

## Oral Clonidine Blunts the Heart Rate Response to Intravenous Atropine in Humans

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Clonidine, recently introduced into anesthesia practice, may cause bradycardia. Whether this bradycardia is reversible with atropine is not known. Accordingly, we studied heart rate (HR) responses to intravenous atropine in 80 patients assigned randomly to either a control group, who received no medication ( $n = 20$ ), or a clonidine group, who received oral clonidine of approximately  $1.2 \mu\text{g} \cdot \text{kg}^{-1}$  ( $n = 20$ ),  $2.5 \mu\text{g} \cdot \text{kg}^{-1}$  ( $n = 20$ ), or  $5 \mu\text{g} \cdot \text{kg}^{-1}$  ( $n = 20$ ). All patients received incremental doses of atropine, 2.5, 2.5, and  $5 \mu\text{g} \cdot \text{kg}^{-1}$ , at 2-min intervals (total dose  $10 \mu\text{g} \cdot \text{kg}^{-1}$ ). Positive chronotropic response to the cumulative atropine dose of  $10 \mu\text{g} \cdot \text{kg}^{-1}$  was attenuated significantly only in patients given clonidine  $5 \mu\text{g} \cdot \text{kg}^{-1}$  ( $7 \pm 1$  beats per min, mean  $\pm$  standard error) when compared with those given smaller doses of clonidine ( $15 \pm 2$ ,  $16 \pm 2$  beats per min) or no clonidine ( $19 \pm 2$  beats per min) ( $P < 0.05$ ). To determine whether HR hyporesponsiveness to atropine induced by clonidine can be overcome by a larger dose of atropine, the authors studied 30 additional patients given clonidine  $5 \mu\text{g} \cdot \text{kg}^{-1}$  or no medication. In all patients not receiving clonidine ( $n = 15$ ), HR increased by more than 20 beats per min when atropine of  $15 \mu\text{g} \cdot \text{kg}^{-1}$  was administered, whereas in only 5 patients (33%) receiving clonidine did the HR increase by 20 beats per min after atropine  $15 \mu\text{g} \cdot \text{kg}^{-1}$  ( $P < 0.001$ ). Furthermore, only slight increases in HR were noted in 4 of 15 patients given clonidine medication (26%) even after the administration of atropine  $40 \mu\text{g} \cdot \text{kg}^{-1}$ . It is concluded that the HR response to intravenous atropine is attenuated in awake humans receiving oral clonidine of  $5 \mu\text{g} \cdot \text{kg}^{-1}$ . The decreased responsiveness to atropine in patients receiving clonidine  $5 \mu\text{g} \cdot \text{kg}^{-1}$  cannot be effectively overcome in all patients by a larger dose of atropine. (Key words: Circulation: blood pressure; heart rate. Complications: sinus bradycardia. Parasympathetic nervous system: atropine. Sympathetic nervous system:  $\alpha$ -2 adrenergic agonists; clonidine.)

SEVERE BRADYCARDIA or an atrioventricular conduction disturbance<sup>1-9</sup> has been known to follow oral administration of clonidine, a partial  $\alpha_2$ -adrenergic agonist recently introduced as preanesthetic medication to reduce opioid or volatile anesthetic requirements,<sup>10-12</sup> maintain hemodynamic stability,<sup>10-13</sup> or provide perioperative sedation<sup>12,13</sup> and postoperative analgesia.<sup>13</sup> There are conflicting reports as to the heart rate (HR) response to atro-

pine in patients with bradycardia after clonidine administration.<sup>1,5,6</sup> To our knowledge, however, no clinical investigation has systematically studied the dose-related hemodynamic interaction between clonidine and atropine in humans. The current clinical study was undertaken to examine these issues.

In the first part of the current study we evaluated the interaction between orally administered clonidine and intravenous atropine, according to dose, in surgical patients. After the demonstration that clonidine  $5 \mu\text{g} \cdot \text{kg}^{-1}$  blunted the HR response to atropine, the second part of the current study was designed to test whether a larger dose of atropine is able to overcome the suppression of HR response induced by clonidine.

