Clonidine produces a dose-dependent impairment of baroreflex-mediated thermoregulatory responses to positive end-expiratory pressure in anaesthetized humans

T. Mizobe1*, Y. Nakajima1, M. Sunaguchi1, H. Ueno1 and D. I. Sessler2

1Department of Anesthesiology, Kyoto Prefectural University of Medicine, Kyoto, Japan.
2The Outcome Research™ Institute and Departments of Anesthesiology and Pharmacology, University of Louisville, Louisville, KY, USA

*Corresponding author: Department of Anesthesiology, Kyoto Prefectural University of Medicine, Kamigyo-ku, Kyoto 602-8566, Japan. E-mail: toshim@koto.kpu-m.ac.jp

Background. Perioperative hypothermia is common and results from anaesthesia-induced inhibition of thermoregulatory control. Hypothermia is blunted by baroreceptor unloading caused by positive end-expiratory pressure (PEEP), and is mediated by an increase in the vasocostriction threshold. Premedication with clonidine impairs normal thermoregulatory control. We therefore determined the effect of clonidine on PEEP-induced hypothermia protection.

Methods. Core temperature was evaluated in patients undergoing combined general and epidural anaesthesia for lower abdominal surgery. They were assigned to an end-expiratory pressure of zero (ZEEP) or 10 cm H2O PEEP. The PEEP group was divided into three blinded subgroups that received placebo (Cl-0), clonidine 150 μg (Cl-150) and clonidine 300 μg (Cl-300) respectively. Placebo or clonidine was given orally 30 min before surgery. We evaluated core temperature and thermoregulatory vasoconstriction. We also determined plasma epinephrine, norepinephrine, angiotensin II concentrations and plasma renin activity.

Results. Core temperature after 180 min of anaesthesia was 35.1 (0.4) °C in the ZEEP group. PEEP significantly increased final core temperature to 35.8 (0.5) °C (Cl-0 group). Clonidine produced a linear, dose-dependent impairment of PEEP-induced hypothermia protection: final core temperatures were 35.4 (0.3) °C in the Cl-150 group and 35.0 (0.6) °C in the Cl-300 group. Similarly, clonidine produced a linear and dose-dependent reduction in vasoconstriction threshold: Cl-0, 36.4 (0.3) °C; Cl-150, 35.8 (0.3) °C; Cl-300, 35.4 (0.6) °C. Plasma norepinephrine, angiotensin II concentrations and plasma renin activity were consistent with the thermoregulatory responses.

Conclusion. Baroreceptor unloading by PEEP normally moderates perioperative hypothermia. However, clonidine premedication produces a linear, dose-dependent reduction in this benefit.

Br J Anaesth 2005; 94: 536–41

Keywords: complications, hypothermia; premedication, clonidine; reflexes, baroreceptor; temperature, regulation; ventilation, positive end-expiratory pressure (PEEP)

Accepted for publication: December 13, 2004

Perioperative hypothermia is common because of the combination of anaesthesia-induced impairment of thermoregulatory vasomotion, a cool operating room environment and surgical exposure promoting excessive heat loss.1–4 Perioperative hypothermia is associated with numerous adverse outcomes, including morbid cardiac events, coagulopathy and impaired immune function.5 Hypothermic patients are also prone to surgical wound infections, delayed suture removal and prolonged hospitalization.6

Peripheral vasoconstriction plays a major role in the thermoregulatory response to reduced body temperature. Non-thermal factors affecting the cardiovascular system thus modulate thermoregulatory control. Cardiopulmonary baroreceptors monitor blood pressure and central blood volume. They trigger a reflex that produces vasoconstriction when right atrial transmural pressure (RATP) decreases and vasodilation when RATP increases. We recently reported that the severity of perioperative hypothermia can be moderated by applying positive end-expiratory pressure (PEEP) to decrease RATP. PEEP, which unloads baroreceptors, attenuates perioperative hypothermia in lower abdominal surgery in anaesthetized humans by increasing the
vasoconstriction threshold (triggering core temperature).\textsuperscript{6} Thermoregulatory vasoconstriction is effective in constraining metabolic heat to the core thermal compartment, thus minimizing further core hyperthermia.\textsuperscript{4}

Clonidine, a partial α\textsubscript{2} adrenergic agonist, is used as a premedication and has a sedative effect; it has both anaesthetic-sparing and favourable haemodynamic properties.\textsuperscript{7} However, clonidine impairs central thermoregulatory control, an impairment that is manifested by reduced vasoconstriction and shivering thresholds.\textsuperscript{8} We therefore tested the hypothesis that clonidine premedication produces dose-dependent impairment of the baroreflex-mediated protective thermoregulatory response to PEEP in anaesthetized humans.

