Clonidine premedication modifies responses to adrenoceptor agonists and baroreflex sensitivity

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Purpose: To evaluate the effects of clonidine on responses to adrenoceptor agonists and baroreflex sensitivity, we examined arterial blood pressure (AP) responses to phenylephrine and heart rate (HR) responses to isoproterenol and baroreflex sensitivity (HR response to AP changes due to phenylephrine or nitroglycerin).

Methods: We studied 60 anesthetized patients who either did or did not receive $5 \mu\text{g}\cdot\text{kg}^{-1}$ clonidine *po* before they were anesthetized. After induction of general anesthesia, the patients received $3 \mu\text{g}\cdot\text{kg}^{-1}$ phenylephrine, $0.02 \mu\text{g}\cdot\text{kg}^{-1}$ isoproterenol, or $2\text{--}3 \mu\text{g}\cdot\text{kg}^{-1}$ nitroglycerin, and haemodynamic measurements were taken. Baroreflex sensitivity was expressed as the slope of the linear regression line ($\text{msec}\cdot\text{mmHg}^{-1}$; in msec of R-R interval change vs mmHg change in systolic arterial pressure) following the administration of phenylephrine and nitroglycerin.

Results: Patients who received clonidine had greater augmented responses in AP to phenylephrine and in HR to isoproterenol ($47.2 \pm 15.6\%$ vs $23.7 \pm 11.9\%$ for increase in systolic AP and $59.8 \pm 22.6\%$ vs $26.2 \pm 11.0\%$ for increase in HR, $P < 0.05$ respectively). There were no differences between the baroreflex sensitivities in the pressor (phenylephrine) test groups (3.77 ± 1.08 vs $4.41 \pm 1.66 \text{ msec}\cdot\text{mmHg}^{-1}$). In contrast, the slopes of depressor (nitroglycerin) test groups were decreased in patients receiving clonidine (1.98 ± 0.73 vs $3.68 \pm 1.72 \text{ msec}\cdot\text{mmHg}^{-1}$, $P < 0.05$).

Conclusion: The results suggest that premedication with clonidine might enhance critical hypotension during anesthesia and surgery, but restoration both of AP and HR decrease can be achieved effectively by phenylephrine and isoproterenol *iv*, respectively.

Objectif : Afin d'évaluer les effets de la clonidine sur les réponses des récepteurs adrénergiques agonistes et sur la sensibilité baroréflexe, nous avons enregistré les changements de tension artérielle (TA) liés à la phényléphrine, les modifications de fréquence cardiaque (FC) liées à l'isoprotérénol et la sensibilité baroréflexe (les réactions de la FC aux changements de TA liées à la phényléphrine ou à la nitroglycérine).

Méthode : Nous avons étudié 60 patients qui avaient reçu ou non $5 \mu\text{g}\cdot\text{kg}^{-1}$ de clonidine *po* avant l'anesthésie. Après l'induction de l'anesthésie générale, les patients ont reçu $3 \mu\text{g}\cdot\text{kg}^{-1}$ de phényléphrine, $0.02 \mu\text{g}\cdot\text{kg}^{-1}$ d'isoprotérénol ou $2\text{--}3 \mu\text{g}\cdot\text{kg}^{-1}$ de nitroglycérine, et on a procédé aux mesures hémodynamiques. La sensibilité baroréflexe était exprimée par la pente du tracé de régression linéaire ($\text{msec}\cdot\text{mmHg}^{-1}$; en msec de changement dans l'intervalle R-R vs en mmHg de changement dans la tension artérielle systolique) à la suite de l'administration de phényléphrine et de nitroglycérine.

