Oral clonidine premedication decreases energy expenditure in human volunteers

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Purpose: Clonidine not only stops postoperative shivering and decreases oxygen consumption, but also decreases energy expenditure with or without a reduction in shivering during recovery from anaesthesia. It is important to see if clonidine decreases energy expenditure at rest since this may contribute to a postoperative decrease in energy expenditure. The authors tested the hypothesis that oral clonidine decreases energy expenditure at rest.

Methods: Twenty healthy male volunteers were randomly assigned to one of two groups. Ten volunteers received oral clonidine approximately $5 \mu\text{g}\cdot\text{kg}^{-1}$ (clonidine group), while the remaining 10 volunteers received placebo (control group). Blood pressure, heart rate, body temperature at the tympanic membrane, sedation score graded from 1 (alert) to 5 (sleeping and difficult to be aroused by tactile stimulation) were measured before and at 30-min intervals for three hours after administration of clonidine or placebo. Measurements of energy expenditure and respiratory quotient were made with a head canopy system at one-minute intervals and averaged over 15 min before, and at 30, 60, 90, 120, and 180 min after administration of clonidine or placebo.

Results: Sedation score increased from 1 to 3 (median) after clonidine administration. Energy expenditure decreased from $1452 \pm 225 \text{ kcal}\cdot 24\text{hr}^{-1}$ (mean $\pm$ SD) at baseline to $1258 \pm 175 \text{ kcal}\cdot 24\text{hr}^{-1}$ at 180 min after clonidine administration ($P < 0.05$).

Conclusion: This study suggests that oral clonidine at a dose of $5 \mu\text{g}\cdot\text{kg}^{-1}$ decreases energy expenditure at rest.

Objectif : En plus de prévenir le frisson postopératoire et de diminuer la consommation en oxygène, la clonidine diminue la dépense énergétique au moment du réveil avec ou sans atténuation du frisson. Il est important de savoir si la clonidine diminue la dépense énergétique au repos étant donné que cet effet contribue à une baisse postopératoire de l'énergie dépensée.

Méthodes : Vingt volontaires en bonne santé de sexe masculin étaient assignés aléatoirement à deux groupes. Dix de ces volontaires recevaient environ $5 \mu\text{g}\cdot\text{kg}^{-1}$ de clonidine (groupe clonidine) alors que les autres recevaient un placebo (groupe contrôle). La pression artérielle, la fréquence cardiaque, la température corporelle et tympanique, le score de sédation coté sur une échelle de 1 (alerte) à 5 (endormi et difficile à réveiller par stimulation tactile) étaient notés avant et à 30 min d'intervalles pendant trois heures suivant l'administration de la clonidine ou du placebo. Les mesures de la dépense énergétique et du quotient respiratoire étaient réalisées à l'aide d'un casque et leurs moyennes calculées sur une période de 15 min avant et 30, 60, 90, 120 et 180 min après l'administration de la clonidine ou du placebo.

Résultats : Le score de sédation a augmenté de 1 à 3 (médiane) après l'administration de la clonidine. La dépense énergétique a diminué de $1452 \pm 225 \text{ kcal}\cdot 24\text{h}^{-1}$ (moyenne $\pm$ ET) initialement, à $1285 \pm 175 \text{ kcal}\cdot 24\text{h}^{-1}$ 180 min après l'administration de la clonidine ($P < 0,05$).

Conclusion : Cette étude suggère qu'au repos, la clonidine orale $5 \mu\text{g}\cdot\text{kg}^{-1}$ diminue la dépense énergétique.

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EXPERIMENTALLY, clonidine reduces shivering¹ and oxygen consumption ($\dot{V}O_2$).² There is still controversy concerning this issue in clinical practice. Clonidine in a small dose of 30 μg *iv* may be useful in suppressing shivering after epidural anaesthesia in parturients.³ Similarly, 200 or 300 μg oral clonidine given prior to and during coronary artery surgery reduced the incidence of postanaesthetic shivering,⁴ and an *iv* infusion of clonidine, 7 $\mu\text{g}\cdot\text{kg}^{-1}$ over two hours, reduced the number of episodes of shivering after aortic surgery.⁵ In contrast, the infusion of 5 $\mu\text{g}\cdot\text{kg}^{-1}$ clonidine did not reduce the incidence of shivering after abdominal surgery.⁶ Although the underlying mechanism for suppression of postoperative $\dot{V}O_2$ by clonidine remains unknown, clonidine may decrease $\dot{V}O_2$ as a result of decreases in shivering and in circulating stress hormones during recovery from anaesthesia, or from reduction in subclinical shivering and basal metabolism under resting conditions.

