

Oral Clonidine Preanesthetic Medication Augments the Pressor Responses to Intravenous Ephedrine in Awake or Anesthetized Patients

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To evaluate the possible interaction between clonidine and ephedrine, the authors studied hemodynamic responses to intravenous ephedrine in 80 patients who received either clonidine preanesthetic medication of approximately $5 \mu\text{g} \cdot \text{kg}^{-1}$ orally ($n = 40$) or no medication ($n = 40$). The patients were studied while they were either awake ($n = 40$) or anesthetized with enflurane and nitrous oxide in oxygen ($n = 40$). Hemodynamic measurements were made at 1-min intervals for 10 min after ephedrine $0.1 \text{ mg} \cdot \text{kg}^{-1}$ was injected as a bolus. Although the responses to ephedrine were always greater in anesthetized patients, the magnitudes of mean blood pressure increases in patients who received clonidine ($10 \pm 8\%$ for awake and $27 \pm 11\%$ for anesthetized subjects, mean \pm standard deviation [SD]) were significantly greater ($P < 0.05$) than in patients not receiving clonidine ($4 \pm 5\%$ for awake and $17 \pm 11\%$ for anesthetized subjects). The enhanced pressor responses to ephedrine observed in both awake and anesthetized patients in the presence of clonidine may be attributed to increased catecholamine storage at sympathetic nerve endings due to clonidine, enhanced sensitivity of tissue receptors to which ephedrine binds, potentiation of α -adrenoceptor mediated vasoconstriction of both agents, or all of these. It is concluded that oral clonidine preanesthetic medication of $5 \mu\text{g} \cdot \text{kg}^{-1}$ does augment rather than attenuate the pressor responses to intravenous ephedrine in patients both prior to and during general anesthesia. (Key words: Blood pressure. Complications: hypotension. Pharmacology: ephedrine. Sympathetic nervous system, α_2 -adrenergic agonists: clonidine.)

ALTHOUGH CLONIDINE, a partial α_2 -adrenergic agonist, has recently been used as preanesthetic medication to reduce opioid or volatile anesthetic requirements and to improve cardiovascular stability,¹⁻³ one of the most detrimental effects of oral clonidine is a frequent occurrence of hypotension during anesthetic and postoperative periods.⁴ These hypotensive episodes have been reported to predispose the surgical patients to myocardial ischemia under certain circumstances.^{5,6} Because of increasing clinical use of oral clonidine, accurate knowledge of in-

teractions between α_2 -adrenergic agonists and other vasoactive agents is important. For example, vasoconstriction mediated by α_2 -adrenergic agonists has been demonstrated to be attenuated by calcium entry blockers.^{7,8}

Ephedrine is one of the most commonly used vasopressor agents during anesthesia.^{9,10} It is well known that ephedrine increases blood pressure (BP) and heart rate (HR) by facilitating the release of catecholamines from the sympathetic nerve endings,¹¹ whereas clonidine has been reported to suppress catecholamine release from the sympathetic nerves.¹² Therefore, it is likely that oral clonidine preanesthetic medication could attenuate the hemodynamic responses to ephedrine. On the other hand, since α -methyldopa (the actions of which resemble those of clonidine) has been known to augment the pressor response to norepinephrine or tyramine in humans^{13,14} and since it is currently believed to exert its antihypertensive effect by conversion to α -methylnorepinephrine—a potent α_2 -adrenergic agonist¹⁵—it is speculated that clonidine also enhances the pressor action of ephedrine.

Recently, we reported no significant changes in the pressor response to intravenous ephedrine in patients receiving epidural clonidine with epidural lidocaine.¹⁶ However, to our knowledge, there is no information regarding the interactions between oral clonidine and intravenous ephedrine in humans. The current clinical study was undertaken to evaluate whether oral clonidine of $5 \mu\text{g} \cdot \text{kg}^{-1}$ could attenuate or augment the hemodynamic effects of intravenous ephedrine in awake patients or in patients under general anesthesia.