### Materials and Methods

One hundred ten surgical patients, ASA physical status I, ranging in age from 16 to 73 yr, were selected for the study. The study protocol was approved by our local Human Investigational Committee, and informed consent was obtained from each patient. All patients had normal sinus rhythms. No patient had any cardiopulmonary and autonomic disorders. In addition, no patient was taking any medication affecting cardiovascular function.

#### PART I: INTERACTION OF CLONIDINE AND ATROPINE

Eighty patients were randomly assigned to one of the following four groups according to the dosage of clonidine. Patients of the control group ( $n = 20$ ) received no preanesthetic medication, whereas patients of the three clonidine groups received oral clonidine (Boehringer Ingelheim Co., Ltd.) in a dose of approximately  $1.2 \mu\text{g} \cdot \text{kg}^{-1}$  ( $n = 20$ ),  $2.5 \mu\text{g} \cdot \text{kg}^{-1}$  ( $n = 20$ ), or  $5 \mu\text{g} \cdot \text{kg}^{-1}$  ( $n = 20$ ) 1.5-2 h before arrival in the operating room (table 1). Every patient had lead II of the electrocardiogram (ECG; NEC San-ei Instrument Co., Ltd., Tokyo) monitored. A 16-G intravenous catheter was inserted for infusion of lactated Ringer's solution at a rate of  $10 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$  during the study.

After a stable hemodynamic state was obtained in each supine patient, all patients received incremental doses of atropine (Tanabe Co., Ltd.), 2.5, 2.5, and  $5 \mu\text{g} \cdot \text{kg}^{-1}$  over 5 s at a 2-min interval. Atropine sulfate solution was diluted in a concentration of  $50 \mu\text{g} \cdot \text{ml}^{-1}$ . HR and blood pressure (BP) were measured at 1-min intervals until 2 min after the last dose of atropine, while the ECG was

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TABLE 1. Patient Characteristics

Group	Clonidine Dose ( $\mu\text{g} \cdot \text{kg}^{-1}$ )	Age (yr)	Weight (kg)	Height (cm)
Control (n = 20)	0	40 $\pm$ 4 (17-74)	56 $\pm$ 1 (44-73)	159 $\pm$ 1 (150-179)
Clonidine 1.2 $\mu\text{g} \cdot \text{kg}^{-1}$ (n = 20)	1.27 $\pm$ 0.02 (1.00-1.53)	42 $\pm$ 3 (17-68)	59 $\pm$ 1 (52-75)	163 $\pm$ 2 (148-181)
Clonidine 2.5 $\mu\text{g} \cdot \text{kg}^{-1}$ (n = 20)	2.55 $\pm$ 0.06 (2.02-2.94)	44 $\pm$ 3 (19-65)	59 $\pm$ 2 (51-73)	158 $\pm$ 2 (146-178)
Clonidine 5.0 $\mu\text{g} \cdot \text{kg}^{-1}$ (n = 20)	5.02 $\pm$ 0.06 (4.41-5.62)	40 $\pm$ 2 (26-61)	59 $\pm$ 2 (41-78)	162 $\pm$ 2 (152-175)

Data are means  $\pm$  standard errors, with ranges in parentheses.

monitored continuously. BP was measured with an automated BP measuring device (BP-308 ET, Nippon Colin Co., Ltd., Tokyo). HR was determined as an average of every 4-s interval from the ECG monitor. Values of HR and BP 2 min after each dose of atropine were recorded and subjected to data analyses, since HR responses in every patient reached plateaus 1-2 min after atropine injection.

Data were expressed as means  $\pm$  standard errors. Changes in HR were plotted against cumulative dose of atropine. Statistical comparisons among the four groups were performed using two-way analysis of variance (ANOVA) followed by Student's *t* test with Bonferroni corrections. HR responses to atropine were analyzed by repeated-measures analysis of variance (one-way ANOVA) followed by a paired Student's *t* test in each group. BP responses to the cumulative dose of atropine within groups were analyzed in the same way. Testing for significance in the incidence of sinus bradycardia and arrhythmias before and after atropine among the groups was accomplished by chi-squared analysis.  $P < 0.05$  was taken as the minimum level of statistical significance.

