

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

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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 vasoconstriction 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 (CI-0), clonidine 150 µg (CI-150) and clonidine 300 µg (CI-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 (CI-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 CI-150 group and 35.0 (0.6)°C in the CI-300 group. Similarly, clonidine produced a linear and dose-dependent reduction in vasoconstriction threshold: CI-0, 36.4 (0.3)°C; CI-150, 35.8 (0.3)°C; CI-300, 35.4 (0.6)°C. Plasma norepinephrine, angiotensin II concentrations and 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.

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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).⁶ Thermoregulatory vasoconstriction is effective in constraining metabolic heat to the core thermal compartment, thus minimizing further core hypothermia.⁴

Clonidine, a partial α_2 adrenergic agonist, is used as a premedication and has a sedative effect; it has both anaesthetic-sparing and favourable haemodynamic properties.⁷ However, clonidine impairs central thermoregulatory control, an impairment that is manifested by reduced vasoconstriction and shivering thresholds.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 H₂O PEEP. Those assigned to PEEP were divided into three groups: placebo (CI-0, $n=8$), clonidine 150 μg (CI-150, $n=8$) and clonidine 300 μg (CI-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.^{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 CI-0 groups), clonidine 150 μg (CI-150 group) or clonidine 300 μg (CI-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 ml kg⁻¹ 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⁻¹ and vecuronium bromide 0.15 mg kg⁻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⁻¹ h⁻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 P_{CO_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⁻¹ for the remainder of surgery. Patients were covered with one cotton sheet. In patients assigned to receive it (CI-0, CI-150, and CI-300), PEEP (10 cm H₂O) was initiated 10 min after the induction of anaesthesia and was maintained for 3 h.

Measurements

Blood pressure, heart rate, oxygen saturation, end-tidal P_{CO_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_{es}), was measured with a thermistor (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 thermistor 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.⁹ Briefly, thermistor 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 norepinephrine were measured by high-performance liquid chromatography with an electrochemical detector after alumina extraction. Radioimmunoassay kits were used to evaluate plasma renin activity (Renin Riabead; 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.⁶ The threshold was determined *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 Scheffé'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 Scheffé'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 CI-300 group decreased significantly after induction of anaesthesia, compared with the CI-0 group (Table 2).

The decrease in core temperature in the CI-150 group became significantly greater than that in the CI-0 group starting at 150 min; in the CI-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 CI-0, 35.4 (0.3)°C in the CI-150 and 35.0 (0.6)°C in the CI-300 group. Clonidine dose-dependently decreased the final core temperature with a significant difference between CI-0 and CI-300 ($P < 0.05$). The final core temperature in the

CI-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 CI-0 group, the gradient became significantly smaller in the CI-150 group starting at 80 min and in

Table 2 Intraoperative haemodynamic, anaesthetic (180 min after induction of anaesthesia) and thermoregulatory responses. *Significantly different from value for CI-0. PEEP, positive end-expiratory pressure

	ZEEP	CI-0	CI-150	CI-300
Final mean arterial pressure (mm Hg)	84 (6)	82 (6)	84 (5)	68 (11)*
Final heart rate (beats min ⁻¹)	70 (8)	69 (12)	70 (11)	59 (11)*
End-tidal isoflurane (%)	0.4 (0.3)	0.4 (0.3)	0.4 (0.3)	0.4 (0.3)
Final core temperature (°C)	35.1 (0.4)*	35.8 (0.5)	35.4 (0.3)*	35.0 (0.6)*
Vasoconstriction threshold (°C)	35.5 (0.6)*	36.4 (0.3)	35.8 (0.3)*	35.4 (0.6)*
Vasoconstriction gain	9.6 (9.0)*	17.4 (12.1)	13.5 (11.7)	10.5 (11.1)*