Materials and Methods

Eighty surgical patients, ASA physical status I, ranging in age from 16 to 73 yr, and scheduled to have general anesthesia for their surgical procedures, were selected for this study. The study protocol was approved by our Clinical Investigation Committee. Informed consent was obtained from each patient. No patient had any cardiopulmonary disorders. In addition, none of the patients was taking any medications affecting cardiovascular function.

Forty patients received clonidine (Boehringer Ingelheim), approximately $5 \mu\text{g} \cdot \text{kg}^{-1}$, orally 1.5–2 h before arrival in the operating room (clonidine group). The remaining 40 patients received no medication (control

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group). 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 patient, positioned supine with a pillow, for several minutes, ephedrine $0.1 \text{ mg} \cdot \text{kg}^{-1}$ was administered intravenously over 5 s in 20 awake patients each of both groups. Ephedrine hydrochloride solution (Dainippon) was diluted in a concentration of $1 \text{ mg} \cdot \text{ml}^{-1}$. BP and HR were measured at 1-min intervals for 10 min after the injection of ephedrine, while lead II of the electrocardiogram (ECG; NEC San-ei Instrument, Tokyo) was continuously monitored. BP was measured oscillometrically with a BP monitoring device (BP-308 ET, Nippon Colin, Tokyo). HR was determined as an average of every 4 s from the ECG monitor.

In the remaining 40 patients, general anesthesia was induced with thiamylal $4\text{--}5 \text{ mg} \cdot \text{kg}^{-1}$, and tracheal intubation was facilitated with administration of vecuronium, approximately $0.2 \text{ mg} \cdot \text{kg}^{-1}$. Subsequently, anesthesia was maintained with enflurane $0.6\text{--}2.0\%$ inspired and 67% nitrous oxide in oxygen. Ephedrine $0.1 \text{ mg} \cdot \text{kg}^{-1}$ was injected after a stable hemodynamic period of at least 10 min had been obtained. Hemodynamic measurements were made at 1-min intervals for 10 min after the injection of ephedrine. Immediately after the last measurements, arterial blood was sampled and analyzed for $p\text{H}$, carbon dioxide tension (Pa_{CO_2}), oxygen tension (Pa_{O_2}), and base excess with a model 178 $p\text{H}$ /Blood Gas Analyzer (Coring, Medfield, MA).

Data were expressed as mean \pm standard deviation (SD). Mean blood pressure (MBP) was calculated as diastolic blood pressure (DBP) plus $\frac{1}{3} \times$ (systolic blood pressure [SBP] - DBP). Statistical comparisons among groups were performed using two-way analysis of variance (ANOVA) followed by Student's t test with Bonferroni corrections. BP and HR responses to ephedrine were analyzed by using repeated-measures ANOVA (one-way ANOVA) followed by a paired Student's t test for paired data in each group. Testing for the incidence among groups was accomplished by chi-squared analysis. $P < 0.05$ was considered the minimum level of statistical significance.

Results

There were no significant differences among the four groups of patients with respect to age, weight, height, and ratio of men to women (table 1). Clonidine doses in awake and anesthetized patients of the clonidine group were $4.92 \pm 0.32 \mu\text{g} \cdot \text{kg}^{-1}$ and $4.84 \pm 0.32 \mu\text{g} \cdot \text{kg}^{-1}$, respectively.

Baseline values of SBP and MBP in awake patients given clonidine were significantly less compared to those in awake patients without clonidine (table 2), whereas the difference in HR between the two groups did not reach statistical significance. In awake patients without clonidine, BP increases above baseline values after intravenous ephedrine were not sustained for longer than 4 min, and thereafter BP decreased below baseline values. In contrast, in awake patients receiving clonidine, BP elevations were more prolonged (table 2). The magnitudes of the pressor responses to ephedrine in awake patients with clonidine were significantly greater ($P < 0.05$) than those without clonidine (fig. 1). The HR increases after ephedrine were sustained during the 10-min study period in both groups, and the magnitudes of positive chronotropic responses to ephedrine in the two groups was comparable (table 2).

