured by a DeltaTrac metabolic monitor (SensorMedics Corp., Yorba Linda, CA), was used to quantify shivering; the system was used in canopy-mode in each case.²⁵⁻²⁷ Measurements were averaged over 1-min intervals and recorded every minute. End-tidal carbon dioxide partial pressure was measured from nasal prongs with an Ultima monitor (Datex-Ohmeda, Helsinki, Finland); exhaust gas from this monitor was returned to an oxygen consumption monitor. Sedation was evaluated with the bispectral index of the electroencephalogram (BIS™ A2000 version 3.21; Aspect Medical, Newton, MA) and by using the Observer's Assessment of Alertness/Sedation Score as in previous studies.²⁸

Data Analysis

The shivering threshold was identified as a sustained 20% increase in oxygen consumption as determined in previous studies.²⁹ The baseline for this analysis was the steady-state value after drug infusion but before cooling had started. Maximum intensity of shivering was identified by an oxygen consumption that failed to increase further despite continued reduction in core temperature. The gain of shivering was defined as the slope of the oxygen consumption *versus* core temperature regression line during its initial ascent towards the maximum observed value. The shivering threshold, gain, and maximum intensity were determined *post hoc* by an investigator blinded to treatment and core temperature.

This was a crossover design, with each subject completing four study days. On the basis of our previous studies of almost identical design and number of subjects,^{14,15} we knew that 8-10 male volunteers would supply meaningful data and allow us to keep the number of subjects required to complete the study to a minimum.

Data for hemodynamic responses, ambient temperature, and relative humidity on each study day were first averaged within each volunteer; data obtained between the onset of shivering and the maximum intensity were included. The resulting values were then averaged among volunteers. Results on the four study days were compared using repeated-measures ANOVA and Newman-Keul's tests. The gains of shivering, as determined by oxygen consumption, were not normally distributed

and were compared using Friedman's nonparametric ANOVA.

As in previous similar studies,¹⁵ synergistic interaction between dexmedetomidine and buspirone was evaluated using the statistical methodology described by Slinker.³⁰ The study was designed as a two-factor factorial experiment with two levels for each factor: presence and absence of each of the two drugs. With this model, a statistically significant positive interaction term between the two drugs indicated that they act synergistically or antagonistically. A nonsignificant interaction term indicated that the drugs' effects are additive. A repeated-measures ANOVA was used since each volunteer received each of the four treatments.³¹

Results

The participating volunteers were 22 ± 4 yr old, 179 ± 5 cm tall, and weighed 78 ± 12 kg. Mean arterial pressure, heart rate, and respiratory rate were slightly lower on the dexmedetomidine and the combination days; however, this difference was clinically irrelevant. Only one participant was a smoker.

Average end-tidal carbon dioxide partial pressure and arterial oxyhemoglobin saturation were similar on each study day. Ambient temperature and relative humidity were comparable on all study days (table 1). Mean skin temperature was maintained near 31°C throughout the study. All volunteers were vasoconstricted before the cold fluid infusion started.

Volunteers were slightly sedated during the dexmedetomidine and on the combination day, as defined by the Observer's Assessment of Sedation/Alertness scale score. In agreement with Observer's Assessment of Sedation/Alertness scale scores, BIS values were reduced to around 80 on the dexmedetomidine and on the combination day. However, at all times volunteers were easily arousable.

Using repeated-measures ANOVA, both buspirone and dexmedetomidine were significant factors associated with the shivering threshold (both, $P < 0.001$). Buspirone reduced the shivering threshold nearly 0.7°C, from $36.6^\circ\text{C} \pm 0.4^\circ\text{C}$ to $35.9^\circ\text{C} \pm 0.4^\circ\text{C}$. In contrast, dexmedetomidine at a target concentration of 0.6 ng/ml reduced the shivering threshold by about 2°C to $34.7^\circ\text{C} \pm 0.5^\circ\text{C}$. The combination of buspirone and dexmedetomidine reduced the shivering threshold by 2.5°C to $34.1 \pm 0.4^\circ\text{C}$ (fig. 1). The interaction effect in the repeated measures ANOVA was not significant ($P = 0.798$), and its estimated effect was 0.04°C. This is consistent with a calculated difference between measurements on the buspirone and on the dexmedetomidine day of 2.56°C. Thus, there was no interaction between the two drugs on the shivering threshold. Consequently, the combination of buspirone and dexmedetomidine additively reduced the shivering threshold.