Stimulation of the sympathetic nervous system associated with the liberation of norepinephrine and epinephrine increases the metabolic rate of various tissues of the body.⁷ The catecholamines exert a direct effect on muscle and liver cells, causing glycogenolysis.⁷ This metabolic alteration, together with other intracellular effects, increases cellular activity. Furthermore, sympathetic stimulation also has some influence on brown fat that produces nonshivering thermogenesis.⁷

Because clonidine inhibits norepinephrine release from sympathetic nerve terminals and thus lowers the plasma norepinephrine concentration,⁸⁻¹⁰ clonidine may decrease energy production not only during postoperative periods, but also at rest. However, there is no information regarding the effect of clonidine on resting metabolism in humans. The aim of this study is to determine whether oral clonidine medication affects metabolic rate in human volunteers.

Methods

After obtaining institutional approval and informed consent, 20 healthy men, aged from 22 to 29 yr were selected for the study. No volunteers had any cardiopulmonary disorders, renal or hepatic dysfunction, past history of thyroid disease, dysautonomia, obesity exceeding standard body weight by 20%, or were taking any medications affecting metabolic function.

Each volunteer was randomly assigned to one of two groups. Ten volunteers received approximately 5 $\mu\text{g}\cdot\text{kg}^{-1}$ clonidine *po* (clonidine group), while the remaining 10 volunteers received placebo (control group). Because clonidine (Catapres,[®] Boehringer Ingelheim & Tanabe, Kawanishi City, Hyogo, Japan) is available only in 75 or 150 μg tablets in Japan,

administered doses of clonidine were determined by choosing the closest doses calculated by multiplying 37.5 μg (one half of a tablet) as a unit. The volunteers were minimally clothed, covered with a single unwarmed cotton blanket,¹¹ and positioned supine with a pillow on a bed in a quiet room. The room temperature was controlled at 25°C.

After overnight fasting, the study protocol started between 9 and 10 am. A 22 G intravenous cannula was placed into the forearm cutaneous vein after local anaesthetic infiltration. Crystalloid solution (Soldem 3A,[®] Na 35 mEq·l⁻¹, K 20 mEq·l⁻¹, Cl 35 mEq·l⁻¹, lactate 20 mEq·l⁻¹, glucose 4.3%; Terumo, Tokyo, Japan) was thereafter infused at a rate of 0.7 ml·kg⁻¹·hr⁻¹ during the study. Arterial blood pressure and heart rate were measured at 30 min intervals using an automatic blood pressure monitoring system (Listmini,TM Nippon Colin Co., Ltd., Tokyo). Core temperature was measured at the tympanic membrane with a thermocouple probe (Mona-Therm,TM St Louis, MO) connected to a thermometer (Model 8700, Mallinckrodt, St. Louis, MO). Sedation was evaluated by a blinded investigator and was graded by a scale of 1 to 5 (1 – alert; 2 – drowsy but easily aroused by verbal command to an alert state; 3 – sleeping and arousal by verbal command; 4 – sleeping not arousal by verbal stimuli, but arousal to a drowsy state by light tactile stimulation; and 5 – sleeping and difficult to be aroused by tactile stimulation).¹²

Energy expenditure and respiratory quotient were measured with a head canopy system (Deltatrac Metabolic Monitor,TM Datex, Helsinki, Finland) which was calibrated before the beginning of the study in each subject. The accuracy of this method is $4 \pm 2\%$.¹³ Measurements of energy expenditure and respiratory quotient were performed automatically at one-minute intervals and averaged over 15 min periods before, and 30 (30–45 min), 60 (60–75 min), 90 (90–105 min), 120 (120–135 min), and 180 (180–195 min) min after ingestion of clonidine or placebo. Basal metabolic rate (BMR) was calculated using the estimation of Harris and Benedict as follows:¹⁴

$\text{BMR (kcal}\cdot 24\text{hr}^{-1}) = 66 + 13.8W + 5H - 6.8A$, where W is body weight (kg), H body height (cm), and A age (yr). Percent difference from BMR (% Difference) was calculated as $(\text{EE}_{30, 60, 90, 120, \text{ or } 180\text{-min}} - \text{BMR}) \times 100/\text{BMR}$. Percent changes in energy expenditure (%EE) was calculated as $(\text{EE}_{30, 60, 90, 120, \text{ or } 180\text{-min}} - \text{EE}_{\text{before}}) \times 100/\text{EE}_{\text{before}}$.

All data except sedation score between groups were analyzed by two-way analysis of variance (ANOVA) followed by unpaired Student's *t*-test. Analyses of consecutive haemodynamic and metabolic data in each group were made with analysis of variance for repeat-

ed measures, and post hoc analysis was performed with Bonferroni/Dunn test. Mann-Whitney U test and the Kruskal-Wallis test were used to compare sedation scores between groups and in each group, respectively. Values were expressed as means $\pm$ SD. $P < 0.05$ was considered to be statistically significant.