Résultats : Les patients qui ont reçu de la clonidine ont présenté des augmentations plus importantes de TA, en réaction à la phényléphrine, et de FC, en réaction à l'isoprotérénol ($47,2 \pm 15,6\%$ vs $23,7 \pm 11,9\%$ concernant l'augmentation de la TA systolique et $59,8 \pm 22,6\%$ vs $26,2 \pm 11,0\%$ concernant l'augmentation de FC, $P < 0,05$ respectivement). Il n'y a pas eu de différence de sensibilité baroréflexe entre les groupes testés pour les réactions au médicament stimulant, phényléphrine, ($3,77 \pm 1,08$ vs $4,41 \pm 1,66 \text{ msec}\cdot\text{mmHg}^{-1}$). En comparaison, les pentes des groupes du test hypotenseur (nitroglycérine) s'abaissaient chez les patients ayant reçu de la clonidine ($1,98 \pm 0,73$ vs $3,68 \pm 1,72 \text{ msec}\cdot\text{mmHg}^{-1}$, $P < 0,05$).

Conclusion : Les résultats laissent voir que la prémédication avec de la clonidine a pu favoriser une hypotension critique pendant l'anesthésie et la chirurgie, mais que le rétablissement de TA et de FC plus basses pouvait être réalisé efficacement avec de la phényléphrine et de l'isoprotérénol *iv*, respectivement.

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C LONIDINE, an α_2 -adrenergic agonist contains antinociceptive and sedative properties.¹ Clonidine attenuates reflex cardiovascular responses to tracheal intubation, improves perioperative haemodynamic stability, and reduces anaesthetic requirements.²⁻⁴ However, patients given oral clonidine have been warned of possible hypotension or bradycardia during anaesthetic and postoperative periods.^{3,5} Nishikawa *et al.* indicated that premedication with oral clonidine augmented the pressor responses to intravenous ephedrine^{6,7} and phenylephrine,⁸ but attenuated heart rate (HR) responses to intravenous atropine in humans.⁹ Also, clonidine has been shown to reduce central sympathetic outflow¹⁰ and the release of noradrenaline from peripheral presynaptic terminals (reduced peak plasma concentration of noradrenaline).^{4,11,12} Such actions may explain why patients receiving clonidine have augmented responses to pressor agents. These actions may be beneficial to stabilize haemodynamic disturbances in critical situations such as acute changes in arterial blood pressure (AP) during anaesthesia. We hypothesized that, if the augmentation to clonidine-induced potentiation to pressor agents was due to a reduction in release of noradrenaline from peripheral presynaptic terminals, HR responses to exogenous β -adrenergic stimulation would be potentiated, as would the pressor responses to α -adrenergic stimulation. In addition, reflex tachycardia induced by hypotension would be attenuated by clonidine.

In the present study, we examined the interaction between orally administered clonidine and intravenous phenylephrine, an α_1 -adrenergic agent, and isoproterenol, a β -adrenergic agent, on haemodynamic responses in anaesthetized patients. We also assessed baroreflex sensitivity during pharmacological changes of AP with phenylephrine and nitroglycerin in anaesthetized patients who received clonidine as anaesthetic premedication.

Methods

The present study was approved by our Clinical Investigation Committee, and informed consent was obtained from each patient. Sixty adult ASA physical status I or II patients (aged 20-63 yr) scheduled for elective surgery under general anaesthesia were studied while in the operating room. No patient had any cardiopulmonary disorders or was taking any medications affecting cardiovascular function.

The patients were randomly allocated into two groups: 30 patients received clonidine (Catapres®, Boehringer Ingelheim & Tanabe, Kawanishi City, Hyogo, Japan) as pre-anaesthetic medication approxi-

mately $5 \mu\text{g}\cdot\text{kg}^{-1}$ *po* 1.5 hr before arrival in the operating room (clonidine group). The remaining 30 patients received no medication (control group).

GENERAL PREPARATION

The BP and HR were measured before administration of clonidine (clonidine group) or 1.5 hr before arrival in the operating room (control group), and before induction of anaesthesia from each group.