Methods
With approval of the Kyoto Prefectural University of Medicine Review Board on Human Experiments and written informed consent, we studied 32 patients (ASA I or II), aged 20–60 yr, scheduled for open lower abdominal surgery. None was obese, febrile or receiving vasodilators or medications likely to alter thermoregulation; none had a history of thyroid disease or autonomic dysfunction.

Thirty-two patients were randomly assigned to zero end-expiratory pressure (ZEEP, \(n=8\)) or 10 cm H\textsubscript{2}O PEEP. Those assigned to PEEP were divided into three groups: placebo (Cl-0, \(n=8\)), clonidine 150 µg (Cl-150, \(n=8\)) and clonidine 300 µg (Cl-300, \(n=8\)). Randomization was based on computer-generated codes and maintained in sequentially numbered envelopes until just before premedication.

Protocol
This study was performed as described previously.\textsuperscript{4-6} All operations were performed between 8:00 a.m. and noon. Patients fasted for more than 8 h before the surgery. They were given a placebo (ZEEP and Cl-0 groups), clonidine 150 µg (Cl-150 group) or clonidine 300 µg (Cl-300 group) with 100 ml of water orally 30 min before entering the operating room. The anaesthetists and investigators were blinded to treatment.

Ambient temperature was maintained at 24°C and relative humidity at 40%. We allowed 30 min for the patients to become acclimatized to the operating room environment; during this time an 18-G catheter was inserted into a left antecubital vein for administration of lactated Ringer's solution at ambient temperature (\(10 \text{ ml kg}^{-1} \text{ h}^{-1}\)). A 22-g catheter was inserted into the left radial artery for blood pressure monitoring and blood sampling. Additionally, an epidural catheter was inserted via the L1-L2 or the L2-L3 vertebral interspace with the patient in lateral position.

Anaesthesia was induced by i.v. administration of propofol 2 mg kg\textsuperscript{-1} and vecuronium bromide 0.15 mg kg\textsuperscript{-1} and was maintained with isoflurane 0.4% and nitrous oxide 66% in oxygen. An i.v. infusion of vecuronium, initially set to 0.025 mg kg\textsuperscript{-1} h\textsuperscript{-1}, was adjusted to maintain one or two twitches in response to supermaximal stimulation of the ulnar nerve at the wrist. Mechanical ventilation was adjusted to maintain end-tidal PCO\textsubscript{2} between 35 and 40 mm Hg. After an initial dose of 7 ml of lidocaine 1% without epinephrine into the epidural catheter, bupivacaine 0.25% was infused at 5 ml h\textsuperscript{-1} for the reminder of surgery. Patients were covered with one cotton sheet. In patients assigned to receive it (Cl-0, Cl-150, and Cl-300), PEEP (10 cm H\textsubscript{2}O) was initiated 10 min after the induction of anaesthesia and was maintained for 3 h.

Measurements
Blood pressure, heart rate, oxygen saturation, end-tidal PCO\textsubscript{2} and end-tidal isoflurane concentrations were recorded at 5-min intervals. Upper- and lower-body sensory block levels were evaluated after emergence from anaesthesia by response to cold sensation.

Core temperature, represented by distal oesophageal temperature (T\textsubscript{es}), was measured with a thermostir (Mon-a-therm; Mallinckrodt, St Louis, MO, USA), the end of which was inserted a distance, measured from the external nares, of one-quarter of the subjects' standing height. The thermostir probes were calibrated in the same environment as that of experiments using distilled water. The resolution of the temperature measurement system was about 0.024°C. We also recorded forearm-minus-fingertip skin temperature gradients.\textsuperscript{9} Briefly, thermostir probes for skin temperature measurement were attached to the right forearm half way between the elbow and the wrist and to the right index finger (opposite the nail bed). To quantify thermoregulatory peripheral vasoconstriction, we employed a forearm-minus-fingertip temperature gradient, because a positive forearm-fingertip temperature gradient is closely correlated with reduction in blood flow in acral regions and less affected by ambient temperature than fingertip temperature alone. Temperatures were recorded at 5-min intervals.