Table 1. Potential Confounding Factors and Important Results

	Control	Buspirone	Dexmedetomidine	Combination
Ambient temperature, °C	23.2 ± 0.5	23.2 ± 0.3	23.2 ± 0.3	23.3 ± 0.4
Mean arterial blood pressure, mmHg	102 ± 7	104 ± 9	94 ± 5*	91 ± 8*
Heart rate, beats/min	73 ± 3	72 ± 5	56 ± 3*	54 ± 3*
Respiratory rate, breaths/minute	18 ± 1	17 ± 1	14 ± 1*	14 ± 1*
Average end-tidal Pco ₂ , mmHg	41 ± 2	43 ± 2	45 ± 3	44 ± 3
Total lactated Ringer's, L	1.6 ± 0.7	2.4 ± 0.5*	3.9 ± 1.1*	4.0 ± 1.2*
Core cooling rate, °C/h	1.5 ± 0.3	1.5 ± 0.6	1.4 ± 0.3	1.5 ± 0.1
OAA/S score, total score	20 ± 0	20 ± 0	17 ± 3*	16 ± 2*
Bispectral index (BIS)	97.4 ± 0.7	96.3 ± 1.8	80.5 ± 2.6*	79.5 ± 8.3*
Thermal comfort, cm on VAS	2.0 ± 0.8	2.4 ± 0.9	2.4 ± 1.2	2.0 ± 0.8

Values above the line were first averaged over the infusion period and then averaged among the volunteers; values below the line are at the shivering threshold. Data are presented as means ± SDs. Thermal comfort was evaluated at 15-min intervals and at each threshold using a 10-cm-long visual analog scale (VAS). 0 cm defined the worst imaginable cold; 5 cm, thermal comfort; 10 cm, the worst imaginable heat. A new, unmarked scale was used each time.

* Significant difference from control ($P < 0.05$).

"OAA/S" stands for Observer's Assessment of Alertness/Sedation.

The gain of shivering, as determined by oxygen consumption (fig. 2) was virtually identical on each day. The maximum shivering intensity was also similar on each study day (table 2).

Discussion

Therapeutic hypothermia has been shown to improve neurologic outcome in patients surviving a cardiac arrest^{32,33} and hypoxic-ischemic encephalopathy in newborns.³⁴ A number of animal studies suggest that mild hypothermia is protective against cerebral ischemia. In particular, experimental ischemic stroke models have been summarized recently by a meta-analysis. The findings in this meta-analysis consisted of a reduction of the infarct size by 43.5% (95% CI 40–47%) and improved

neurobehavioral scores by 45.7% when hypothermia was applied.³ Therapeutic hypothermia has potentially deleterious side effects such as shivering with a subsequent increase in heart rate and blood pressure. We tested a new drug combination using dexmedetomidine and buspirone to suppress shivering.

Our results showed that dexmedetomidine and buspirone had an additive interaction. That is, the measured shivering threshold yielded a similar result to the sum of the measured thresholds with buspirone and dexmedetomidine alone (fig. 1). This outcome disproves our first hypothesis and is in contrast with the results of a previous study using the combination of buspirone and meperidine that showed that the drugs had a synergistic effect. Dexmedetomidine and buspirone have distinctly different mechanisms of action: α -2 adrenoreceptor agonism and serotonin 1A receptor partial antagonism. These mechanisms seem to independently inhibit the hypothalamic input without potentiating its effect.

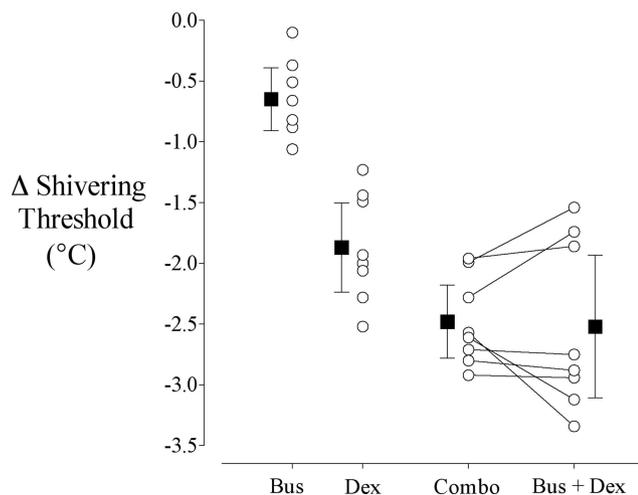


Fig. 1. Reductions in the shivering threshold (compared with Control day) for buspirone (Bus), dexmedetomidine (Dex), and combined Bus and Dex (Combo) days. Also shown is the expected reduction for the combination of buspirone and dexmedetomidine — calculated as the sum of the individual effects — assuming the two drugs had an additive effect. Squares represent group means ± SDs. Open circles = the value for each of the eight volunteers (two volunteers had the same value).