#### PART 2: ATROPINE AND HEART RATE RESPONSE

Thirty patients were randomly administered either no preanesthetic medication (n = 15) or clonidine (n = 15) 5  $\mu\text{g} \cdot \text{kg}^{-1}$  orally 1.5-2 h before arrival in the operating room. Hemodynamic monitoring devices and recording, the infusion rate of crystalloid solution, and the preparation of diluted atropine sulfate solution were identical to those in part 1, described above.

After a stable hemodynamic state of at least several minutes was obtained in each patient, all patients received incremental doses of atropine 5  $\mu\text{g} \cdot \text{kg}^{-1}$  over 5 s at 2-min intervals until HR increased by 20 beats per min from baseline values; *i.e.*, no patients received additional atropine if HR increased more than 20 beats per min from their baseline values, whereas patients received additional atropine 5  $\mu\text{g} \cdot \text{kg}^{-1}$  when they did not attain an HR increase of 20 beats per min. The total dose of atropine was limited to 40  $\mu\text{g} \cdot \text{kg}^{-1}$ .

The cumulative number of patients in whom the HR

increased more than 20 beats per min was plotted against the cumulative dose of atropine. Testing for significance in the incidence of positive HR responses after atropine between the two groups was accomplished by chi-squared analysis. Other statistical analyses of data were similar to those described above in part 1.

#### Results

##### PART 1: INTERACTION OF CLONIDINE AND ATROPINE

There were no significant differences among the four groups with respect to age, weight, and height (table 1). Compared with that in the other three groups, basal HR (before atropine injection) in patients given clonidine 5  $\mu\text{g} \cdot \text{kg}^{-1}$  tended to be less, but the difference did not reach statistical significance. None of patients given no medication, none of the patients given clonidine 1.2  $\mu\text{g} \cdot \text{kg}^{-1}$ , one patient given clonidine 2.5  $\mu\text{g} \cdot \text{kg}^{-1}$ , and two patients given clonidine 5.0  $\mu\text{g} \cdot \text{kg}^{-1}$  had a basal HR of less than 50 beats per min ( $P > 0.05$  among the four groups).

After intravenous atropine 2.5  $\mu\text{g} \cdot \text{kg}^{-1}$ , HR significantly decreased in all groups (table 2). When the cumulative atropine dose of 5  $\mu\text{g} \cdot \text{kg}^{-1}$  was given, HR returned to baseline in all groups. When the cumulative dose of atropine reached 10  $\mu\text{g} \cdot \text{kg}^{-1}$ , HR increased from baseline by 19  $\pm$  2 in patients not receiving clonidine and by 15  $\pm$  2, 16  $\pm$  2, and 7  $\pm$  1 beats per min in those receiving clonidine 1.2, 2.5, and 5.0  $\mu\text{g} \cdot \text{kg}^{-1}$ , respectively. The magnitude of HR increase in patients who received clonidine 5.0  $\mu\text{g} \cdot \text{kg}^{-1}$  was significantly less than that in patients receiving no clonidine or the smaller doses of clonidine (table 2 and fig. 1). There was no significant difference in the HR responses to atropine among the groups of patients receiving no clonidine, clonidine 1.2  $\mu\text{g} \cdot \text{kg}^{-1}$ , and clonidine 2.5  $\mu\text{g} \cdot \text{kg}^{-1}$ .

When the cumulative dose of atropine reached 2.5  $\mu\text{g} \cdot \text{kg}^{-1}$  and 5  $\mu\text{g} \cdot \text{kg}^{-1}$ , mean BP decreased significantly from baseline in the control and clonidine 1.2  $\mu\text{g} \cdot \text{kg}^{-1}$  groups (table 2). When the cumulative dose of atropine reached 10  $\mu\text{g} \cdot \text{kg}^{-1}$ , mean BP returned to baseline in