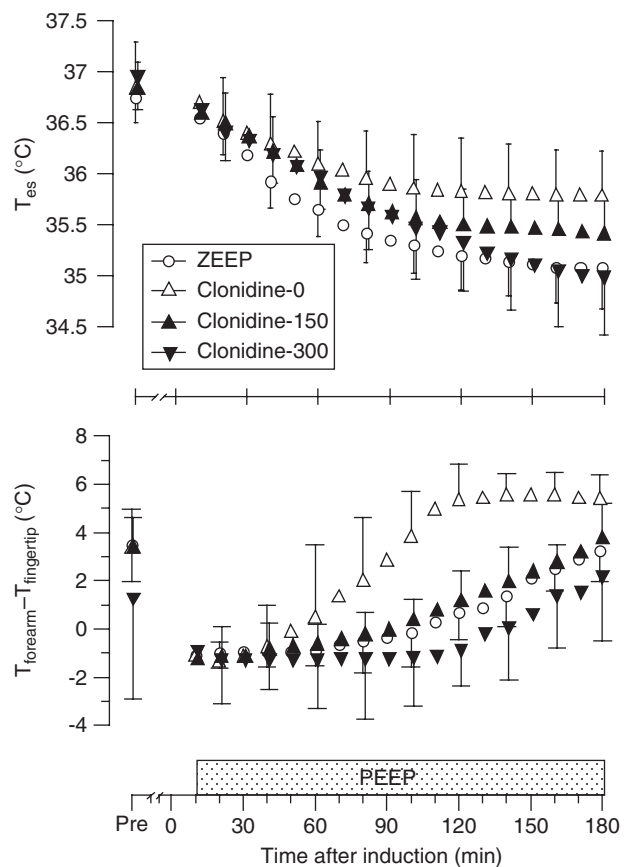


Fig 1 Time course of core temperature, represented by distal oesophageal temperature (T_{es}) and the forearm-minus-fingertip temperature gradient ($T_{forearm}-T_{fingertip}$). The decrease in T_{es} became significantly greater, and the increase in $T_{forearm}-T_{fingertip}$ was delayed in both clonidine premedication groups compared with that in the CI-0 group ($P < 0.05$). Data are mean and SD. ZEEP, control ($n=8$); CI-0, positive end-expiratory pressure (PEEP) ($n=8$); CI-150, PEEP with oral clonidine 150 μg ($n=7$); CI-300, PEEP with oral clonidine 300 μg ($n=7$).

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

	ZEEP	CI-0	CI-150	CI-300
Age (yr)	52 (40–59)	53 (28–60)	47 (27–60)	48 (30–59)
Weight (kg)	57 (12)	60 (12)	54 (17)	53 (11)
Height (cm)	160 (14)	157 (12)	156 (20)	156 (15)
Sex (M/F)	4/4	4/4	3/4	2/5
Mean arterial pressure (mm Hg)	87 (6)	90 (6)	85 (11)	84 (11)
Heart rate (beats min ⁻¹)	82 (6)	81 (11)	82 (14)	75 (23)
Core temperature (°C)	36.8 (0.3)	36.8 (0.3)	36.7 (0.3)	36.9 (0.6)

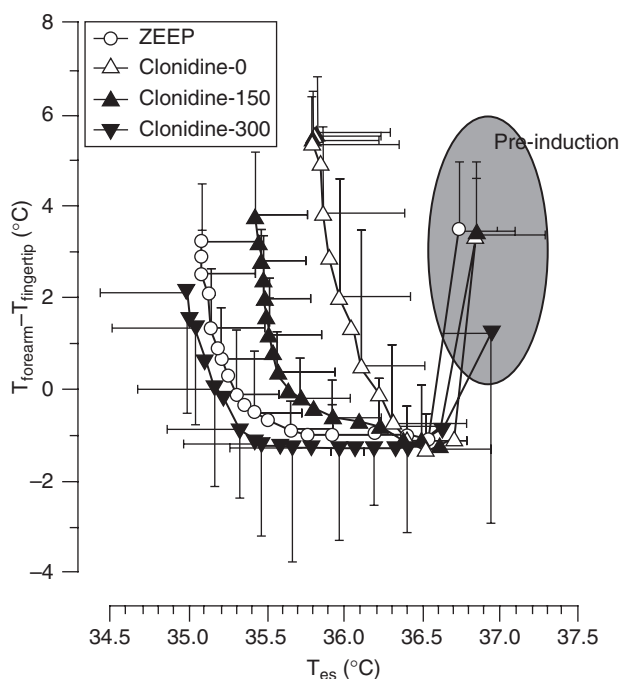


Fig 2 The functional relationship between $T_{\text{forearm}} - T_{\text{fingertip}}$ and T_{es} . Patients assigned to the Cl-150 and Cl-300 groups vasoconstricted at significantly lower core temperatures than those in the Cl-0 group ($P < 0.05$). Data are mean and SD.

the Cl-300 group starting at 70 min after induction of anaesthesia ($P < 0.05$).