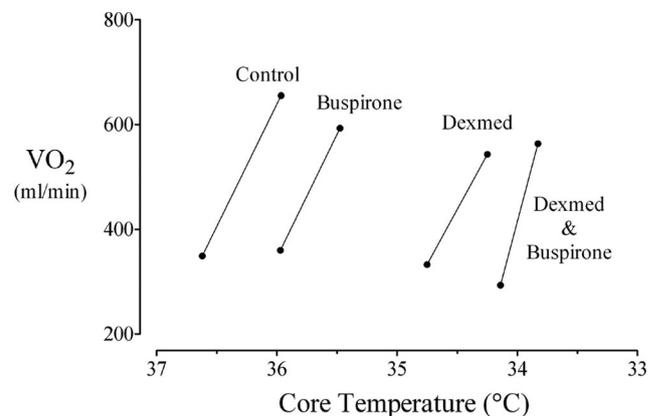


Fig. 2. The gain of shivering, as determined by oxygen consumption (VO_2) on the Control, Buspirone, Dexmedetomidine (Dexmed), and Combination (Dexmed & Buspirone) days. The slopes of the lines were virtually identical on each day, indicating that the drugs did not alter the gain of shivering. Bottom circles = VO_2 before cooling; top circles = VO_2 at the shivering threshold.

Table 2. Thermoregulatory Data

	Control	Buspirone	Dexmedetomidine	Combination
Mean skin temperature throughout the trial, °C	31.2 ± 0.2	31.0 ± 0.3	31.1 ± 0.2	31 ± 0.2
Core temperature at shivering, °C	36.4 ± 0.6	36.0 ± 0.6*	34.9 ± 0.6*	34.2 ± 0.5*
Gain of shivering, ml · min ⁻¹ · °C ⁻¹	-559 ± 129	-663 ± 167	-493 ± 260	-644 ± 183
Shivering maximum intensity, ml/min	655 ± 107	593 ± 91	543 ± 90	563 ± 130

Values were first averaged for each the volunteers and then for each study day. Data are presented as means ± SD.

* Value is significantly different from the control group.

The gain of shivering and the maximum intensity were similar on all four tested days. In contrast to our second hypothesis, neither gain nor maximum intensity was reduced by dexmedetomidine or by buspirone. This is in sharp contrast to volatile anesthetics that significantly reduce the gain and maximum intensity of shivering. Obviously, the magnitude of shivering, once triggered, is independent of α -2 activation or serotonin 1A receptor blockage.

Our data yielded a shivering threshold of roughly 34°C. It is unknown if 34°C may be the correct target temperature. Temperatures ranging from 24°C to 33°C have been used in animal models of transient and permanent cerebral ischemia and infarct size or recovery was reduced in these models. A recent study has shed some light on target temperatures in a rat model, where the middle cerebral artery was occluded for 90 min. The results suggest that the optimal depth of therapeutic hypothermia in temporary middle cerebral artery occlusion is 34°C.³⁵ The combination of dexmedetomidine and buspirone reduced the shivering threshold to about the same temperature. Despite recent animal data, there is little evidence for recommending a certain target temperature for therapeutic hypothermia in patients. Clinically, target temperatures from 32 to 34°C are being used by some physicians on a routine basis³⁶ and for clinical trials.††

The observed shivering threshold of 34.1°C was obtained by a mean skin temperature maintained at 31°C, which is about 3°C less than typical for stroke patients in a ward or intensive care unit setting. As in previous studies, we used a skin temperature of 31°C, with the goal to raise the shivering threshold to minimize the risk from infusion of large amounts of cold fluid. Skin temperature contributes 20% to control of vasoconstriction and shivering.³⁷ A typical skin temperature in awake stroke patients is about 34°C.³⁸ Consequently, administering dexmedetomidine and buspirone to stroke patients with a skin temperature of around 34°C would lower their shivering threshold by approximately 0.6°C.

