Clonidine decreases vasoconstriction and shivering thresholds, without affecting the sweating threshold

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Purpose: This study was conducted to test the hypothesis that clonidine produces a dose-dependent increase in the sweating threshold and dose-dependent decreases in vasoconstriction and shivering thresholds.

Methods: Six healthy subjects (two female) were studied on four days after taking clonidine in oral doses of either 0 (control), 3, 6 or 9 $\mu g \cdot kg^{-1}$. The order followed a balanced design in a double-blind fashion. Oesophageal temperature and mean skin temperature (from 12 sites) were measured. Subjects were seated in 37°C water which was gradually warmed until sweating occurred (sweat rate increased above 50 $g \cdot m^{-2} \cdot h^{-1}$). The water was then cooled gradually until thresholds for vasoconstriction (onset of sustained decrease in fingertip blood flow) and shivering (sustained elevation in metabolism) were determined. Thresholds were then referred to as the core temperature, adjusted to a designated mean skin temperature of 33°C.

Results: High dose clonidine similarly decreased the adjusted core temperature thresholds for vasoconstriction by 1.16 ± 0.30°C and for shivering by 1.63 ± 0.23°C ($P<0.01$). The dose response effects were linear for both cold responses with vasoconstriction and shivering thresholds decreasing by 0.13 ± 0.05 and 0.19 ± 0.09°C·μg^{-1} respectively ($P<0.0001$). The sweating threshold was unaffected by clonidine, however the interthreshold range between sweating and vasoconstriction thresholds increased from control (0.19 ± 0.48°C) to high dose clonidine (1.31 ± 0.54°C).

Conclusion: The decreases in core temperature thresholds for cold responses and increased interthreshold range are consistent with the effects of several anaesthetic agents and opioids and is indicative of central thermoregulatory inhibition.

Objectif : Vérifier si la clonidine provoque une augmentation du seuil de sudation et une diminution des seuils de vasoconstriction et de frisson proportionnellement à la dose.

Méthodes : Six patients en bonne santé (dont deux femmes) qui avaient reçu des doses orales de clonidine de 0 (contrôle), 3, 6 et 9 $\mu g \cdot kg^{-1}$ ont été étudiés pendant quatre jours. L'étude suivait un plan équilibré et en double insu. Les températures moyennes oesophagiennes et cutanées (à 12 endroits) ont été mesurées. Les sujets étaient assis dans l'eau à 37°C réchauffée graduellement jusqu'à l'apparition de la sudation (un taux de sudation à 50 $g \cdot m^{-2} \cdot h^{-1}$). L'eau était par la suite refroidie progressivement jusqu'aux seuils de vasoconstriction (début de la diminution du flux sanguin à l'extrémité des doigts) et de frissonnement. Ces seuils ont été reconnus comme la température centrale ajustée à une température cutanée désignée de 33°C.

Résultats : Les hautes doses de clonodine abaissent également les seuils de vasoconstriction ajustés à la température centrale de 1,16 ± 0,30°C et du frissonnement de 1,63 ± 0,23C ($P < 0,01$). Les effets dose-réponse sont linéaires pour les deux réponses au froid avec des seuils de vasoconstriction et de frissonnement diminuant respectivement de 0,13 ± 0,05 et de 0,19 ± 0,09°C·μg^{-1} ($P < 0,0001$). Le seuil de sudation n'est pas affecté par le clonodine ; toutefois l'écart entre les seuils de sudation et de vasoconstriction s'élargit entre le contrôle (0,19 ± 0,48°C) et la clonodine à haute dose (1,31 ± 0,54°C).

Conclusion : La baisse des seuils de la température centrale pour les réponses au froid et l'augmentation de l'écart entre les seuils sont consistants avec les effets de plusieurs agents anesthésiques et morphiniques et démontrent une inhibition de la thermorégulation centrale.