Upon arrival in the operating room, HR was monitored from lead II of the ECG, and a blood pressure cuff and a pulse oximeter device were applied throughout the operative period. An 18-G catheter was inserted into a forearm vein and used for fluid and drug administration. All patients received 400 - 800 ml Ringer's lactate solution to compensate for overnight fluid losses and the rate of fluid infusion during and after induction of anaesthesia, and during data collection was $2 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{hr}^{-1}$. General anaesthesia was induced with $4 \text{ mg}\cdot\text{kg}^{-1}$ thiopentone, and 2-3 $\mu\text{g}\cdot\text{kg}^{-1}$ fentanyl. Muscle relaxation was obtained by administration of $0.2 \text{ mg}\cdot\text{kg}^{-1}$ vecuronium. Following tracheal intubation, anaesthesia was maintained with nitrous oxide 50% in oxygen. The lungs were mechanically ventilated with a tidal volume of approximately $10 \text{ ml}\cdot\text{kg}^{-1}$ for maintaining the $P_{\text{ET}}\text{CO}_2$ between 35 and 40 mmHg. A 22-G catheter was inserted into the radial artery for direct measurements of AP in each patient and analysis of arterial blood gas tensions and pHa. After induction of general anaesthesia and general preparation, all patients were allowed to obtain stable haemodynamic states for at least 15 min, then pre-drug AP and HR were measured from each patient.

Protocol 1: Responses to phenylephrine and isoproterenol

Twenty patients received phenylephrine and another 20 received isoproterenol. In both groups 10 subjects had and 10 had not received clonidine premedication. After pre-drug measurements, $3 \mu\text{g}\cdot\text{kg}^{-1}$ phenylephrine *iv* or $0.02 \mu\text{g}\cdot\text{kg}^{-1}$ isoproterenol *iv* was administered as a bolus. Measurements of AP and beat-to-beat electronic calculation HR were made at one minute intervals for 10 min after the administration of drugs.

Protocol 2: Baroreflex responses

To assess the baroreflex sensitivity during pressor and depressor testing, each group of 20 patients (10 with and 10 without clonidine) was given $3 \mu\text{g}\cdot\text{kg}^{-1}$ phenylephrine to increase AP (same patients as in Protocol 1) or 2-3 $\mu\text{g}\cdot\text{kg}^{-1}$ nitroglycerin to decrease AP. After injection of phenylephrine or nitroglycerin, AP and ECG were sampled at 200 Hz using a computer equipped

TABLE Patients Characteristics, Arterial Blood Gases, Plasma Sodium, Potassium Concentrations, Blood glucose values, Haemodynamic Data of Pre-Premedication, Pre-Induction, and Pre-Drug