If therapeutic hypothermia were achieved with internal heat exchange catheters in stroke patients, aggressive cutaneous warming would further reduce the shiv-

ering threshold. In a recent study, the combination of meperidine and skin surface warming reduced the shivering threshold to 33.8°C *via* an additive interaction.³⁹ By applying our drug combination with an internal cooling device and simultaneous cutaneous warming, the shivering threshold should drop to roughly 33°C. Using this setup could help to determine the effect of therapeutic hypothermia on outcome in awake stroke patients.

We did not analyze blood samples for dexmedetomidine or buspirone. We used target-controlled infusion for dexmedetomidine using STANPUMP software. We have previously shown that this target infusion system reliably titrates the drug to a preset blood concentration.¹⁵ For buspirone, we used a drug regimen similar to that of a previous study.¹⁴ The plasma concentrations of buspirone in the current study, therefore, should have been similar to those measured in that study (1.9 ± 1.2 µg/ml).

Another limitation of the study is that dexmedetomidine is currently approved for postoperative care of critically ill patients for a period of 24 h. A Federal Food and Drug Administration-mandated study is currently underway to prove safety and efficacy of the drug for a longer period under intensive care unit conditions. Publication is likely to ensue later this year.

Although our study was performed in men, the results can be generalized to women as well. In a previous study, data from Lopez *et al.*⁴⁰ demonstrated that, although the interthreshold range does not differ in men and women, women do thermoregulate at a significantly higher temperature than do men. As a result, by only including men in the study, we were able to minimize the number of volunteers required to complete the study.

The combination of dexmedetomidine and buspirone reduced mean arterial pressure and heart rate significantly in our volunteers (table 2). However, the change was not more than 10% for mean arterial pressure and not more than 20% for heart rate. It is unknown if stroke patients react to this drug combination in a similar way. A reduction in hemodynamic parameters might even have a beneficial effect on stroke patients. Similarly, respiratory rate was reduced on the dexmedetomidine and combination days. However, no significant change in end tidal carbon dioxide could be detected, most

†† <http://www.clinicaltrials.gov>. Identifier: NCT00283088, NCT00299416; accessed May 13, 2009.

likely because any change was offset by larger tidal volumes.

In summary, we tested the combination of dexmedetomidine and buspirone to reduce the thermoregulatory threshold for shivering. The shivering threshold for the combination was $34.1 \pm 0.4^\circ\text{C}$, which is comparable to the thresholds achieved when meperidine was given in combination with dexmedetomidine ($34.7 \pm 0.6^\circ\text{C}$) and with buspirone ($35.9 \pm 0.7^\circ\text{C}$). These data indicate that supplementing dexmedetomidine with buspirone blocks shivering without the potential negative side effects of meperidine and its metabolite. In addition, this drug combination causes only minimal sedation and no respiratory compromise, two side effects that are of paramount importance in rendering patients hypothermic after stroke. This drug combination does not cause respiratory depression; therefore, it enables hypothermia to be induced in patients without the risk of ventilator assistance during therapeutic hypothermia.

The authors thank Gilbert Haugh, M.S., for statistical assistance and Nancy Alsip, Ph.D., for editing the manuscript (both of the Office of Clinical Research Services and Support of the University of Louisville, Louisville, Kentucky).