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CLONIDINE is a selective, partial α_2 adrenergic receptor agonist, which has both central and peripheral effects. This drug is primarily used as an antihypertensive agent, but also has sedative and analgesic properties.[1–3] Recently, it has been shown that the intravenous administration of clonidine is effective in the treatment of postoperative shivering.[4] Although the authors suggested that the inhibition of shivering resulted from resetting of the central threshold for shivering, the possibility of other mechanisms, such as generalized muscle flaccidity, could not be ruled out. In a subsequent study, central cooling was conducted on humans with and without clonidine (75 μg *iv*) and it was concluded that core temperature (T_{co}) thresholds for vasoconstriction and shivering were decreased by 0.5 and 0.6°C respectively.[5] Further investigation of the effects of clonidine on thermoregulatory thresholds would allow comparison of its effects with those of anaesthetics and other sedatives which lower thresholds for cold responses and either raise or lower thresholds for sweating.[6–12]

We intended to extend the findings of previous work by determining the effect of clonidine on cold response thresholds in a protocol where shivering and peripheral blood flow were quantified. As well, skin temperature was initially increased until sweating was also initiated.

Accordingly, we identified the dose response effects of clonidine on both cold and warm thermoregulatory response thresholds in a protocol where all responses were quantified and skin temperature was measured and controlled. On four occasions subjects were given either oral placebo, or clonidine 3, 6 or 9 $\mu g \cdot kg^{-1}$. They were immersed in a thermoneutral water bath, which was gradually warmed until sweating was established, and then gradually cooled until vasoconstriction and shivering occurred. We hypothesized that clonidine would produce a dose-dependent increase in the core temperature threshold for sweating and dose-dependent decreases in core temperature thresholds for vasoconstriction and shivering (i.e., cooling to a lower core temperature would be required to stimulate the latter two responses).

Methods

Subjects

With approval from our Faculty Human Ethics Committee, six healthy human subjects (two female and four male) participated after giving their written, informed consent. They were 22.8 ± 5.1 (SD) yr of age, weighed 66.5 ± 12.8 kg, and were 173.1 ± 11.3 cm tall. None was obese or taking any medication. Female subjects were tested during the follicular phase (days 1–9) of their menstrual cycles.

Instrumentation

Oesophageal temperature (T_{oes}) was monitored during the experimental trials with a Mon-a-Therm oesophageal thermocouple (Mallinckrodt, St. Louis, MO) inserted through a nostril to the level of the heart[13] because this site gives the best noninvasive representation of core temperature.[14] Heart rate was monitored continuously with a DC battery-operated 43100A Defibrillator/ECG monitor (Hewlett-Packard) with leads in a modified V_5 arrangement. A Dinamap automated blood pressure cuff (Critikon, Tampa, FL) was used to take blood pressure measurements at five minute intervals.

Sweat rate was measured by using a ventilated capsule (≈5.0 × 3.5 cm) placed on the forehead. Anhydrous compressed air was passed through the capsule over the skin surface at a rate of 1 $l \cdot min^{-1}$ (Brooks 5850 mass flow controller, Emerson Electric, Hatfield, PA). Vapor density of the effluent air was determined based on the relative humidity and temperature of the air measured by an Omega HX93 humidity and temperature sensor (Omega Engineering, Stanford, CT), which was calibrated by placing it above saturated salt solutions. Sweat rate was the product of the difference in water content between effluent and influent air, and the flow rate. This value was adjusted for the skin surface area under the capsule and expressed in $g \cdot m^{-2} \cdot hr^{-1}$. Flow meters in the inlet and outlet tubing of the capsule allowed the detection and correction of any leaks in the system. Sweat rate was monitored for 15 min following the initiation of sweating.

Peripheral vessel tone, as indicated by fingertip blood flow, was assessed using a Perfusion Index (PI_{avg}) derived from an Ohmeda Biox 3700 pulse oximeter (Ohmeda, Louisville, CO) with a clamp-type oximeter probe placed on the middle digit. The oximeter was modified, and a programme was developed by Ohmeda to compute a perfusion index. This method correlates well with blood flow as measured by volume plethysmography ($r^2 = 0.88$).[15]

Oxygen consumption ($\dot{V}O_2$) was determined by an open-circuit method from measurements of expired minute volume and mixed expired O_2 concentrations sampled from a 10-litre fluted mixing box. Subjects wore a snugly fitting facemask with a one-way valve that was connected to the appropriate instrumentation by corrugated plastic tubing. Minute ventilation was monitored by a pneumotachometer (Hewlett Packard 47304A Flow Transducer) in the expiratory circuit proximal to the mixing box. Mixed expired air was

continuously sampled from the mixing box at the rate of 500 ml·min^{-1} and analyzed by a Beckman OM-11 O_2 sensor (Beckman, Anaheim, CA).