Blood was sampled from the radial artery 20, 90 and 180 min after induction of anaesthesia. Samples were immediately centrifuged at 4°C and aliquots of the plasma were stored at −80°C until assayed. Plasma epinephrine and nor-epinephrine were measured by high-performance liquid chromatography with an electrochemical detector after alumina extraction. Radioimmunoassay kits were used to evaluate plasma renin activity (Renin Riahead; Dainabot, Tokyo, Japan) and plasma angiotensin II concentrations (Angiotensin II; Nichols Institute Diagnostics, San Juan Capistrano, CA, USA).

Data analysis
As in previous studies, we defined the vasoconstriction threshold as the core temperature that triggered a rapid increase in the skin-temperature gradient.\textsuperscript{8} The threshold was determined \textit{post hoc}, individually for each patient by an investigator blinded to treatment. Once the threshold was
reached, thermal responsiveness (gain) was defined by the slope of a regression between the skin temperature gradient and core temperature in each individual.

Baseline values were averaged over the final 30 min before the induction of general anaesthesia. Intraoperative values were presented over time or first averaged within each patient, and then averaged among the patients in each group. Thermal responsiveness (gain) and vasoconstriction thresholds were analysed with general linear regression models for one-way analysis of variance (ANOVA with one between factor), followed by Scheffe’s multiple comparison tests. The effects of clonidine and time on the cardiovascular, thermoregulatory, and hormonal responses were analysed by general linear regression model procedures for two-way ANOVA with repeated measures (one between and one within factor), followed by Scheffe’s multiple comparison tests. Results are presented as mean (SD). P<0.05 was considered statistically significant.

Results

There were no statistically significant differences among the four groups in terms of demographic data, initial arterial pressure, heart rate or body temperature (Table 1). Total blood loss and fluid replacement volume 180 min after induction of anaesthesia did not differ significantly among the groups (data not shown). No patient received a blood transfusion. There were no significant differences in gender between the four groups. In each of the two clonidine groups, one patient was excluded because of insufficient data.

Both mean arterial pressure and heart rate in the Cl-300 group decreased significantly after induction of anaesthesia, compared with the Cl-0 group (Table 2).

The decrease in core temperature in the Cl-150 group became significantly greater than that in the Cl-0 group starting at 150 min; in the Cl-300 group it was significantly greater 110 min after induction of anaesthesia (Fig. 1). Final core temperature was 35.1 (0.4)°C in the ZEEP, 35.8 (0.5)°C in the Cl-0, 35.4 (0.3)°C in the Cl-150 and 35.0 (0.6)°C in the Cl-300 group. Clonidine dose-dependently decreased the final core temperature with a significant difference between Cl-0 and Cl-300 (P<0.05). The final core temperature in the Cl-300 patients was similar to that in the ZEEP patients. The increase in forearm-minus-fingertip temperature gradient was delayed in both clonidine premedication groups; compared with that in Cl-0 group, the gradient became significantly smaller in the Cl-150 group starting at 80 min and in

Table 1 Morphometric and demographic characteristics and baseline core temperature and haemodynamic responses. Data are mean (range) or mean (SD)

<table>
<thead>
<tr>
<th></th>
<th>ZEEP</th>
<th>Cl-0</th>
<th>Cl-150</th>
<th>Cl-300</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>52 (40–59)</td>
<td>53 (28–60)</td>
<td>47 (27–60)</td>
<td>48 (30–59)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>57 (12)</td>
<td>60 (12)</td>
<td>54 (17)</td>
<td>53 (11)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>160 (14)</td>
<td>157 (12)</td>
<td>156 (20)</td>
<td>156 (15)</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>4/4</td>
<td>4/4</td>
<td>4/4</td>
<td>4/4</td>
</tr>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>87 (6)</td>
<td>90 (6)</td>
<td>85 (11)</td>
<td>84 (11)</td>
</tr>
<tr>
<td>Heart rate (beats min⁻¹)</td>
<td>82 (6)</td>
<td>81 (11)</td>
<td>82 (14)</td>
<td>75 (23)</td>
</tr>
<tr>
<td>Core temperature (°C)</td>
<td>36.8 (0.3)</td>
<td>36.8 (0.3)</td>
<td>36.7 (0.3)</td>
<td>36.9 (0.6)</td>
</tr>
</tbody>
</table>