Results

There were no differences between groups with respect to age, body weight, height, body surface area, or BMR (Table I). The clonidine dose administered was $5.09 \pm 0.19 \mu\text{g}\cdot\text{kg}^{-1}$.

Baseline haemodynamic variables, body temperature, energy expenditure, and respiratory quotient were similar between groups (Table II). There were no differences between groups in mean arterial blood pressure, heart rate, and body temperature at any

observation period, except in mean arterial blood pressure at 90 and 180 min and heart rate at 180 min after administration of clonidine or placebo (Table II). Respiratory quotient was lower in the clonidine group than in the control group at 30 min after clonidine administration ($P < 0.05$), but was within normal limits. Energy expenditure decreased from $1452 \pm 225 \text{ kcal}\cdot 24 \text{ hr}^{-1}$ at baseline to $1258 \pm 175 \text{ kcal}\cdot 24 \text{ hr}^{-1}$ at 180 min after clonidine administration, whereas it remained unchanged in the control group; values at 90–180 min in the clonidine group were lower than in the control group ($P < 0.05$). The reductions in %EE attained a plateau at 120 min after clonidine administration. The %EE values at 60–180 min in the clonidine group were lower than in the control group ($P < 0.05$). The % difference values were also greater from 90 to 180 min in the clonidine group than in the

TABLE I Demographic data

Group	Clonidine (n = 10)	Control (n = 10)
Age (yr)	26 $\pm$ 2 (22–29)	26 $\pm$ 2 (22–29)
Weight (kg)	65 $\pm$ 8 (53–78)	64 $\pm$ 8 (53–80)
Height (cm)	171 $\pm$ 4 (165–177)	172 $\pm$ 5 (165–179)
Body Surface Area (m ²)	1.76 $\pm$ 0.12 (1.58–1.95)	1.75 $\pm$ 0.13 (1.58–1.98)
BMR (kcal·24hr ⁻¹)	1650 $\pm$ 127 (1430–1850)	1633 $\pm$ 133 (1430–1890)
Clonidine ($\mu\text{g}\cdot\text{kg}^{-1}$)	5.09 $\pm$ 0.19 (4.80–5.36)	

Mean $\pm$ SD (range)

Basal metabolic rate (BMR)

TABLE II Haemodynamic and metabolic variables and sedation score before and after clonidine $5 \mu\text{g}\cdot\text{kg}^{-1} \text{ po}$.

	Group	Before	30 min	60 min	90 min	120 min	180 min
MABP (mmHg)	Clonidine	85 $\pm$ 10	80 $\pm$ 11	77 $\pm$ 13	74 $\pm$ 13 [†]	75 $\pm$ 11	74 $\pm$ 11 ^{††}
	Control	84 $\pm$ 6	83 $\pm$ 6	83 $\pm$ 9	85 $\pm$ 9	83 $\pm$ 9	88 $\pm$ 9
HR (bpm)	Clonidine	58 $\pm$ 7	51 $\pm$ 6	49 $\pm$ 7	49 $\pm$ 6	50 $\pm$ 8	51 $\pm$ 7 [†]
	Control	58 $\pm$ 5	56 $\pm$ 8	55 $\pm$ 9	53 $\pm$ 6	54 $\pm$ 6	59 $\pm$ 8
Temp (°C)	Clonidine	36.5 $\pm$ 0.3	36.4 $\pm$ 0.3	36.3 $\pm$ 0.3	36.3 $\pm$ 0.3	36.4 $\pm$ 0.3	36.4 $\pm$ 0.3
	Control	36.6 $\pm$ 0.2	36.5 $\pm$ 0.3	36.4 $\pm$ 0.3	36.5 $\pm$ 0.2	36.4 $\pm$ 0.3	36.5 $\pm$ 0.3
EE (kcal·24hr ⁻¹)	Clonidine	1452 $\pm$ 225	1327 $\pm$ 186	1279 $\pm$ 174	1281 $\pm$ 172 [†]	1258 $\pm$ 202 [†]	1258 $\pm$ 175 [†]
	Control	1453 $\pm$ 228	1413 $\pm$ 186	1431 $\pm$ 174	1447 $\pm$ 173	1469 $\pm$ 212	1479 $\pm$ 211
RQ	Clonidine	0.83 $\pm$ 0.05	0.83 $\pm$ 0.03 ^{††}	0.89 $\pm$ 0.05	0.88 $\pm$ 0.04	0.87 $\pm$ 0.03	0.88 $\pm$ 0.04
	Control	0.86 $\pm$ 0.03	0.88 $\pm$ 0.03	0.90 $\pm$ 0.05	0.88 $\pm$ 0.06	0.91 $\pm$ 0.06	0.88 $\pm$ 0.06
Sedation score	Clonidine	1.0	2.0*	2.5*	3.0* [†]	3.0* ^{††}	2.5* ^{††}
	Control	1.0	2.0*	2.0*	2.0*	1.5*	1.0*
% EE ^a	Clonidine		-7.6 $\pm$ 5.1	-10.7 $\pm$ 7.0 ^{††}	-10.8 $\pm$ 9.4 ^{††}	-12.4 $\pm$ 12.0 [†]	-12.3 $\pm$ 11.0 ^{††}
	Control		-2.7 $\pm$ 5.6	0.4 $\pm$ 6.2	0.72 $\pm$ 5.8	0.77 $\pm$ 8.4	1.4 $\pm$ 5.6
% Difference EE ^b	Clonidine	-10 $\pm$ 12	-17 $\pm$ 11	-20 $\pm$ 10	-21 $\pm$ 9 [†]	-22 $\pm$ 11 [†]	-22 $\pm$ 8 [†]
	Control	-12 $\pm$ 11	-14 $\pm$ 9	-12 $\pm$ 8	-11 $\pm$ 9	-11 $\pm$ 9	-11 $\pm$ 11