TABLE 2. Heart Rate and Blood Pressure Before and After Intravenous Atropine

Group		Baseline	Cumulative Dose of Atropine ( $\mu\text{g} \cdot \text{kg}^{-1}$ )		
			2.5	5	10
Control (n = 20)	HR	69 ± 2	64 ± 2*	68 ± 2	88 ± 3*
	BP	86 ± 3†	84 ± 3*†	83 ± 3*†	85 ± 3‡
Clonidine 1.2 $\mu\text{g} \cdot \text{kg}^{-1}$ (n = 20)	HR	73 ± 3	68 ± 3*	72 ± 3	88 ± 3*
	BP	85 ± 3‡	83 ± 3†§	81 ± 3*†	85 ± 3‡
Clonidine 2.5 $\mu\text{g} \cdot \text{kg}^{-1}$ (n = 20)	HR	70 ± 2	66 ± 2*	69 ± 2	86 ± 3*
	BP	82 ± 2‡	80 ± 2‡	80 ± 2†	86 ± 2†§
Clonidine 5.0 $\mu\text{g} \cdot \text{kg}^{-1}$ (n = 20)	HR	62 ± 2	59 ± 2*	61 ± 2	69 ± 2*
	BP	71 ± 2	70 ± 2	69 ± 2	74 ± 2

Values are mean ± SE.

HR = heart rate (beats per min); BP = blood pressure (mmHg).

\*  $P < 0.01$  versus baseline.

†  $P < 0.01$  versus clonidine 5.0  $\mu\text{g} \cdot \text{kg}^{-1}$ .

‡  $P < 0.05$  versus clonidine 5.0  $\mu\text{g} \cdot \text{kg}^{-1}$ .

§  $P < 0.05$  versus baseline.

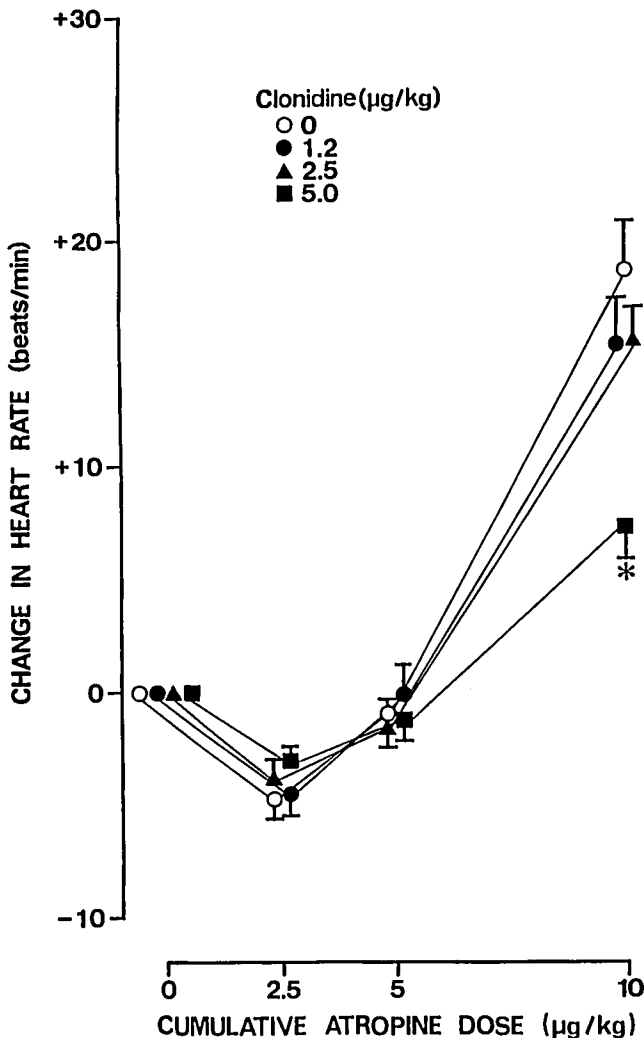


FIG. 1. Heart rate responses to the cumulative intravenous atropine dose of 2.5, 5, and 10  $\mu\text{g} \cdot \text{kg}^{-1}$  in patients receiving oral clonidine of 0 (n = 20), 1.2 (n = 20), 2.5 (n = 20), and 5.0  $\mu\text{g} \cdot \text{kg}^{-1}$  (n = 20). An asterisk denotes significant differences in heart rate responses to atropine in the patients given clonidine 5.0  $\mu\text{g} \cdot \text{kg}^{-1}$  when compared with those receiving clonidine 1.2  $\mu\text{g} \cdot \text{kg}^{-1}$  ( $P < 0.05$ ) or no clonidine or clonidine 2.5  $\mu\text{g} \cdot \text{kg}^{-1}$  ( $P < 0.01$ ).