References

- Campbell K, Meloni BP, Knuckey NW: Combined magnesium and mild hypothermia (35 degrees C) treatment reduces infarct volumes after permanent middle cerebral artery occlusion in the rat at 2 and 4, but not 6 h. *Brain Res* 2008; 1230:258-64
- Lee SH, Kim YH, Kim YJ, Yoon BW: Atorvastatin enhances hypothermia-induced neuroprotection after stroke. *J Neurol Sci* 2008; 275:18-21
- Van der Worp HB, Sena ES, Donnan GA, Howells DW, Macleod MR: Hypothermia in animal models of acute ischaemic stroke: A systematic review and meta-analysis. *Brain* 2007; 130:3063-74
- Peterson K, Carson S, Carney N: Hypothermia treatment for traumatic brain injury: A systematic review and meta-analysis. *J Neurotrauma* 2008; 25:62-71
- Hutchison JS, Ward RE, Lacroix J, Hebert PC, Barnes MA, Bohn DJ, Dirks PB, Doucette S, Fergusson D, Gottesman R, Joffe AR, Kirpalani HM, Meyer PG, Morris KP, Moher D, Singh RN, Skippen PW: Hypothermia therapy after traumatic brain injury in children. *N Engl J Med* 2008; 358:2447-56
- Hoehn T, Hansmann G, Buhner C, Simbruner G, Gunn AJ, Yager J, Levene M, Hamrick SE, Shankaran S, Thoresen M: Therapeutic hypothermia in neonates. Review of current clinical data, ILCOR recommendations and suggestions for implementation in neonatal intensive care units. *Resuscitation* 2008; 78:7-12
- Jacobs S, Hunt R, Tarnow-Mordi W, Inder T, Davis P: Cooling for newborns with hypoxic ischaemic encephalopathy. *Cochrane Database Syst Rev* 2007; 4:CD003311
- Todd MM, Hindman BJ, Clarke WR, Torner JC: Mild intraoperative hypothermia during surgery for intracranial aneurysm. *N Engl J Med* 2005; 352:135-45
- Kurz A, Go JC, Sessler DI, Kaer K, Larson M, Bjorksten AR: Alfentanil slightly increases the sweating threshold and markedly reduces the vasoconstriction and shivering thresholds. *ANESTHESIOLOGY* 1995; 83:293-9
- Leslie K, Sessler DI, Bjorksten A, Ozaki M, Matsukawa T, Schroeder M, Lin S: Propofol causes a dose-dependent decrease in the thermoregulatory threshold for vasoconstriction, but has little effect on sweating. *ANESTHESIOLOGY* 1994; 81:353-60
- Talke P, Tayefeh F, Sessler DI, Jeffrey R, Noursalehi M, Richardson C: Dexmedetomidine does not alter the sweating threshold, but comparably and linearly reduces the vasoconstriction and shivering thresholds. *ANESTHESIOLOGY* 1997; 87:835-41
- Xiong J, Kurz A, Sessler DI, Plattner O, Christensen R, Dechert M, Ikeda T: Isoflurane produces marked and non-linear decreases in the vasoconstriction and shivering thresholds. *ANESTHESIOLOGY* 1996; 85:240-5
- Zeisberger E, Roth J: Central regulation of adaptive responses to heat and cold. *Handbook of Physiology*. Section 4: Environmental Physiology. Edited by Fregly MJ, Blatteis CM. New York, Oxford, Oxford University Press, 1996, pp 579-95
- Mokhtarani M, Mahgob AN, Morioka N, Doufas AG, Sessler DI: Buspirone and meperidine synergistically reduce the shivering threshold. *Anesth Analg* 2001; 93:1233-9
- Doufas AG, Lin CM, Suleman MI, Liem EB, Lenhardt R, Morioka N, Akca O, Shah YM, Bjorksten AR, Sessler DI: Dexmedetomidine and meperidine additively reduce the shivering threshold in humans. *Stroke* 2003; 34:1218-23
- Armstrong PJ, Bersten A: Normeperidine toxicity. *Anesth Analg* 1986; 65:536-8
- Kaiko RF, Foley KM, Grabinski PY, Heidrich G, Rogers AG, Inturrisi CE, Reidenberg MM: Central nervous system excitatory effects of meperidine in cancer patients. *Ann Neurol* 1983; 13:180-5
- Dyck JB, Maze M, Haack C, Azamoff DL, Vuorilehto L, Shafer SL: Computer-controlled infusion of intravenous dexmedetomidine hydrochloride in adult human volunteers. *ANESTHESIOLOGY* 1993; 78:821-8
- Dyck JB, Maze M, Haack C, Vuorilehto L, Shafer SL: The pharmacokinetics and hemodynamic effects of intravenous and intramuscular dexmedetomidine hydrochloride in adult human volunteers. *ANESTHESIOLOGY* 1993; 78:813-20