	<i>Phenylephrine</i>	<i>Control group</i> <i>Isoproterenol</i>	<i>Nitroglycerin</i>	<i>Phenylephrine</i>	<i>Clonidine group</i> <i>Isoproterenol</i>	<i>Nitroglycerin</i>
No. of patients	10	10	10	10	10	10
Clonidine ($\mu\text{g}\cdot\text{kg}^{-1}$)	0	0	0	4.83 ± 0.27	4.79 ± 0.31	4.81 ± 0.28
Sex (M/F)	4/6	5/5	4/6	5/5	6/4	5/5
Age (yr)	39 ± 13	44 ± 12	40 ± 10	41 ± 11	42 ± 13	38 ± 10
Height (cm)	161 ± 10	158 ± 8	161 ± 5	156 ± 7	158 ± 7	160 ± 6
Weight (kg)	58 ± 13	58 ± 8	60 ± 8	56 ± 9	52 ± 8	$53 \pm 5^*$
pHa	7.42 ± 0.04	7.43 ± 0.03	7.44 ± 0.04	7.45 ± 0.04	7.43 ± 0.05	7.46 ± 0.03
PaCO ₂ (mmHg)	36 ± 4	35 ± 3	35 ± 3	36 ± 5	37 ± 5	34 ± 2
PaO ₂ (mmHg)	259 ± 40	282 ± 39	258 ± 31	249 ± 35	238 ± 28	250 ± 27
Na (mEq·L ⁻¹)	135 ± 2	138 ± 3	139 ± 2	134 ± 3	135 ± 3	135 ± 3
K (mEq·L ⁻¹)	3.4 ± 0.3	3.7 ± 0.3	3.4 ± 0.2	3.6 ± 0.3	3.4 ± 0.2	3.6 ± 0.3
Glu (mg·dl ⁻¹)	99 ± 21	113 ± 52	100 ± 28	107 ± 18	102 ± 35	105 ± 20
<i>pre-premedication</i>						
SAP (mmHg)	124 ± 9	128 ± 12	127 ± 7	128 ± 10	125 ± 10	130 ± 10
DAP (mmHg)	70 ± 9	73 ± 9	75 ± 7	74 ± 12	72 ± 11	75 ± 11
MAP (mmHg)	88 ± 12	90 ± 7	85 ± 7	89 ± 9	87 ± 11	91 ± 12
HR (beats·min ⁻¹)	75 ± 8	71 ± 9	75 ± 7	73 ± 6	75 ± 6	76 ± 10
<i>pre-induction</i>						
SAP (mmHg)	125 ± 8	124 ± 16	129 ± 6	$111 \pm 8^*$	112 ± 16	$110 \pm 12^*$
DAP (mmHg)	70 ± 11	69 ± 10	70 ± 9	64 ± 9	64 ± 13	$54 \pm 6^*$
MAP (mmHg)	87 ± 9	87 ± 11	90 ± 7	$78 \pm 9^*$	80 ± 11	$79 \pm 6^*$
HR (beats·min ⁻¹)	73 ± 8	75 ± 7	75 ± 10	70 ± 4	$65 \pm 4^*$	68 ± 4
<i>pre-drug</i>						
SAP (mmHg)	$115 \pm 12^\dagger$	$111 \pm 13^\dagger$	$118 \pm 23^\dagger$	$101 \pm 6^*\dagger$	$103 \pm 15^\dagger$	$102 \pm 5^\dagger$
DAP (mmHg)	$65 \pm 10^\dagger$	$62 \pm 8^\dagger$	$61 \pm 13^\dagger$	$57 \pm 8^\dagger$	$58 \pm 11^\dagger$	$56 \pm 6^\dagger$
MAP (mmHg)	$83 \pm 12^\dagger$	$77 \pm 9^\dagger$	$80 \pm 14^\dagger$	$74 \pm 8^\dagger$	$76 \pm 10^\dagger$	$73 \pm 6^\dagger$
HR (beats·min ⁻¹)	$65 \pm 10^\dagger$	$64 \pm 4^\dagger$	$63 \pm 4^\dagger$	$57 \pm 4^*\dagger$	$57 \pm 5^*\dagger$	$58 \pm 5^*\dagger$

Values are mean $\pm$ 1 SD. (n = 10 in each group)

PaCO₂=arterial blood carbon dioxide tension; PaO₂=arterial blood oxygen tension; Na=plasma sodium concentration; K=plasma potassium concentration; Glu = blood glucose concentration.

pre-premedication=before administration of clonidine (clonidine group) or 1.5 hr before arrival in the operating room (control group)

pre-induction=before induction of anesthesia from each group; pre-drug=before injection of each drug:

SAP=systolic arterial blood pressure (mmHg); DAP=diastolic arterial blood pressure (mmHg);

MAP=mean arterial blood pressure (mmHg); HR=heart rate (beats·min⁻¹).

* $P < 0.05$ vs control group; $^\dagger P < 0.05$ vs pre-premedication group

Phenylephrine group of Protocol 1 and Protocol 2 are same group.

with an analogdigital converter, and both signals were stored on floppy disk and used for later graphical and statistical analysis.

Baroreflex sensitivity was expressed as the slope of the linear regression line derived by plotting R-R interval versus systolic AP (in msec of R-R interval of ECG over mmHg change in systolic AP; msec·mmHg⁻¹) over the increased or decreased period induced by phenylephrine or nitroglycerin.

In all patients, arterial blood was sampled and analyzed for pHa, PaCO₂, PaO₂, and plasma concentrations of sodium, potassium, and glucose before pre-drug measurements and 10 min after injection of drugs.