Mean skin temperature (T_{skavg}) was determined by an area weighted average from 12 sites with regional percentages based on those of Layton *et al.*[16] Analog data from the thermocouples and gas analyzers were acquired using an electrically isolated Macintosh IIci computer equipped with a NB-MIO-16L 16-channel analog-digital converter (National Instruments, Austin, TX). Data were digitized asynchronously at 2 Hz, averaged over five seconds, and scaled using appropriate corrections. At 30 sec intervals, the results for the previous 30 sec were averaged, displayed graphically on the computer screen, and recorded in spreadsheet format on a hard disk. The process was controlled by a "virtual instrument" written using LabVIEW 2 graphical signal processing software (National Instruments, Austin, TX).

Protocol

Each subject participated in four trials, each on separate days at least 72 hr apart. Subjects reported to the laboratory after a minimum eight hour fast with the time of day standardized for each subject. They were instructed to abstain from alcohol, caffeine, and heavy exercise before the test session. Ninety minutes before each trial began (i.e., water immersion) subjects ingested a gelatin capsule containing either no drug (control), or clonidine in doses of 3, 6 or 9 μg·kg^{-1}; peak plasma levels are reached within 60 to 90 min of oral ingestion.[1] The order of treatments followed a balanced design in a double-blind fashion. During the instrumentation period (≈30 min), subjects were dressed in a swimming suit and rested on a chair. Following instrumentation, subjects were covered by a cotton blanket. Baseline values were then determined over 30 min at an ambient temperature of ≈22°C.

The subjects then sat immersed to the level of the sternal notch in stirred water. The initial water temperature (T_w) upon entry was approximately 37°C. After an immersion baseline period of 15 min, T_w was then increased by 4°C·hr^{-1} until 15 min after the initiation of sweating. The water temperature was then decreased at a rate of 4°C·hr^{-1} until fingertip vasoconstriction occurred and the subject shivered vigorously for 30 min. The experiment was then terminated and the subject was rewarmed by immersion in warm water.

Data analysis

The sweating threshold was defined as the onset of a sustained and continuous increase in sweat rate above 50 g·m^{-2}·hr^{-1}.[17] The threshold for vasoconstriction was defined as the onset of a sustained decrease in fingertip blood flow below maximal vasodilation values. The shivering threshold was indicated by a sustained elevation in $\dot{V}O_2$ above the baseline level.[18] This method for determination of the shivering threshold has been validated in our laboratory against subjects' self-report of shivering onset and an increase in EMG activity (unpublished data). The difference between sweating and vasoconstriction thresholds was defined as the interthreshold range.[17]

In order to compare thresholds between conditions in which both oesophageal and skin temperatures were changing, the following equation[10] was used to correct the T_{oes} ($T_{oes(calculated)}$) for a designated skin temperature ($T_{sk(designated)}$):

$$T_{oes(calculated)} = T_{oes} + (ß/1–ß)\,[T_{skavg} - T_{sk(designated)}],$$

where T_{oes} is the actual T_{oes}, T_{skavg} is the actual average T_{sk}, $T_{sk(designated)}$ was set at 33°C, and $T_{oes(calculated)}$ was the T_{oes} equivalent at a T_{skavg} of 33°C. ß is the proportional contribution of the skin to a thermoregulatory response and was set at 0.1 for sweating[19] and 0.2 for vasoconstriction and shivering.[20] $T_{sk(designated)}$ was set at 33°C because this was the midrange of skin temperatures observed throughout the experiments (i.e., 25–41°C).