The vasoconstriction thresholds were $35.5 (0.6)^\circ\text{C}$ in the ZEEP, $36.4 (0.3)^\circ\text{C}$ in the Cl-0, $35.8 (0.3)^\circ\text{C}$ in the Cl-150 and $35.4 (0.6)^\circ\text{C}$ 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

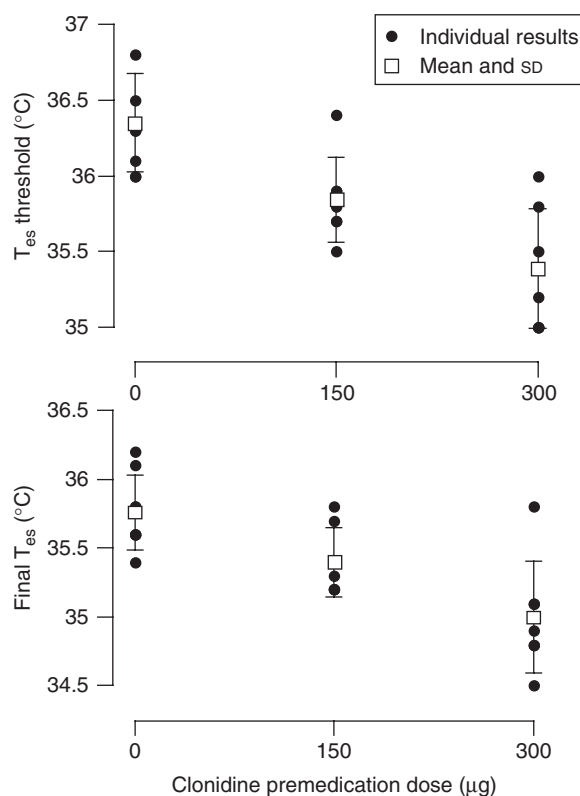


Fig 3 In patients exposed to PEEP, clonidine linearly reduced the vasoconstriction threshold (T_{es} threshold) and T_{es} at 180 min after induction of anaesthesia (Final T_{es}).

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 α_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 α_{2B} adrenergic receptor subtype causes initial direct vasoconstriction in the peripheral vascular smooth muscle. Subsequently, activation of α_{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

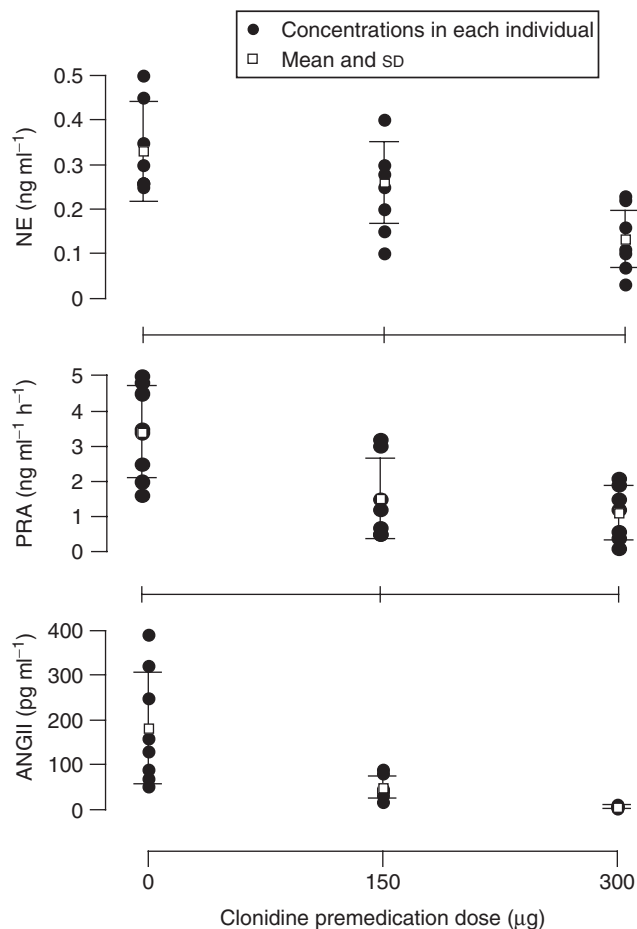


Fig 4 In patients exposed to PEEP, clonidine linearly reduced plasma norepinephrine (NE) concentration, plasma renin activity (PRA) and plasma angiotensin II (ANGII) concentration.

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 α_2 adrenergic agonists, such as clonidine and dexmedetomidine, decrease the thermoregulatory thresholds for vasoconstriction and shivering, producing a dose-dependent impairment of central thermoregulatory control.^{8,11} 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.^{12,13} Clonidine also has sedative/hypnotic and analgesic properties.⁷ Activation of α_2 adrenoceptors produces a potent analgesic response involving both supraspinal and spinal sites and α_2 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.¹⁴ However, clonidine premedication, which has no subtype selectivity, may produce initial vasoconstriction due to α_{2B} adrenergic stimulation,¹⁰ which prevents body heat redistribution. In this study, mean arterial pressure in the CI-300 group was decreased significantly compared with the CI-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.¹⁵ Applying PEEP (baroreceptor unloading) prevents hypothermia by enhancing peripheral vasoconstriction, which is mediated by activation of the sympathetic nervous system via baroreceptors.⁶ 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 anaesthesia¹⁶) 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.³ 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.^{8,17,18} 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 h¹⁹ 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.

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