STATISTICAL ANALYSIS

Data were expressed as mean $\pm$ standard deviation (SD). Statistical comparisons among groups were performed using two-way analysis of variance (ANOVA) followed by an unpaired Student's t test with Bonferroni's corrections. The AP and HR responses to phenylephrine and isoproterenol were analyzed by using repeated-measure ANOVA (one-way ANOVA) followed by a paired Student's t test with Bonferroni's corrections for paired data in each group. An unpaired Student's t test was used to make comparisons between groups of the baroreflex slope of both pressor and depressor tests. A P -value < 0.05 was considered statistically significant.

Results

There were no differences among the six groups of patients with respect to sex distribution, age, height, or weight (Table). The doses of clonidine were 4.83 ± 0.27 for patients given phenylephrine, 4.79 ± 0.31 for those given isoproterenol, and $4.81 \pm 0.28 \mu\text{g}\cdot\text{kg}^{-1}$ for those given nitroglycerin (P : NS).

Haemodynamic data before premedication (pre-pre-medication), before induction of anaesthesia (pre-induction), and before administration of phenylephrine, isoproterenol or nitroglycerin (pre-drug) are presented in Table. Pre-drug values of SAP, DAP, MAP, and HR in all groups were less than pre-pre-medication values. Pre-drug values of HR in patients with clonidine were less than those in patients without clonidine, whereas the differences in pre-induction values of HR between patients with and without clonidine did not reach statistical significance except in the isoproterenol group. In the comparison of AP in patients with and without clonidine, clonidine was likely to decrease AP, but some of them were not statistically significantly different.

Protocol 1: Responses to phenylephrine and isoproterenol

Patients receiving clonidine had lower pre-drug HR and SAP than patients who did not receive clonidine, (Table: statistically significant only in phenylephrine group). Mean pre-drug values of PaO_2 , PaCO_2 , pH, plasma sodium and potassium concentrations, and blood glucose levels were similar among the groups (Table).

The AP and HR responses to $3 \mu\text{g}\cdot\text{kg}^{-1}$ phenylephrine were much greater in patients who received clonidine than in those who did not (Figures 1,2). Phenylephrine produced increases of AP lasting for only two or three minutes in control patients, but a prolonged increase for 10 min in patients receiving clonidine. The time course of HR decreases after phenylephrine differed somewhat; the decreases lasted no longer than five minutes in patients with clonidine, but lasted for up to 10 min in patients without clonidine. The magnitudes of the pressor responses to phenylephrine in patients with clonidine were greater than those in patients without clonidine (Figure 2). No patient showed severe bradycardia ($\text{HR} < 40 \text{ beat}\cdot\text{min}^{-1}$) after injection of phenylephrine in the present study.

The HR responses to $0.02 \mu\text{g}\cdot\text{kg}^{-1}$ isoproterenol *iv* were greater and more prolonged in patients with clonidine than in those without it (Figure 1). The magnitude of positive chronotropic responses to isoproterenol was greater in patients with clonidine (Figure 2). Isoproterenol produced a similar increase (about 10 mmHg) of AP 2-3 min after administration in both groups of patients.

FIGURE 1

above: Haemodynamic responses to $3 \mu\text{g}\cdot\text{kg}^{-1}$ phenylephrine in anesthetized patients receiving clonidine or no premedication. *below:* Haemodynamic responses to $0.02 \mu\text{g}\cdot\text{kg}^{-1}$ isoproterenol in anesthetized patients receiving clonidine or no premedication. SAP=systolic arterial blood pressure (mmHg); DAP=diastolic arterial blood pressure (mmHg); MAP=mean arterial blood pressure (mmHg); HR=heart rate ($\text{beats}\cdot\text{min}^{-1}$) pre-drug=before injection of phenylephrine or isoproterenol. Values are mean $\pm$ 1 SD. ($n=10$ in each group)