- Shafer SL, Gregg KM: Algorithms to rapidly achieve and maintain stable drug concentrations at the site of drug effect with a computer-controlled infusion pump. *J Pharmacokinetic Biopharm* 1992; 20:147-69
- Lamberg TS, Kivisto KT, Neuvonen PJ: Effects of verapamil and diltiazem on the pharmacokinetics and pharmacodynamics of buspirone. *Clin Pharm Ther* 1998; 63:640-5
- Sessler DI, McGuire J, Hynson J, Moayeri A, Heier T: Thermoregulatory vasoconstriction during isoflurane anesthesia minimally decreases cutaneous heat loss. *ANESTHESIOLOGY* 1992; 76:670-5
- Tayefeh F, Plattner O, Sessler DI, Ikeda T, Marder D: Circadian changes in the sweating-to-vasoconstriction interthreshold range. *Pflügers Arch* 1998; 435:402-6
- Sessler DI, Lee KA, McGuire J: Isoflurane anesthesia and circadian temperature cycles. *ANESTHESIOLOGY* 1991; 75:985-9
- Meriläinen PT: Metabolic monitor. *Int J Clin Monit Comput* 1987; 4:167-77
- Tissot S, Delafosse B, Bertrand O, Bouffard Y, Viale JP, Annat G: Clinical validation of the Deltatrac monitoring system in mechanically ventilated patients. *Int Care Med* 1995; 21:149-53
- Weyland A, Weyland W, Sydow M, Weyland C, Kettler D: [Inverse fick's principle in comparison to measurements of oxygen consumption in respiratory gases. Does intrapulmonary oxygen uptake account for differences shown by different system methods?]. *Anaesthesist* 1994; 43:658-66
- Leslie K, Sessler DI, Smith WD, Larson MD, Ozaki M, Blanchard D: Prediction of movement following painful stimulation during propofol/nitrous oxide anesthesia in volunteers. *ANESTHESIOLOGY* 1996; 84:52-63
- Matsukawa T, Kurz A, Sessler DI, Bjorksten AR, Merrifield B, Cheng C: Propofol linearly reduces the vasoconstriction and shivering thresholds. *ANESTHESIOLOGY* 1995; 82:1169-80
- Slinker BK: The statistics of synergism. *J Mol Cell Cardiol* 1998; 30:723-31
- Tallarida RJ, Porreca F, Cowan A: Statistical analysis of drug-drug and site-site interactions with isobolograms. *Life Sci* 1989; 45:947-61
- Barnard MS, Voss TJ, Barnard CN: The treatment of congenital heart disease in infants. Surface cooling, deep hypothermia, limited cardiopulmonary bypass and circulatory arrest. *S Afr Med J* 1973; 47:469-71
- Sterz F, Behringer W, Holzer M: Global hypothermia for neuroprotection after cardiac arrest. *Acute Card Care* 2006; 8:25-30
- Shankaran S, Laptok AR, Ehrenkranz RA, Tyson JE, McDonald SA, Donovan EF, Fanaroff AA, Poole WK, Wright LL, Higgins RD, Finer NN, Carlo WA, Duara S, Oh W, Cotten CM, Stevenson DK, Stoll BJ, Lemons JA, Guillet R, Jobe AH: Whole-body hypothermia for neonates with hypoxic-ischemic encephalopathy. *N Engl J Med* 2005; 353:1574-84
- Kollmar R, Blank T, Han JL, Georgiadis D, Schwab S: Different degrees of hypothermia after experimental stroke: Short- and long-term outcome. *Stroke* 2007; 38:1585-9
- Hemmen TM, Lyden PD: Induced hypothermia for acute stroke. *Stroke* 2007; 38:794-9
- Cheng C, Matsukawa T, Sessler DI, Kurz A, Merrifield B, Lin H, Olofsson P: Increasing mean skin temperature linearly reduces the core-temperature thresholds for vasoconstriction and shivering in humans. *ANESTHESIOLOGY* 1995; 82:1160-8
- Wilson TE, Sauder CL, Kearney ML, Kuipers NT, Leuenberger UA, Monahan KD, Ray CA: Skin-surface cooling elicits peripheral and visceral vasoconstriction in humans. *J Appl Physiol* 2007; 103:1257-62
- Kimberger O, Ali SZ, Markstaller M, Zmoos S, Lauber R, Hunkeler C, Kurz A: Meperidine and skin surface warming additively reduce the shivering threshold: A volunteer study. *Crit Care* 2007; 11:R29
- Lopez M, Sessler DI, Walter K, Emerick T, Ozaki M: Rate and gender dependence of the sweating, vasoconstriction, and shivering thresholds in humans. *ANESTHESIOLOGY* 1994; 80:780-8