In the comparison of anesthetized patients with and without clonidine, there were no significant differences in doses of thiamylal and vecuronium; inspired concentration of enflurane given for induction and maintenance of general anesthesia; infusion rate of lactated Ringer's solution prior to injection of ephedrine; arterial blood gas values; and basal hemodynamic variables (tables 3 and 4). In anesthetized patients with and without clonidine, pressor responses to ephedrine were more sustained compared to those in awake patients (figs. 1 and 2; tables 2 and 4). In anesthetized patients receiving clonidine, the magnitudes of BP increases up to 3 min after ephedrine were similar to those in anesthetized control patients. Subsequent pressor responses to ephedrine were approximately twice as great in patients who received clonidine compared to control patients ($P < 0.05$, fig. 2). HR did not consistently show positive chronotropic effects after injection of ephedrine during the 10-min study period in anesthetized patients of both groups (table 4).

Hypotensive episodes in which SBP decreased to less

TABLE 1. Patient Characteristics and Clonidine Doses

Group	Age (yr)	Weight (kg)	Height (cm)	Sex (F/M)	Clonidine dose ($\mu\text{g} \cdot \text{kg}^{-1}$)
Awake					
Control (n = 20)	42 ± 15	57 ± 10	160 ± 9	11/9	—
Clonidine (n = 20)	42 ± 17	58 ± 8	160 ± 9	10/10	4.92 ± 0.32
Anesthetized					
Control (n = 20)	39 ± 16	61 ± 8	163 ± 8	8/12	—
Clonidine (n = 20)	42 ± 16	58 ± 8	160 ± 10	10/10	4.84 ± 0.32

Values are mean \pm SD.

TABLE 2. Hemodynamic Responses to Intravenous Ephedrine 0.1 mg · kg⁻¹ in Awake Patients

Group		Baseline	Time after Ephedrine (min)									
			1	2	3	4	5	6	7	8	9	10
Control (n = 20)	SBP	126 ± 9	128 ± 10	136 ± 11*	131 ± 11*	131 ± 9*	126 ± 11	125 ± 12	124 ± 12	123 ± 14	124 ± 13	124 ± 13
	DBP	72 ± 8	74 ± 8	77 ± 8*	75 ± 8*	72 ± 8	71 ± 9	70 ± 9	68 ± 8*	68 ± 9*	67 ± 9*	67 ± 10*
	MBP	89 ± 7	92 ± 7*	96 ± 9*	93 ± 8*	92 ± 8*	89 ± 9	88 ± 9	87 ± 9*	86 ± 10*	86 ± 9*	86 ± 10*
	HR	72 ± 13	76 ± 15*	78 ± 15*	77 ± 16*	78 ± 15*	78 ± 15*	79 ± 16*	77 ± 14*	77 ± 14*	79 ± 14*	79 ± 15*
Clonidine (n = 20)	SBP	112 ± 15†	113 ± 15†	121 ± 16*†	123 ± 15*	123 ± 14*†	121 ± 13*	120 ± 13*	118 ± 13*	118 ± 13*	119 ± 13*	118 ± 13*
	DBP	65 ± 11	63 ± 11†	69 ± 11*†	71 ± 10*	70 ± 10*	69 ± 10*	68 ± 11	68 ± 11	67 ± 11	67 ± 10	65 ± 11
	MBP	80 ± 12†	79 ± 12†	85 ± 11*†	88 ± 11*	87 ± 11*	86 ± 10*	85 ± 11*	84 ± 11*	84 ± 11*	84 ± 10*	82 ± 10
	HR	66 ± 10	72 ± 12*	72 ± 9*	70 ± 10*	71 ± 10*	70 ± 10*	71 ± 10*	70 ± 10*	70 ± 10*	70 ± 10*	70 ± 9*

Values are mean ± SD.

SBP = systolic blood pressure (mmHg); DBP = diastolic blood pressure (mmHg); MBP = mean blood pressure (mmHg); HR = heart rate (beats per min).