* $P < 0.05$ vs pre-drug value

† $P < 0.05$ vs control group

Protocol 2: Baroreflex responses

All regression slopes with correlation coefficients were > 0.80 . There was no differences in the slope of the pressor (phenylephrine) test between the groups: $3.77 \pm 1.08 \text{ msec}\cdot\text{mmHg}^{-1}$ in patients with clonidine and $4.41 \pm 1.66 \text{ msec}\cdot\text{mmHg}^{-1}$ in those without it. In

contrast, the slope of the depressor (nitroglycerin) test was depressed in patients with clonidine; the mean slopes of the depressor test in the patients with or without clonidine were 1.98 ± 0.73 and 3.68 ± 1.72 msec·mmHg⁻¹, respectively ($P < 0.05$).

Discussion

The major findings of the present study were that the pre-anaesthetic medication of clonidine, approximately $5 \mu\text{g}\cdot\text{kg}^{-1}$ *po*, enhanced AP and HR responses to both $3 \mu\text{g}\cdot\text{kg}^{-1}$ phenylephrine and $0.02 \mu\text{g}\cdot\text{kg}^{-1}$ isoproterenol and caused the arterial baroreflex sensitivity to attenuate when blood pressure decreased in anaesthetized humans. This observed enhancement of the pressor responses to phenylephrine agrees with previous results in patients receiving $5 \mu\text{g}\cdot\text{kg}^{-1}$ clonidine *po*.⁸ The positive chronotropic responses to isoproterenol in patients receiving clonidine were greater than in those who did not receive it.

Nishikawa *et al.*^{6,8} attributed this augmentation to clonidine-induced potentiation to α_1 -adrenoceptor-mediated vasoconstriction and also to supersensitivity of vascular receptors to which the drug was bound. Although the augmented pressor effect of phenylephrine observed in the present study was consistent with these previous reports, the response to β_1 -adrenergic agonist was also augmented in patients receiving clonidine as a pre-anaesthetic medication in the present study. As to HR responses, Nishikawa *et al.*⁹ observed that HR responses to atropine *iv* were markedly depressed in patients receiving $5 \mu\text{g}\cdot\text{kg}^{-1}$ clonidine. The discrepancy in the responses between isoproterenol and atropine may be due to their pharmacological property as well as their potential interaction with clonidine. Atropine increases HR primarily by suppression of postganglionic parasympathetic nervous activity,¹³ although the responses can be affected by a patient's age,¹⁴ sympathetic nerve activity,¹⁵ co-existing disease,¹⁶ basal HR,¹⁷ and the anaesthetic agents used.¹⁸ The attenuation of HR responses to atropine may be attributed primarily to decreased sympathetic nerve activity due to clonidine given preoperatively. Unlike atropine, isoproterenol stimulates the postsynaptic adrenergic receptors and thus has a significant effect on β_1 -adrenoceptors in patients receiving clonidine. Since clonidine has been reported to blunt the endocrine stress response and to reduce the increase in plasma catecholamine concentration,¹¹ it might be possible that a short term up-regulation of adrenoceptor-agonists occurs in patients receiving clonidine. A previous study on experimental postganglionic neurons noted that phenomena of supersensitivity, "central" and "peripheral" type, could occur

FIGURE 2

above: Percent changes in mean blood pressure after $3 \mu\text{g}\cdot\text{kg}^{-1}$ phenylephrine in anaesthetized patients receiving clonidine or no premedication.

below: Percent changes in heart rate after $0.02 \mu\text{g}\cdot\text{kg}^{-1}$ isoproterenol in anaesthetized patients receiving clonidine or no premedication.

