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Clonidine Comparably Decreases the Thermoregulatory Thresholds for Vasoconstriction and Shivering in Humans

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Background: Clonidine stops postoperative shivering, but its underlying mechanism of action is unknown. Clonidine may impair central control of thermoregulation or act on peripheral receptors. Accordingly, the authors tested the hypothesis that clonidine reduces both the vasoconstriction and shivering thresholds, a pattern consistent with central thermoregulatory impairment.

Methods: Seven healthy volunteers participated in the study. Thermoregulatory vasoconstriction was evaluated using forearm minus fingertip, skin-temperature gradients; values exceeding 4° C were considered to be significant vasoconstriction. Systemic oxygen consumption ($\dot{V}O_2$) was measured with a canopy system. In addition, shivering was qualitatively evaluated using a simple scale, graduated from 0 (no shivering) to 2 (intense shivering). The tympanic membrane temperatures triggering significant vasoconstriction and grade 1 shivering were considered to be the thresholds for the two thermoregulatory responses. Measurements were performed after a 10-min steady state period and during cooling by central venous infusion of Ringer's lactate solution at 4° C. Each subject was evaluated at two sessions, separated by at least 48 h. They were randomly and blindly assigned to received either an intravenous bolus of 75 µg clonidine or a placebo before cooling. When the shivering score equaled 2, 75 µg clonidine was injected intravenously, and repeated if necessary, to completely stop shivering.

Results: Clonidine significantly decreased the thermoregulatory threshold for shivering by $0.6 \pm 0.3^\circ \text{C}$ (mean \pm SD). Similarly, the threshold for cutaneous vasoconstriction was significantly reduced by $0.5 \pm 0.2^\circ \text{C}$. Additional clonidine administration always stopped shivering, at whatever temperature it occurred.

Conclusions: This study confirms that clonidine administration stops shivering, and suggests that it acts by impairing central thermoregulatory control. That an additional dose of clonidine stops shivering in subjects already given one dose, indicates that the effect of clonidine is dose dependent. (Key words: Sympathetic nervous system, α_2 -adrenergic agonists: clonidine. Thermoregulation: shivering; thresholds; vasoconstriction.)

CLONIDINE has been extensively studied in the perioperative period because of its hemodynamic and analgesic properties.¹ In one of the first clinical evaluations of clonidine in anesthetized patients, Flacke *et al.* reported that the incidence of postoperative shivering was reduced in patients given the drug.² More recently, studies demonstrated that intravenous clonidine is an effective treatment for postanesthetic shivering.^{3,4} However, the mechanism by which clonidine stops shivering is unknown.

Normal thermoregulatory shivering is a complex and poorly understood response requiring polysynaptic transmission of neural impulses throughout the brain, the brainstem, and the spinal cord. Postanesthetic shivering contains abnormal tremor patterns,⁵ and its genesis may be even more complex.

Since α_2 receptors are widely distributed within the central nervous system, clonidine may specifically impair shivering at any number of sites. Specific inhibition of shivering would decrease the core temperature, triggering shivering, but leave the threshold for vasoconstriction unaltered. Alternatively, clonidine has sedative properties⁶ and may, like other sedatives and anesthetics, generally impair central thermoregulatory control.^{7,8,9} Such generalized inhibition of thermoregulatory control would most likely be manifested as a

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comparable reduction in the vasoconstriction and shivering thresholds. Accordingly, we tested the hypothesis that clonidine synchronously reduces the thermoregulatory thresholds for both vasoconstriction and shivering.

Materials and Methods

With ethical committee approval, seven healthy male volunteers participated in this study. Their mean age, weight, and height were, respectively, 33 ± 4 yr, 74 ± 16 kg, and 176 ± 16 cm. None was obese, was taking medication, or had a history of thyroid disease, dysautonomia, or Raynaud's syndrome.