* *P* < 0.05 versus baseline.

† *P* < 0.05 versus control group.

than 80 mmHg prior to intravenous ephedrine were found in two anesthetized patients who had received clonidine, but they responded well to ephedrine during the study. There were, however, no significant differences between the patients with and without clonidine in the incidence of hypotension. None of patients developed arrhythmias, severe hypertension after intravenous ephedrine, or acute postoperative clonidine withdrawal syndrome. There were no other adverse reactions possibly related to ephedrine or clonidine or to interaction between the two agents.

Discussion

Results from the current study demonstrate that pressor responses to intravenous ephedrine 0.1 mg · kg⁻¹ were augmented in awake and anesthetized patients who had received clonidine 5 µg · kg⁻¹ as preanesthetic medication.

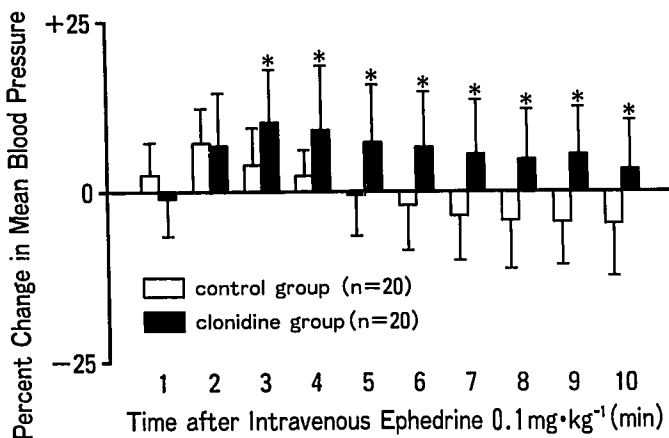


FIG. 1. Percent changes (±SD) in mean blood pressure after intravenous ephedrine 0.1 mg · kg⁻¹ in awake patients receiving approximately 5 µg · kg⁻¹ clonidine po (clonidine group) or no premedication (control group). *Significant differences (*P* < 0.05) between the two groups.

None of patients receiving clonidine showed abnormally exaggerated pressor responses to intravenous ephedrine in either the awake or the anesthetized state.

Clonidine hydrochloride, a partial α₂-agonist, has recently been used as part of a preanesthetic regimen in a dose of approximately 5 µg · kg⁻¹.¹⁻⁵ Although the principal aims of its administration include reduced requirements of anesthetics and improved cardiovascular stability,¹⁻³ several studies have suggested that clonidine preanesthetic medication may cause a greater incidence of hypotension and more frequent requirements of vasopressor agents.^{4,5} In the current study, only two anesthetized patients given clonidine became hypotensive (SBP less than 80 mmHg) prior to intravenous ephedrine; however, they responded well to ephedrine.

Ephedrine is a partial, indirectly acting sympathomimetic amine exerting its effect primarily by the release of endogenous catecholamines from the adrenergic nerve terminals and the adrenal medulla, although it also has some direct action on cardiovascular systems.⁹ Experimentally, the cardiovascular-stimulating effects of ephedrine have been demonstrated not to depend solely on the integrity of catecholamines stores, since they were not suppressed by acute or chronic treatment with reserpine.¹⁷

Similar to the findings in patients receiving clonidine in this study, other antihypertensive agents such as α-methyldopa and guanethidine have been reported to augment the pressor responses to tyramine or norepinephrine in humans^{13,14} and animals.¹⁸⁻²⁰ α-Methyldopa is transformed into α-methylnorepinephrine, which acts as an α₂-adrenoceptor agonist similar to clonidine.¹⁵ Therefore, the enhanced pressor actions of ephedrine observed in patients with clonidine pretreatment is likely to be due to increased sensitivity to a vasopressor through its α₂-adrenergic effects. The greater pressor responses to ephedrine may be related to increased catecholamine storage at the axoplasm and the synaptic vesicles secondary to inhibition of its release by clonidine; enhanced sensi-