both the control and the clonidine 1.2  $\mu\text{g} \cdot \text{kg}^{-1}$  groups and increased significantly above baseline in the clonidine 2.5  $\mu\text{g} \cdot \text{kg}^{-1}$  group (table 2). Basal mean BP in the clonidine 5.0  $\mu\text{g} \cdot \text{kg}^{-1}$  group was significantly less than that in the other groups, and the BP did not change after the injection of atropine. Mean BP after atropine in the clonidine 5.0  $\mu\text{g} \cdot \text{kg}^{-1}$  group was significantly less than that in the other three groups of patients (table 2).

One patient receiving no clonidine, one receiving clonidine 1.2  $\mu\text{g} \cdot \text{kg}^{-1}$ , and one receiving clonidine 5.0  $\mu\text{g} \cdot \text{kg}^{-1}$  developed junctional rhythm, premature atrial contractions, and premature ventricular contractions, respectively, for brief periods after the cumulative dose of atropine reached 10  $\mu\text{g} \cdot \text{kg}^{-1}$  ( $P > 0.05$  among the four groups). No other adverse effect possibly related to atropine or clonidine or to interaction between these agents was observed.

PART 2: ATROPINE AND HEART RATE RESPONSE

Basal HR and mean BP in patients who received oral clonidine (4.72–5.51  $\mu\text{g} \cdot \text{kg}^{-1}$ ) were significantly less than in those not receiving clonidine (table 3). Two patients given clonidine had a basal HR of less than 50 beats per min before atropine injection ( $P > 0.05$  vs. the control group).

TABLE 3. Clonidine Dose, Patient Characteristics, and Basal Hemodynamic Data

	Control Group (n = 15)	Clonidine Group (n = 15)
Clonidine dose ( $\mu \cdot \text{kg}^{-1}$ )	0	5.13 ± 0.07
Age (yr)	41 ± 4	40 ± 3
Weight (kg)	60 ± 3	60 ± 3
Height (cm)	158 ± 2	164 ± 2*
Heart rate (beats per min)	70 ± 3	62 ± 3*
Blood pressure (mmHg)	92 ± 4	77 ± 3†

Data are mean ± SE.

\*  $P < 0.05$  versus control group.

†  $P < 0.01$  versus control group.

In patients receiving clonidine, HR did not change ( $\pm 1$  beats per min) with the cumulative atropine dose of  $5 \mu\text{g} \cdot \text{kg}^{-1}$  but increased by  $8 \pm 2$  beats per min when the cumulative dose of atropine reached  $10 \mu\text{g} \cdot \text{kg}^{-1}$ . These changes in HR were significantly less than those in patients not receiving clonidine in whom atropine 5 and  $10 \mu\text{g} \cdot \text{kg}^{-1}$  caused HR increases of  $6 \pm 2$  and  $30 \pm 3$  beats per min, respectively ( $P < 0.01$ ). When the cumulative atropine dose reached  $15 \mu\text{g} \cdot \text{kg}^{-1}$  (fig. 2), HR had increased more than 20 beats per min in all 15 patients studied in the control group, whereas in only 5 of 15 patients in the clonidine group (33%) did the HR increase by more than 20 beats per min ( $P < 0.001$  vs. the control group, fig. 2). In the clonidine group, when the cumulative dose of atropine reached  $30 \mu\text{g} \cdot \text{kg}^{-1}$ , an additional 6 patients demonstrated HR increases of more than 20 beats per min. In the remaining 4 patients receiving clonidine, no significant additional increase in HR was observed even when the cumulative dose of atropine reached  $40 \mu\text{g} \cdot \text{kg}^{-1}$ . In these 4 patients, maximum HR increases were 10, 11, 18, and 19 beats per min during the study.