Values are mean $\pm$ 1 SD. (n=10 in each group)

* $P < 0.05$ between the two groups

and is known to be moderate in degree and relatively nonspecific.¹⁹ Clonidine reduces central sympathetic outflow²⁰ and reduces release of noradrenaline from peripheral presynaptic terminals.^{4,11,12} After a central reduction of sympathetic activity induced by clonidine, it is reported that a clear short term up-regulation of β -adrenoceptors can occur in peripheral blood mononuclear cells.²¹ Leighton *et al.* reported that 5

μg isoproterenol *iv* increased HR approximately 45%²² and Tanaka also found that 3 μg isoproterenol *iv* increased HR approximately 30-40% in adult patients during isoflurane anaesthesia.²³ Compared with the HR responses in these previous studies, the present results in patients receiving clonidine showed much larger HR increases (approximately 60% at one minute after isoproterenol *iv*) to a smaller dose 0.02 $\mu\text{g}\cdot\text{kg}^{-1}$ isoproterenol (Figure 2). The studies of Leighton and Tanaka and our study differed in the ages of the patients and by the presence or absence of anaesthesia. Also, we could not determine shift of the dose-response curve because no dose-response study was made. Such differences suggest that up-regulation may occur in patients receiving clonidine. Thus the potential for an immediate up-regulatory effect occurring in patients receiving clonidine may contribute not only to the chronotropic effect of isoproterenol but also, partly, to the pressor effect of phenylephrine observed in the present study.

Clonidine administration in awake humans enhances arterial baroreflex sensitivity²⁴ while others¹² have demonstrated no effect. Muzi *et al.*¹² reported that, in awake healthy volunteers, 0.3 mg clonidine did not modify the ability of the baroreceptors to respond to AP perturbations but reduced sympathetic nerve activity and the sympathetic response to the cold pressor test. The present results using a similar dose of clonidine demonstrate that baroreflex responses during hypertensive (phenylephrine) stress remain unchanged, but those during hypotensive (nitroglycerin) stress are attenuated in anaesthetized patients. The reasons for this difference between our results and those of Muzi are unclear. The baroreflex response to increasing AP appears to be predominantly vagal and responses to decreased pressure predominantly sympathetic.¹⁰ Thus, we believe the suppression by clonidine of the release of noradrenaline from peripheral presynaptic terminals may be an underlying mechanism for the attenuation of the baroreflex response during hypotensive stress. In contrast, the lack of alteration in baroreflex response during hypertensive stress may imply that clonidine seems unlikely to produce suppression of parasympathetic nervous system activity. Although, in the present study, we measured neither sympathetic nerve activity nor plasma catecholamine concentration, we cannot exclude the possibility that the baroreflex response via nitroglycerin-induced hypotension could not be modulated with an interaction between circulating catecholamines, action and neuronal effects.

The ability of a vasopressor or vasodilator drug to produce vascular constriction or dilatation not only may depend on a specific mechanism of action of the

drug and the mode by which vasoconstriction or dilatation preceded but also may be critically influenced by anaesthesia. The effects of chronotropic or inotropic drugs would be similar to vasoactivators. Anaesthetic state *per se* should affect cardiovascular function directly, as well as the balance between sympathetic and parasympathetic nervous activities.²⁵ The present results, studied in ASA I or II patients, should not be extended to patients with cardiovascular diseases for whom clonidine medication is beneficial.^{3,4} Moreover, patients with another anaesthetic technique with other agents may have different combinations of effect of clonidine. We cannot exclude the possibility that a similar dose of clonidine given to anaesthetized patients with underlying cardiac or vascular disease would have a different result. Since atropine-resistant bradycardia in anaesthetized patients receiving clonidine is a clinical problem,³ the present results indicate that an easy restoration or an augmented chronotropic response and increase in AP to isoproterenol may be of use in the face of bradycardic and hypotensive episodes during anaesthesia.

In conclusion, oral 5 $\mu\text{g}\cdot\text{kg}^{-1}$ clonidine pre-anaesthetic medication augmented the haemodynamic responses to phenylephrine and isoproterenol, and attenuated baroreflex sensitivity to hypotension (reflex tachycardia). These effects of clonidine might be due to a reduction in the release of noradrenaline from peripheral presynaptic terminals. The findings imply that preanaesthetic medication of clonidine can exacerbate critical hypotension such as that caused by induction of anaesthesia or acute haemorrhage during surgery, but restoration of AP and HR can be achieved effectively by intravenous infusion of phenylephrine and isoproterenol, respectively in hypotensive and bradycardic states.

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