TABLE 3. Anesthetic Agents, Infused Crystalloid, and Arterial Blood Gas Values during General Anesthesia

Group	Thiamylal (mg·kg ⁻¹)	Vecuronium (mg·kg ⁻¹)	Enflurane (%)	Lactated Ringer's Solution (ml·kg ⁻¹ ·h ⁻¹)	pHa	PaCO ₂ (mmHg)	PaO ₂ (mmHg)	Base Excess (mEq·l ⁻¹)
Control (n = 20)	4.6 ± 0.3	0.20 ± 0.01	1.6 ± 0.5	14.3 ± 3.5	7.45 ± 0.04	34 ± 4	160 ± 32	0.7 ± 2.8
Clonidine (n = 20)	4.6 ± 0.2	0.20 ± 0.01	1.3 ± 0.4	14.7 ± 3.5	7.44 ± 0.03	35 ± 2	165 ± 34	1.3 ± 1.8

Values are mean ± SD.

pHa = arterial blood pH; PaCO₂ = arterial CO₂ tension; PaO₂ = arterial O₂ tension.

tivity of tissue receptors to which ephedrine binds¹³; or potentiation of α -adrenoceptor-mediated vasoconstriction of both ephedrine and clonidine²¹; or all of these. Further, augmented pressor effects of ephedrine in patients given clonidine may be attributable to an impairment of the ability of tissue to bind norepinephrine at the sites where it is stored, similar to the impairment after administration of α -methyl dopa.²²

Reasons for greater pressor responses to ephedrine in anesthetized patients, both those who did and those who did not receive clonidine preanesthetic medication, are unclear. As far as we know, the cardiovascular effects of ephedrine, particularly in clinical anesthetic settings, have never been studied extensively. Furthermore, comparative pressor effects of ephedrine in awake and anesthetized patients have not been described. The current results suggest that general anesthetics augment the pressor effects of ephedrine primarily by potentiating α -adrenoceptor-mediated vasoconstriction (table 4). In contrast, the effect of ephedrine in awake patients compared with anesthetized patients is predominantly a β -adrenergic effect, especially in patients in this study who did not receive clonidine (tables 2, 4).

On the other hand, a recent study has reported that the α -adrenoceptor-mediated direct pressor response was

depressed by halothane or isoflurane anesthesia in dogs after ganglionic, cholinergic, and β -adrenergic blockade.²³ Whether α_1 - or α_2 -adrenoceptor-mediated vasoconstriction could be predominantly affected by volatile anesthetics remains controversial,^{24,25} and a recent report has shown that halothane has no effect on the cardiovascular responses to phenylephrine in humans.²⁶ The differences in the pressor responses to vasoactive agents during anesthesia may be due to species differences (dogs or rats *vs.* humans), types of vasopressors (directly *vs.* indirectly acting), the presence or absence of autonomic blockade, and underlying general anesthesia (volatile anesthetics with *vs.* without nitrous oxide). The indirect pressor action of ephedrine probably is augmented further by general-anesthesia-induced elevations of plasma catecholamine concentrations.²⁷⁻³⁰ Nitrous oxide,²⁸ which in the current study was added to enflurane, may counteract the suppressive effects of enflurane upon catecholamine release.^{31,32} In contrast, the pressor effect of direct-acting α -adrenoceptor agonists appears to be attenuated primarily by potent vasodilating properties of volatile anesthetics.^{33,34} Furthermore, the hemodynamic alterations after ephedrine in anesthetized patients may be related to the fact that since enflurane and nitrous oxide anesthesia is reported to suppress arterial baroreceptor re-

TABLE 4. Hemodynamic Responses to Intravenous Ephedrine 0.1 mg·kg⁻¹ in Patients Anesthetized with Enflurane and Nitrous Oxide in Oxygen