Each test started between 9:00 and 10:00 AM, after an overnight fast. The volunteers were minimally clothed and lay resting on a bed, in a room with the temperature controlled to 25°C . After a 10-min control period, hypothermia was produced by central venous infusion of 4°C isotonic saline solution at a rate of $0.6\text{--}0.8\text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$. The cold solution was infused until patients shivered, and then continued at the same rate to maintain constant core temperature for 10 min. Shivering was evaluated using a clinical scale graduated as follows: 0 = no shivering, 1 = moderate shivering, and 2 = intense shivering.

Each volunteer participated on two separate days, at 48-h intervals. On one day, volunteers were given an intravenous placebo before the cold saline infusion; on the other, they were given a bolus of $75\ \mu\text{g}$ clonidine. Treatment order was allocated randomly and the trials were performed in a double-blind fashion. On both days, a $75\text{-}\mu\text{g}$ bolus of clonidine was administered intravenously when the shivering score was 2, and repeated, if necessary, 2 min later, to completely stop shivering.

Arterial blood pressure and heart rate were measured at 5-min intervals, using a Dinamap (Critikon, Tampa, FL). Core temperatures were measured at the tympanic membrane with a thermocouple probe (Ellab, Røedovre, Denmark). Forearm and fingertip skin temperatures were measured with thermocouple probes (Mon-a-Therm, St Louis, MO) connected to Mallinckrodt Model 8700 thermometers (St. Louis, MO). As in previous studies,^{7,8} a 4°C gradient between the forearm and fingertip was considered to be significant cutaneous vasoconstriction. The forearm minus fingertip, skin-temperature gradient correlates well with fingertip blood flow.¹⁰ The tympanic membrane temperature at which a 4°C cutaneous temperature gradient occurred

was considered the thermoregulatory threshold for cutaneous vasoconstriction. Similarly, the tympanic membrane temperature triggering grade 1 shivering was considered to be the threshold for shivering.

Whole-body oxygen consumption ($\dot{V}\text{O}_2$) was measured with a head canopy system (Deltatrac Metabolic Monitor, Datex Instrumentarium, Helsinki, Finland). The accuracy of the method is $4 \pm 2\%$.¹¹ Measurements of $\dot{V}\text{O}_2$ were performed at 1-min intervals and averaged over 10-min periods before, during, and after shivering.

Differences between the thresholds were analyzed using two-tailed paired *t* tests. A general, mixed-model analysis of variance (three factors: treatment, period, and subject) was used to compare $\dot{V}\text{O}_2$ values, and a Student–Newman–Keuls multiple-range test was used for intragroup means comparison. Values are expressed as means \pm SD; $P < 0.05$ was considered to be statistically significant.

Results

The rate of core cooling was $2.0 \pm 0.2^\circ\text{C/h}$ after placebo administration and $2.0 \pm 0.7^\circ\text{C/h}$ when volunteers were given clonidine ($P = \text{NS}$). The threshold for vasoconstriction was $36.3 \pm 0.3^\circ\text{C}$ after the placebo bolus and $35.8 \pm 0.4^\circ\text{C}$ after the clonidine bolus ($P < 0.05$). The shivering threshold was $35.9 \pm 0.2^\circ\text{C}$ after the placebo bolus and $35.4 \pm 0.3^\circ\text{C}$ after the clonidine bolus ($P < 0.05$). Administration of clonidine, therefore, decreased both the vasoconstriction and shivering thresholds approximately 0.5°C .

When the subjects shivered, a $75\text{-}\mu\text{g}$ intravenous bolus dose of clonidine completely stopped shivering within 2 min in all but one volunteer, who required a second bolus to obtain complete cessation.

Systemic oxygen consumption increased significantly during shivering, at whatever temperature it occurred. Administration of clonidine during shivering significantly decreased $\dot{V}\text{O}_2$ (fig. 1). Throughout the study, $\dot{V}\text{O}_2$ values were significantly less when the volunteers were given clonidine (fig. 2).