Fig 1 Time course of core temperature, represented by distal oesophageal temperature (Tₑₑₑ) and the forearm-minus-fingertip temperature gradient (Tₑₑₑ−Tₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉ>e). The decrease in Tₑₑₑ became significantly greater, and the increase in Tₑₑₑₑₑₑₑₑₑₑₑₑₑₑᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉᵉ>e) was delayed in both clonidine premedication groups compared with that in the Cl-0 group (P<0.05). Data are mean and SD. ZEEP, control (n=8); Cl-0, positive end-expiratory pressure (PEEP) (n=8); Cl-150, PEEP with oral clonidine 150 μg (n=7); Cl-300, PEEP with oral clonidine 300 μg (n=7).
the Cl-300 group starting at 70 min after induction of anaesthesia \((P<0.05)\).

The vasoconstriction thresholds were 35.5 (0.6)°C in the ZEEP, 36.4 (0.3)°C in the Cl-0, 35.8 (0.3)°C in the Cl-150 and 35.4 (0.6)°C in the Cl-300 group (Fig. 2). Patients assigned to the Cl-300 group vasoconstricted at significantly lower core temperatures than those in the Cl-0 group \((P<0.05)\). Vasoconstriction occurred at similar core temperatures in the ZEEP and Cl-300 groups. The gain of vasoconstriction (slope of the forearm-minus-fingertip temperature gradient/core temperature relationship below the threshold) was significantly reduced by clonidine, the gain of vasoconstriction in the Cl-300 group being similar to that in ZEEP group (Table 2).

In patients exposed to PEEP, clonidine linearly reduced the vasoconstriction threshold: \([\text{threshold}] = -0.003 \text{[clonidine]}+36.3, r=0.73\). Clonidine also linearly reduced core temperature 180 min after induction of anaesthesia: \([\text{temperature}] = -0.002 \text{[clonidine]}+35.8, r=0.67\) (Fig. 3). In patients exposed to PEEP, clonidine linearly reduced plasma norepinephrine concentration: \([\text{NE}] = -0.0007 \text{[clonidine]}+0.33, r=0.69\). Clonidine also linearly reduced plasma renin activity \([\text{PRA}] = -0.0007 \text{[clonidine]}+3.18, r=0.66\) and plasma angiotensin II concentration \([\text{angiotensin II}] = -0.54 \text{[clonidine]}+158, r=0.67\) (Fig. 4). Plasma norepinephrine in the Cl-300 group and plasma renin activity and plasma angiotensin II in both clonidine groups were significantly less than those in the Cl-0 group \((P<0.05)\). Clonidine premedication did not significantly reduce plasma epinephrine concentration under the PEEP condition.

Discussion

Clonidine is currently used in the management of surgical patients because of its sedative, analgesic and anaesthetic sparing properties.\(^7\) Non-selective \(\alpha_2\) adrenergic agonists give a biphasic blood pressure response: after a short hypertensive phase, arterial pressure falls below the baseline. This is because stimulation of the \(\alpha_{2B}\) adrenergic receptor subtype causes initial direct vasoconstriction in the peripheral vascular smooth muscle. Subsequently, activation of \(\alpha_{2A}\) adrenergic receptor subtypes causes hypotension by inhibiting central sympathetic outflow as well as norepinephrine release from sympathetic nerves.\(^7\)\(^10\)

We previously demonstrated that baroreceptor unloading by PEEP attenuates anaesthetic-induced perioperative hypothermia by increasing the threshold and gain of thermoregulatory vasoconstriction. Relative preservation of thermoregulatory vasoconstriction was associated with sympathetic nervous system activation.\(^6\) Our current major results are that oral clonidine premedication produces a dose-dependent impairment of the thermoregulatory benefit normally elicited by PEEP; specifically, oral premedication
with 300 μg obliterated the thermoregulatory protection normally produced by 10 cm H₂O PEEP.