Mean $\pm$ SD or median. MABP - mean arterial blood pressure; HR - heart rate; EE - energy expenditure; RQ - respiratory quotient.

% EE^a = $(\text{EE}_x - \text{EE}_{\text{before}}) \times 100 / \text{EE}_{\text{before}}$. % difference EE^b = $(\text{EE}_x - \text{BMR}) \times 100 / \text{BMR}$

EE_x is energy expenditure at 30, 60, 90, 120, or 180 min after treatment.

* $P < 0.05$ vs before treatment. [†] $P < 0.05$ vs control. ^{††} $P < 0.01$ vs control.

control group ($P < 0.05$, Table II). Although increases in sedation scores were noted from 30 to 180 min after clonidine or placebo ($P < 0.05$), sedation scores were higher from 90 to 180 min in the clonidine group than in the control group ($P < 0.05$).

Discussion

The present results show that the energy expenditure decreased 90 to 180 min after oral clonidine in a dose of $5.09 \pm 0.19 \mu\text{g}\cdot\text{kg}^{-1}$ in healthy volunteers and this was associated with increases in sedation scores.

Energy expenditure is affected by food, age, sex, circulating concentrations of thyroid hormones, epinephrine and norepinephrine, environmental temperature, emotional state, and muscular exertion before and during measurement.¹⁵ The present study was performed in fasting healthy, young men under resting conditions. The maximum sedative effect of clonidine appeared 90 to 120 min after clonidine administration as reported previously.^{16,17} We had speculated that the sedative effect of clonidine would decrease energy expenditure at rest, because metabolic rate decreases by 10 to 15 % during sleep due to decreased skeletal musculature tone and decreased sympathetic nervous system activity.⁷ This assumption appears to have been reasonable, since the maximum decrease in energy expenditure after clonidine administration was 12% in the present study.

Our results show that clonidine decreased energy expenditure in subjects without shivering. In previous studies, energy expenditure decreased regardless of the presence of shivering during recovery from anaesthesia.^{5,6} Similarly, clonidine attenuated the increase in VO_2 and VCO_2 associated with recovery from anaesthesia,^{6,18} which was associated with¹⁸ and without⁶ a reduction in shivering. According to a recent study, clonidine may impair central control of thermoregulation, thus reducing the thresholds for vasoconstriction and shivering.¹⁹ Interestingly, even a small bolus dose of clonidine $75 \mu\text{g}$ *iv* decreased VO_2 before and after the occurrence of shivering.¹⁹ This finding shows that clonidine can decrease VO_2 even if it does not stop shivering.

Clonidine inhibits thyroid function *via* an α_2 -adrenoceptor²⁰ directly or indirectly, because clonidine decreases plasma norepinephrine concentration,⁸⁻¹⁰ which stimulates thyroid hormone secretion by activating the adrenoceptor.²¹ In addition, clonidine suppresses sympathoadrenal outflow,^{8,22} and stress-induced adrenocorticotrophic hormone and cortisol release.²³ It is likely that clonidine decreases energy expenditure through suppressing stress hormone release, although clonidine stimulates growth hormone secretion,²⁴ and increases serum glucose due to inhibition of insulin release.^{25,26}

Although we did not measure hormone concentrations during the experiment, a future study involving such measurements would be worthwhile considering the diffuse action of clonidine on the hormonal milieu as noted above.

In summary, oral clonidine in a dose of $5 \mu\text{g}\cdot\text{kg}^{-1}$ decreases energy expenditure at rest in healthy volunteers.

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