Group		Baseline	Time after Ephedrine (min)									
			1	2	3	4	5	6	7	8	9	10
Control (n = 20)	SBP	93 ± 8	96 ± 7*	116 ± 10*	112 ± 8*	110 ± 10*	109 ± 8*	107 ± 10*	104 ± 8*	104 ± 8*	102 ± 8*	102 ± 9*
	DBP	49 ± 7	51 ± 7	60 ± 9*	61 ± 8*	58 ± 8*	56 ± 7*	57 ± 7*	56 ± 8*	53 ± 8*	53 ± 8*	52 ± 8
	MBP	64 ± 6	66 ± 5	77 ± 8*	77 ± 7*	75 ± 8*	74 ± 7*	73 ± 7*	72 ± 7*	70 ± 8*	69 ± 7*	68 ± 7*
	HR	72 ± 11	76 ± 13*	76 ± 12*	75 ± 12	74 ± 12	74 ± 11*	74 ± 11	75 ± 11*	73 ± 11	74 ± 11	74 ± 12
Clonidine (n = 20)	SBP	92 ± 9	92 ± 11	104 ± 14*†	113 ± 13*	112 ± 13*	112 ± 13*	111 ± 13*	111 ± 12*	110 ± 13*	108 ± 12*	108 ± 13*
	DBP	50 ± 10	52 ± 10	59 ± 13*	64 ± 14*	65 ± 13*	63 ± 12*	63 ± 12*	62 ± 13*	61 ± 12*†	61 ± 12*†	61 ± 12*†
	MBP	63 ± 9	65 ± 9	74 ± 13*	80 ± 13*	81 ± 12*	79 ± 12*	78 ± 12*	78 ± 12*	77 ± 12*	76 ± 11*†	77 ± 12*†
	HR	69 ± 9	72 ± 10*	75 ± 11*	72 ± 10	72 ± 10*	73 ± 11*	72 ± 11	72 ± 11*	72 ± 10*	72 ± 10	71 ± 10

Values are mean ± SD.

SBP = systolic blood pressure (mmHg); DBP = diastolic blood pressure (mmHg); MBP = mean blood pressure (mmHg); HR = heart rate (beats per min).

*P < 0.05 versus baseline.

†P < 0.05 versus control group.

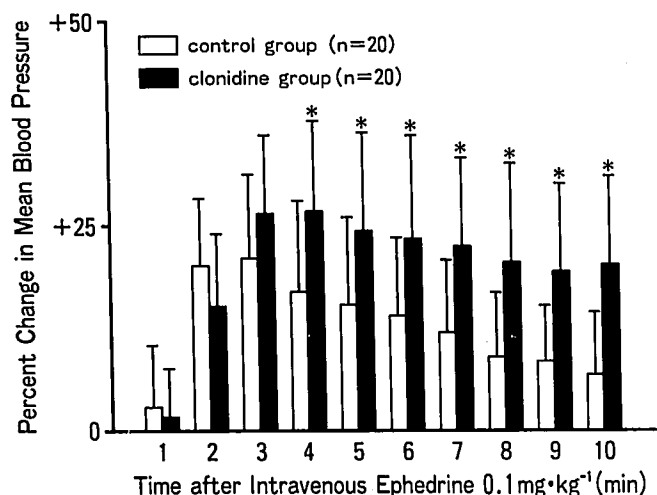


FIG. 2. Percent changes (\pm SD) in mean blood pressure after intravenous ephedrine $0.1 \text{ mg} \cdot \text{kg}^{-1}$ in anesthetized patients receiving approximately $5 \mu\text{g} \cdot \text{kg}^{-1}$ clonidine po (clonidine group) or no premedication (control group). *Significant differences ($P < 0.05$) between the two groups.

flexes,³⁵ the greater pressor responsiveness to ephedrine can be explained by this suppression and thus inconsistent changes in HR by activating the baroreceptors.

In conclusion, the pressor effects of ephedrine were augmented in patients receiving clonidine $5 \mu\text{g} \cdot \text{kg}^{-1}$ as preanesthetic medication; this response was magnified in the presence of enflurane anesthesia. Thus, hypotension in these patients should be effectively treated by ephedrine without any particular adverse effects.

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