Several mechanisms may account for the effect of clonidine premedication on thermoregulatory responses by PEEP. Intravenous α₂ adrenergic agonists, such as clonidine and dexmedetomidine, decrease the thermoregulatory thresholds for vasoconstriction and shivering, producing a dose-dependent impairment of central thermoregulatory control. It is therefore likely that clonidine’s central inhibition of thermoregulatory control blunts the normal beneficial effects of PEEP. Several anaesthetic agents decrease the thermoregulatory vasoconstriction threshold in a dose-dependent manner. Clonidine also has sedative/hypnotic and analgesic properties. Activation of α₂ adrenoceptors produces a potent analgesic response involving both supraspinal and spinal sites and α₂ agonists are able to reduce the MAC of volatile anaesthetics (e.g. MAC for isoflurane by 85% and for halothane by >95%). Therefore, clonidine itself might inhibit the thermoregulatory response, which antagonizes the thermoregulatory effect of baroreceptor unloading by PEEP. Alternatively, the relatively high concentration of isoflurane combined with clonidine in this study may exert a more potent inhibitory effect on the thermoregulatory centre, which could overwhelm the PEEP effect on the thermoregulatory response.

Cutaneous vasodilation induced by clonidine premedication may reduce the core-to-periphery temperature gradient and enhance body heat redistribution, which mimics the effect of nifedipine premedication. However, clonidine premedication, which has no subtype selectivity, may produce initial vasoconstriction due to α₂B adrenergic stimulation, which prevents body heat redistribution. In this study, mean arterial pressure in the Cl-300 group was decreased significantly compared with the Cl-0 group. This suggests that the main effect was vasodilation produced by clonidine, combined with the effect of anaesthetic agents.

Clonidine produces cutaneous vasodilation by reducing sympathetic nerve activity. Applying PEEP (baroreceptor unloading) prevents hypothermia by enhancing peripheral vasoconstriction, which is mediated by activation of the sympathetic nervous system via baroreceptors. Therefore, clonidine seems to inhibit the thermoregulatory vasoconstriction and the baroreceptor reflex-induced vasoconstriction through the sympathetic nervous system. The plasma norepinephrine and angiotensin II concentrations in the present study, both of which are increased by baroreceptor unloading with PEEP, indicated that clonidine, in a dose-dependent manner, attenuated either the sympathetic outflow centrally, the sympathetic tone peripherally, or both.

The amount of redistribution hypothermia (reduction in core temperature during the first hour of anaesthesia) was greater with ZEEP than PEEP. However, redistribution was similar with each dose of clonidine in the patients given PEEP. This suggests that clonidine premedication has little effect on core-to-peripheral internal heat redistribution of body heat. The second linear phase of the hypothermia curve results from heat loss exceeding production. This phase was short in our patients and is thus difficult to evaluate. In contrast, the plateau phase, which results from re-emergence of thermoregulatory vasoconstriction, was a strong function of both PEEP and clonidine dose. An additional factor is that clonidine premedication reduces systemic oxygen consumption, which would also contribute to hypothermia. It is thus likely that both thermoregulatory and metabolic factors contribute during the third (plateau) phase of hypothermia.

Clonidine has a half-life of roughly 12 h and it is thus unlikely that plasma concentrations decreased much over the study period, although these were not measured.

A limitation of this study is that gender, which is known to influence thermoregulation, was uncontrolled. However, there were no significant gender differences among our four study groups.

In summary, baroreceptor unloading by PEEP during anaesthesia normally moderates perioperative hypothermia by activating thermoregulatory vasoconstriction at temperatures closer to awake values. The mechanism for this protective response appears to be early activation of the sympathetic nervous system. In contrast, clonidine...
Premedication produces a linear, dose-dependent impairment in sympathetic nervous system activation and a dose-dependent reduction in the vasoconstriction threshold in the presence of PEEP. The consequence is a dose-dependent impairment of the beneficial thermoregulatory effect otherwise provided by PEEP. Premedication with 300 μg of clonidine obliterates the benefit that otherwise results from 10 cm H₂O PEEP.

Acknowledgements
This work was supported by NIH Grant GM 061655 (Bethesda, MD, USA), the Gheens Foundation (Louisville, KY, USA), the Joseph Drown Foundation (Los Angeles, CA, USA) and the Commonwealth of Kentucky Research Challenge Trust Fund (Louisville, KY, USA). None of the authors has any personal financial interest related to this report.

References
4 Kurz A, Sessler DI, Christensen R, Dechert M. Heat balance and distribution during the core-temperature plateau in anesthetized humans. Anesthesiology 1995; 83: 491–9
5 Sessler DI. Complications and treatment of mild hypothermia. Anesthesiology 2001; 95: 531–43
11 Talke P, Tayefeh F, Sessler DI, et al. Dexmedetomidine does not alter the sweating threshold, but comparably and linearly decreases the vasoconstriction and shivering thresholds. Anesthesiology 1997; 87: 835–41