Mean (±SD) data for $T_{oes(calculated)}$, T_{skavg}, heart rate and blood pressure were plotted for the in-water baseline period, and at each thermoregulatory response threshold, for each of the four conditions. Each of these variables was analyzed by two way ANOVA (SuperANOVA, Abacus, Berkely, CA) for repeated measures with a blocked repeated measures design to determine differences between or within conditions (α=0.05). Linear contrasts were used for post-hoc analysis of significant differences.

Regression analysis was used to determine the relationship between oral clonidine dose and corrected core temperature threshold for each of the three thermoregulatory responses.

Results

The time from immersion until sweating onset (31–39 min) was similar for the four conditions. The immersion time at which shivering occurred was dose-dependant, increasing from ≈160 min for control trials to ≈226 min for high dose clonidine trials. Cardiovascular and temperature data for the three response thresholds in each of the clonidine conditions are presented in Table I. Core temperature thresholds for both vasoconstriction and shivering were decreased as clonidine dose increased. For example, at the highest dose of clonidine (9 μg·kg^{-1}) the calculated core temperature thresholds for vasoconstrici-

TABLE I Cardiovascular and temperature responses at the sweating (SW), vasoconstriction (VC) and shivering (SH) thresholds for placebo (control) and three oral doses of clonidine [3, 6 and 9 $\mu g \cdot kg^{-1}$]. Mean (SD), *less than control; †less than low dose; ‡less than moderate dose ($P<0.05$). Note, n=5 for SW because the sweat rate monitor failed in one trial.

		Control	*3 $\mu g \cdot kg^{-1}$*	*6 $\mu g \cdot kg^{-1}$*	*9 $\mu g \cdot kg^{-1}$*
SW	MBP (mmHg)	84.4 (12.0)	79.0 (7.9)	67.2 *† (4 5)	79.8‡ (7.5)
	HR ($b \cdot min^{-1}$)	88.3 (14.3)	78.7* (15.6)	65.2*† (11.7)	63.7*† (8.2)
	Tskavg (°C)	37.01 (0.83)	36.89 (0.41)	37.2 (0.27)	37.19 (0.38)
	Toes (°C)	37.39 (0.62)	37.30 (0.53)	37.29 (0.57)	37.24 (0.53)
	Toes (calculated)(°C)	37.83 (0.70)	37.74 (0.56)	37.75 (0.60)	37.70 (0.57)
VC	MBP (mmHg)	80.6 (7.3)	74.8 (6.7)	71.2* (4.8)	73.2* (7.0)
	HR ($b \cdot min^{-1}$)	76.0 (12.9)	63.2* (15.8)	61.8* (11.1)	55.7* (11.4)
	Tskavg (°C)	34.54 (0.52)	33.75* (0.96)	33.01*† (0.97)	32.46*† (0.86)
	Toes (°C)	37.23 (0.28)	37.05* (0.22)	36.8*† (0.19)	36.6*†‡ (0.18)
	Toes (calculated)(°C)	37.62 (0.23)	37.24* (0.39)	36.8*† (0.36)	36.46*†‡ (0.38)
SH	MBP (mmHg)	91.2 (7.3)	78.2* (12.2)	77.2* (12.8)	84.2 (9.0)
	HR ($b \cdot min^{-1}$)	74.9 (13.7)	66.9* (12.5)	62.4* (13.3)	61.5* (8.7)
	Tskavg (°C)	31.52 (1.13)	30.35* (1.27)	29.48*† (1.14)	29.32*† (1.33)
	Toes (°C)	36.95 (0.32)	36.48* (0.34)	36.06*† (0.39)	35.87*†‡ (0.31)
	Toes (calculated)(°C)	36.58 (0.55)	35.73* (0.8)	35.18*† (0.61)	34.95*† (0.61)

ton and shivering were decreased ($P< 0.01$) from 37.6 ± 0.2 to 36.46 ± 0.4°C and from 36.6 ± 0.6 to 35.0 ± 0.6°C respectively. The relationships between clonidine dose and cold response thresholds were significant with vasoconstriction and shivering thresholds decreasing by $0.13 \pm 0.01°C \cdot \mu g^{-1}$ and $0.19 \pm 0.01°C \cdot \mu g^{-1}$ ($P < 0.0001$) (Figure 1). There were no differences between responses for vasoconstriction and shivering conditions. The sweating threshold was unaffected by clonidine (Table I, Figure 1) however, the interthreshold range increased from control (0.19 ± 0.48°C) to high dose clonidine (1.31 ± 0.54°C).