The mean value of BP in the clonidine group remained unchanged after the administration of atropine  $5 \mu\text{g} \cdot \text{kg}^{-1}$  but significantly increased, by  $6 \pm 2$  mmHg, after the cumulative atropine dose reached  $10 \mu\text{g} \cdot \text{kg}^{-1}$ . Mean BP in the control group did not change with these doses of atropine.

Premature atrial contractions and junctional rhythms developed in one control patient after the cumulative administration of atropine  $5 \mu\text{g} \cdot \text{kg}^{-1}$  and after  $10 \mu\text{g} \cdot \text{kg}^{-1}$ ,

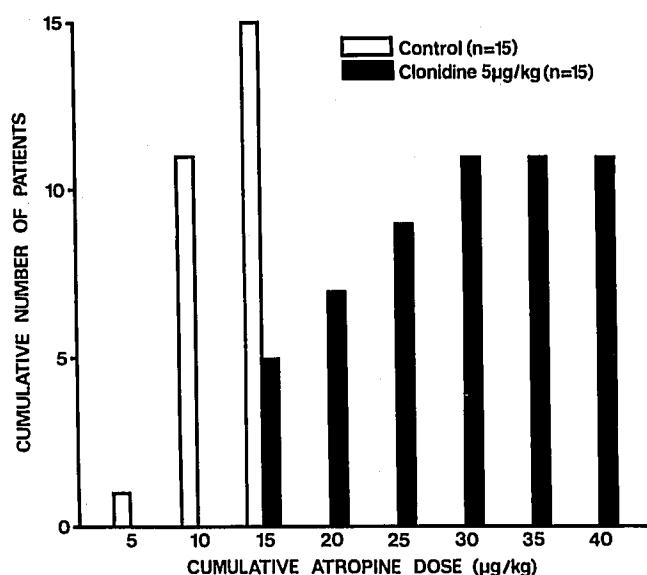


FIG. 2. Cumulative number of patients whose heart rate increased more than 20 beats per min from baseline values after the cumulative intravenous administration of atropine in patients receiving no clonidine (control) or oral clonidine  $5 \mu\text{g} \cdot \text{kg}^{-1}$ .

respectively. However, no patient receiving clonidine developed any arrhythmia after atropine injection ( $P > 0.05$  vs. the control group). There were no other adverse effects related to large doses of atropine or to clonidine-atropine interaction.

## Discussion

The current clinical study demonstrated that HR responses to intravenous atropine are attenuated in patients receiving clonidine  $5 \mu\text{g} \cdot \text{kg}^{-1}$  as a preanesthetic medication, but that the HR responses in patients receiving smaller doses of clonidine do not differ significantly from those in patients without clonidine medication. No detrimental effects related to clonidine medication, no greater incidence of arrhythmia due to atropine, and no serious clonidine-atropine interaction were observed. However, the hyporesponsiveness to atropine induced by clonidine  $5 \mu\text{g} \cdot \text{kg}^{-1}$  could not be reversed effectively by as much as  $40 \mu\text{g} \cdot \text{kg}^{-1}$  atropine in all patients.

Several concomitant effects of clonidine preanesthetic medication, in a dose of  $5 \mu\text{g} \cdot \text{kg}^{-1}$ , have been reported in patients undergoing aortic or coronary artery surgery; these include a greater incidence of hypotension, a decreased HR, and more frequent requirements of vasopressor infusion.<sup>14,15</sup> Although in a recent study<sup>16</sup> we demonstrated that the BP responses to intravenous ephedrine are augmented in awake or anesthetized patients receiving oral clonidine  $5 \mu\text{g} \cdot \text{kg}^{-1}$ , there are few clinical data regarding the interaction between clonidine and other vasoactive agents.<sup>17</sup> Furthermore, there is a difference of opinion as to the efficacy of atropine treatment for increasing HR in patients who develop severe bradycardia or atrioventricular conduction disturbances after clonidine administration.<sup>1,5,6</sup> The previous studies show that the hyporesponsiveness to atropine is observed primarily in patients receiving long-term clonidine or in patients concomitantly receiving digitalis, calcium entry blockers, or beta-adrenergic blockade.<sup>1,2,5,6</sup> The results of the current study also indicate that even a single administration of clonidine  $5 \mu\text{g} \cdot \text{kg}^{-1}$  can modify the response of HR to atropine in otherwise healthy patients.