Clonidine, administered before cooling, did not significantly decrease mean arterial pressure (from 68 ± 5 to 65 ± 4 mmHg), and no bradycardia (<50 beats/min) was detected. Sedation was minimal. Mean blood pressure increased significantly during shivering.

Discussion

This study confirms the efficacy of clonidine in stopping thermoregulatory shivering. In addition, it shows

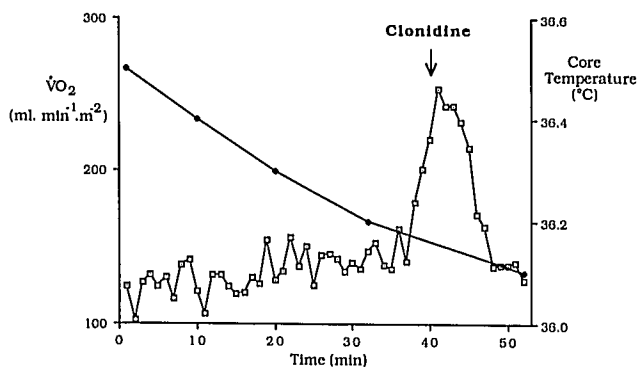


Fig. 1. This figure depicts the typical evolution of $\dot{V}O_2$ (white squares, left vertical scale) and core temperature (black diamonds, right vertical scale) in one volunteer given placebo. Shivering occurred at 36.2°C tympanic membrane temperature, and produced a marked increase in $\dot{V}O_2$. A bolus of 75 μ g clonidine (arrow) stopped shivering and decreased $\dot{V}O_2$ to values comparable to those preceding shivering.

that clonidine produces a generalized impairment of thermoregulation, comparably reducing the thresholds for vasoconstriction and shivering.

Several mechanisms may account for the effect of clonidine on shivering. Its peripheral stimulation of α_2 -adrenergic receptors may decrease cutaneous blood flow and temperature. However, a decrease in skin temperature would increase response thresholds.¹² Because cutaneous vasoconstriction and shivering occurred at lower core temperatures in subjects given clonidine, this hypothesis is unlikely. Alternately, clonidine may inhibit transmission of cold signals by A- δ fibers, but our protocol did not test this hypothesis. α_2 -Adrenergic agonists produce flaccidity in laboratory animals and patients.^{13,14} A similar effect may explain the observed decrease in shivering magnitude, as indirectly documented in our study by a smaller increase in $\dot{V}O_2$, but an unchanged shivering threshold.

That clonidine decreases the thermoregulatory threshold because of generalized impairment of thermoregulatory control is supported by the comparable decreases in the thresholds triggering cutaneous vasoconstriction and shivering. α_2 -Adrenergic receptors are present in the hypothalamus, and may mediate clonidine's inhibition of vasoconstriction and shivering.¹⁵ Stimulation of these receptors may inhibit firing of the temperature-sensitive neurons within the hypothalamus. Alternatively, clonidine may alter afferent processing of thermal information at other central nervous system levels.

Shivering induced by core hypothermia is, by definition, normal thermoregulatory shivering. Most post-

anesthetic shivering is also normal thermoregulatory shivering,¹⁶ but it includes abnormal clonic components apparently resulting from spinal reflex hyperreactivity.¹⁷ Both tremor types are, however, thermoregulatory.⁵ Thus, it is not surprising that clonidine, which lowers the shivering threshold, should be an effective treatment for both normal and postanesthetic shivering.

In volunteers initially given clonidine, shivering occurred at a lower core temperature than in those given placebo. However, additional clonidine obliterated shivering once it did occur. These data indicate that clonidine-induced reduction of the shivering threshold is dose dependent. Consistent with this theory, several previous studies report that slow infusions of clonidine are minimally effective in preventing postanesthetic shivering.^{18,19} The uniform efficacy in our study probably resulted because bolus administration produced higher plasma and effect-site²⁰ drug concentrations.