Subjects were noticeably sedated during trials with the two higher doses of clonidine. In general, mean blood pressure and heart rate decreased as clonidine dose increased (Table I). Compared with control conditions, heart rate was decreased with all three doses of clonidine at each response threshold ($P < 0.05$). Mean blood pressure was decreased with moderate and high doses at the sweating and vasoconstriction thresholds, and with all doses at the shivering threshold ($P < 0.05$), with the exception of the high dose at the sweating and vasoconstriction thresholds. None of the subjects required treatment for hypotension or bradycardia.

Discussion

This study established the dose dependent effects of clonidine on both warm and cold thermoregulatory thresholds. While clonidine produced dose dependent decreases in both vasoconstriction and shivering thresholds, no effect was seen on sweating thresholds. Our data confirm the inhibitory effect of clonidine on cold responses, as indicated by parallel decreases in vasoconstriction and shivering thresholds. Although no effect was seen on sweating thresholds, the increased interthreshold range with clonidine is consistent with that seen with volatile anaesthetics,[6–9] propofol[10] and opioids.[11,12]

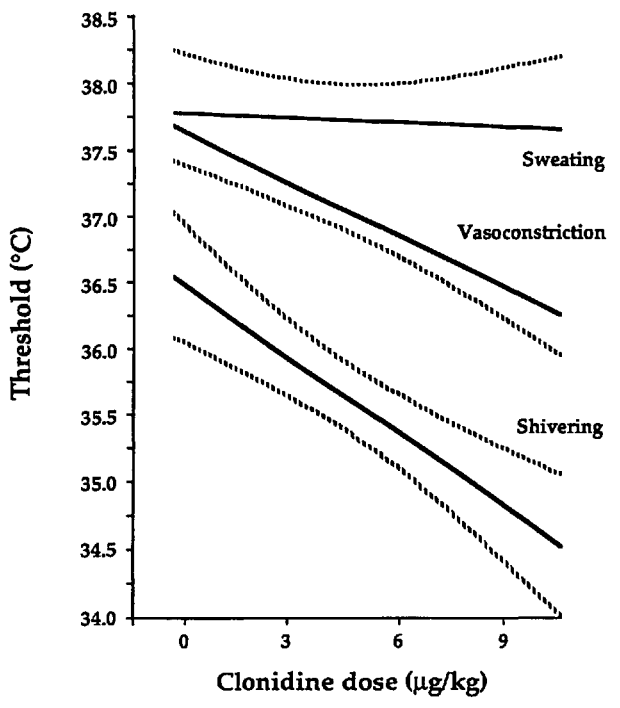

FIGURE 1 Relationships (and 95% confidence intervals) between oral clonidine dose and thresholds for sweating, vasoconstriction and shivering. For clarity, only one confidence interval is shown for sweating and vasoconstriction. Vasoconstriction and shivering thresholds decrease by 0.13 ± 0.01 (SE) C·μg^{-1} (y intercept 37.6 ± 0.1°C) and 0.19 ± 0.01°C·μg^{-1} (y intercept, 36.5 ± 0.2°C) respectively (P<0.0001). There was no difference between the slopes for these two conditions. The sweating threshold was unaffected by clonidine.

In the present study the 0.38 and 0.85°C decreases in vasoconstriction and shivering thresholds, at the lowest oral doses (about 200 μg) were comparable with respective decreases of 0.5 and 0.6°C (following doses of 75 and 150 μg) demonstrated previously.[5] Our dose response data also confirm the relationship inferred by these authors. They also reported no effect of clonidine on blood pressure and heart rate. In the present study, moderate dose clonidine (6 μg·kg^{-1}) decreased mean blood pressure at the sweating and vasoconstriction thresholds, while MBP was decreased at the shivering threshold by as little as 3 μg·kg^{-1} clonidine.