In addition to its response to dose,<sup>18</sup> HR responses to atropine seem to be affected by various factors, such as the patient's age,<sup>19</sup> sympathetic nervous activity,<sup>20</sup> co-existing disease,<sup>21-25</sup> and resting basal HR.<sup>26</sup> Previously, the positive chronotropic effect of intravenous atropine ( $4.9$ – $13.6 \mu\text{g} \cdot \text{kg}^{-1}$ ) has been shown to be augmented in patients receiving oral pentobarbital and diphenhydramine, intramuscular meperidine, or no drugs as preanesthetic medication<sup>26</sup> when baseline HR was lower prior to atropine. However, in the current study the patients receiving clonidine  $5 \mu\text{g} \cdot \text{kg}^{-1}$  had lower basal HR and a lesser increase in HR to atropine. This finding agrees with Cham-

berlain *et al.*'s findings<sup>27</sup> of a significant negative correlation between resting HR and the dose of atropine necessary to produce the maximum effect on HR. Since a 12% increase in HR after atropine  $10 \mu\text{g} \cdot \text{kg}^{-1}$  in patients given clonidine  $5 \mu\text{g} \cdot \text{kg}^{-1}$  in the current study is indeed consistent with the previous study<sup>28</sup> in which an approximately 15% increase in HR was noted in patients receiving propranolol of  $0.2 \text{ mg} \cdot \text{kg}^{-1}$ , the attenuation of HR responsiveness to atropine may be attributed primarily to decreased sympathetic activity due to large doses of clonidine.<sup>5,6</sup> This assumption is supported further by the previous clinical study that demonstrated augmentation of the positive chronotropic effect of atropine after pretreatment with sympathomimetic agents.<sup>20</sup>

Although intravenous atropine  $10 \mu\text{g} \cdot \text{kg}^{-1}$  in anesthetized patients produces clinically significant changes in systolic BP ( $-7$ – $+37$  mmHg),<sup>29</sup> no such change was observed in awake patients in the present as well as previous<sup>20</sup> results. The differences in the responses between awake and anesthetized humans may be due to anesthesia-induced suppression of the autonomic nervous activity, especially of the parasympathetic nervous system.<sup>29,30</sup> Because a larger atropine dose did not reverse the HR hyporesponsiveness in some patients receiving clonidine  $5 \mu\text{g} \cdot \text{kg}^{-1}$  and because an adequate parasympathetic block of the sinoatrial node<sup>27</sup> could be obtained with atropine  $40 \mu\text{g} \cdot \text{kg}^{-1}$ , clonidine seems unlikely to produce concomitant suppression of the parasympathetic nervous system. No increased occurrence of arrhythmia after a large dose of atropine in patients given clonidine would preclude the possibility of profound interaction. Thus, profound suppression of sympathetic activity due to clonidine is suggested to be an underlying mechanism of the HR hyporesponsiveness to atropine. The anesthetic agents used and probably their depth should also affect or modify the HR responses to atropine-like drugs through their effects on the autonomic nervous system activity.<sup>16,29,30</sup> Indeed, reflex bradycardia seems easily to occur associated with anesthetic and surgical manipulations in patients receiving clonidine.<sup>31</sup>

In conclusion, the HR response to intravenous atropine was attenuated in awake humans receiving oral clonidine  $5 \mu\text{g} \cdot \text{kg}^{-1}$ , but not in those receiving oral clonidine  $2.5 \mu\text{g} \cdot \text{kg}^{-1}$  or less. This attenuation of HR responses to atropine cannot be effectively overcome by large doses of atropine in all patients. These results suggest that oral clonidine  $5 \mu\text{g} \cdot \text{kg}^{-1}$  can induce pronounced depression of the sympathetic nervous system, and a potent beta-adrenergic agonist may be required to restore the normal HR or to increase the HR up to a desired level in certain patients receiving clonidine  $5 \mu\text{g} \cdot \text{kg}^{-1}$ .

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