The duration of clonidine's effect on shivering is unknown. No clinical studies report recurrence of shivering after intravenous bolus administration of clonidine. However some studies evaluated shivering only for short periods.^{3,4} In other cases, patients may rewarm before the effect of clonidine dissipates.¹⁸ We did not measure plasma clonidine concentrations in our volunteers, in part, because the other effects of the drug (analgesia and hypotension) are not necessarily related to plasma concentrations.²¹

Systemic oxygen consumption was lower after clonidine than placebo administration, the difference being most striking during shivering. Because the in-

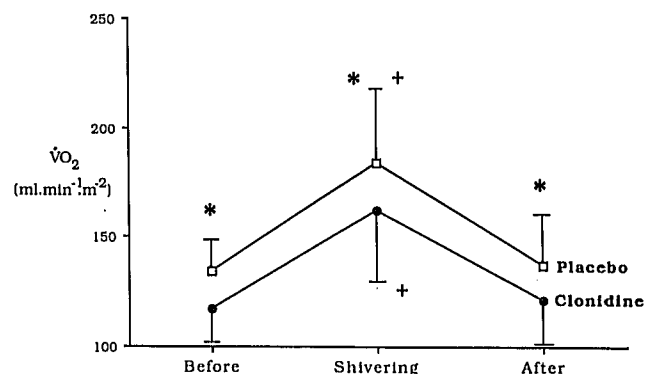


Fig. 2. Changes in values (mean \pm SD) of $\dot{V}O_2$ in the seven volunteers before, during, and after shivering. Asterisks (*) indicate significant difference in $\dot{V}O_2$ values between the placebo and clonidine trials; the crosses (+) indicate that $\dot{V}O_2$ was significantly higher during shivering than before or after shivering.

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crease in $\dot{V}O_2$ associated with shivering results from increased muscular activity,²² it appears that preventive administration of clonidine not only decreased the thermoregulatory threshold for shivering, but also decreased its magnitude, once triggered.

Other drugs have been used to treat thermoregulatory and postoperative shivering. Magnesium sulfate, methylphenydate, calcium chloride, and a placebo have been compared in a triple-blind study, but were effective only in 60, 40, 35, and 17% of postoperative patients.²³ Sarma *et al.* documented that doxapram stopped shivering in 75% of patients recovering from volatile anesthetics,²⁴ and several studies have demonstrated that intravenous meperidine is effective in 80–90% of cases.^{25,26} All these drugs, except meperidine, appear to be less effective than clonidine, but they have yet to be directly compared. Additionally, the mechanism of action remains unknown in all the cases.

Thermoregulatory vasoconstriction threshold was evaluated using forearm-fingertip, skin-temperature gradients, which correlate well with fingertip blood flow measured using laser Doppler flowmetry⁷ and plethysmography.¹⁰ The potential problem with skin-temperature gradients is that they respond relatively slowly to abrupt changes in flow ($T_{1/2} = 6.6$ min).¹⁰ Vasoconstriction must, therefore, have started before we observed a 4° C gradient. However, the delay would be comparable on both days, so the difference between the two treatment days remains valid.

We evaluated shivering with oxygen consumption, which generally is considered the most reliable indicator of shivering thermogenesis. Electromyography is essential for accurate analysis of tremor patterns,¹³ but is a less sensitive measure of shivering intensity. Cold-induced spontaneous muscular activity in the absence of anesthetic is, by definition, normal shivering; therefore, we did not record electromyography tremor patterns in our volunteers.

We conclude that a 75- μ g intravenous bolus of clonidine abolishes normal thermoregulatory shivering in mildly hypothermic volunteers. Inhibition apparently results from synchronous $\approx 0.5^\circ$ C reduction in the thermoregulatory thresholds for vasoconstriction and shivering, indicating generalized thermoregulatory impairment, rather than a specific action of clonidine on shivering.

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