There are several possible mechanisms to explain the clonidine-induced decrease in cold response thresholds such as peripheral effects on α_1 and α_2 adrenergic receptors, inhibition of afferent information, disruption of central integration, or decreased output to effector organs.

First, direct stimulation of peripheral α_2 adrenergic receptors mediates peripheral vasoconstriction.[21] If this action predominated, earlier vasoconstriction would be interpreted as an actual *increased* vasoconstriction threshold. The consequent effect of peripheral vasoconstriction would be skin cooling, cold thermoreceptor stimulation and earlier shivering which would be interpreted as an increased shivering threshold. The fact that both cold response thresholds decrease with clonidine indicates that these peripheral mechanisms are not likely involved. Second, it is unlikely that clonidine inhibits afferent thermal transmission in either A-δ fibres or at the level of the spinal cord. Although the effects of clonidine have not been tested on thermal pathways, it is known that this drug does not block peripheral ganglia, neurons or receptors that are active in haemodymanic control.[22] Third, clonidine causes flaccidity by decreasing skeletal muscle tone,[23] an effect which could partly explain the delay in shivering onset. However, the parallel decrease in the vasoconstriction threshold indicates that the effect of clonidine is not simply due to inhibition of voluntary skeletal muscle and shivering.

Finally, clonidine likely affects central processing and resultant efferent output. Impairment of central thermoregulation is usually manifest by decreasing cold response thresholds and increasing warm response thresholds. Although there was no effect of clonidine on the sweating threshold (which is different from the increase seen with anaesthetics and opioids[6–12] and the decrease seen with midazolam[11]), the interthreshold range was increased in a dose dependent fashion and this is consistent with central thermoregulatory inhibition. The density of α_2 adrenergic receptors is high in the hypothalamus[24] and these receptors may be involved in the observed thermoregulatory inhibition. This conclusion is consistent with the mechanisms for the haemodynamic depressant effects of clonidine which result from activation of a_2 adrenergic receptors in the lower brainstem region.[25]

Thermoregulatory responses are modulated by both central and peripheral (skin) temperatures. Several methods induce core temperature changes with constant sentient skin temperature in order to identify thermoregulatory effects in terms of changes in core temperature. Unfortunately these methods all have limitations including vigorous exercise,[18] epidural anaesthesia[26] or central venous infusion of large fluid volumes.[27] Recently, a minimally invasive method was developed in which both core and skin temperatures fluctuate during thermal stress. Core temperature was then corrected for the changes in skin temperature.[20] This method has been validated using propofol[10] and is now in common use as a safe protocol for drug testing.

Although blood concentrations of clonidine were not measured, it is known that clonidine is rapidly and almost completely absorbed after oral administration and reaches a peak plasma concentration within 60–90 min.[1] In humans a single dose of 390 μg (approximating the moderate dose of the present study) results in a clinically significant plasma concentration of 2 $ng \cdot ml^{-1}$.[22] As the half-life of this drug is 9–12 hr,[1] it can be assumed that plasma concentrations varied little over the ≈3–5 hour duration of this study.

In summary, clonidine inhibits cold thermoregulatory responses, likely due to an effect on central integration, control and output from the thermoregulatory centers. These data confirm that clonidine can be used as an effective agent for inhibition of perioperative shivering (which adversely increases metabolic rate and cardiac work and may also disrupt surgical repair or result in wound dehiscence[28]). It is important to note that any inhibition of shivering thermogenesis will delay rewarming, thus active warming measures should be taken to avoid cold-related complications such as impaired coagulation,[29] slowed drug metabolism,[30] and decreased resistance to surgical wound infection.[31] In some conditions clonidine may be advantageous because of its relatively long half life and avoidance of the opioid-induced respiratory depression of other shivering inhibitors such as meperidine. Further study on the effectiveness of combinations of these two agents for shivering suppression and analgesia may be of interest.

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