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Reduction of cardiovascular response to endotracheal intubation in normotensive patients by urapidil

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Abstract

Purpose. Urapidil is an antihypertensive drug with actions of α_1-receptor blockade and 5-HT_{1A} (5-hydroxytryptamine) receptor stimulation. Although many agents have been used to attenuate the cardiovascular response to endotracheal intubation, few of them are related to urapidil. This study was done to evaluate the effects of urapidil on reducing the cardiovascular response to intubation.

Methods. In this randomized, double-blind, placebo-controlled study, 30 ASA I–II adult surgical patients without cardiovascular disease were divided into two groups of 15 each, receiving either an i.v. bolus of 0.6 mg·kg^{-1} urapidil 5 min before intubation or an equivalent volume of saline as control. The heart rate and the systolic and diastolic blood pressure were determined intermittently for 5 min before and 10 min after intubation. The mean blood pressure, product of systolic blood pressure and heart rate, and coefficient of variation (CV) of these variables around intubation were calculated.

Results. Urapidil had no effects on the heart rate ($P > 0.05$), could effectively attenuate the increases in the diastolic and mean arterial pressures ($P < 0.05$) caused by intubation, but had a weak effect on the systolic pressure ($P > 0.05$) and its product with heart rate. In addition, the CV of the diastolic pressure and mean arterial pressure was greater ($P < 0.05$) in the urapidil group than in the control group, which meant that the induction procedure with urapidil was not more stable than that when saline was used as placebo.

Conclusion. The effects of urapidil on reducing the cardiovascular response to intubation are mild when uradipil is used 5 min before intubation. As urapidil mainly decreases diastolic blood pressure, an important determinant of cardiac blood supply, and it makes systolic, diastolic, and mean blood pressure fluctuate strongly during induction, we should be alert about its latent detrimental effect on patients, especially those with ischemic heart disease.

Key words: Endotracheal intubation, Cardiovascular response, Urapidil

Introduction

Endotracheal intubation during the induction of general anesthesia often causes cardiovascular responses, such as marked hypertension and tachycardia. A severe cardiovascular response is life-threatening to patients with systemic hypertension, coronary heart disease, intracranial aneurysm, or cerebrovascular disease [1,2]. Until now many agents or methods have been used to alleviate the cardiovascular response during intubation, including spraying the orolarynx or blocking the supralaryngeal nerve with local anesthetics, intravenous lidocaine [3,4], prostaglandin E_1 [5], sodium nitroprusside [6], esmolol [7], and others.

Urapidil is an antihypertensive drug of moderate potency with a half-life of 2.7 h [8] and an onset time within 15 min after intravenous administration. Its hypotensive effect may persist for 4 to 6 h [9]. It possesses a dual mechanism to reduce blood pressure by decreasing peripheral resistance by blocking α_1-receptors and by blunting the feedback of sympathetic adjustment by stimulating 5-HT_{1A} receptors in the brain [10]. Nowadays it is widely used in the treatment of hypertension. Its perioperative use includes controlling hypertension in the dissection of pheochromocytoma [11] and in coronary artery surgery [12]. However, few studies have been done to observe its effects on reducing the cardiovascular response to intubation, and the results of such studies are still preliminary [13]. Therefore we decided to evaluate the efficacy and safety of urapidil for attenuating cardiovascular responses to intubation.

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Materials and methods

The study protocol was approved by the Human Subjects Ethical Committee of the First Hospital of Beijing Medical University, and informed consent was obtained from the patients. Thirty patients without cardiovascular disease undergoing laparoscopic cholecystectomy, partial or subtotal gastrectomy, or enterectomy, graded as ASA I–II, were enrolled in the study. They were randomly divided into two groups of 15: one group received urapidil and the other received saline as control during anesthetic induction. All the patients were sedated with i.m. injection of 50 mg pethidine, 25 mg promethazine, and 0.3 mg scopolamine 30 min before induction. A radial artery catheter was inserted to measure systolic, diastolic, and mean blood pressure (Hewlett Packard Model 54S, Boeblingen, Germany). A five-lead electrocardiograph (Hewlett Packard Model 54S) was used to continuously monitor heart rate and monitor cardiac arrhythmia with lead II or V5. A pulse oximeter (Hewlett Packard Model 54S) was also used for all patients. Ringer's lactate solution was infused i.v. at a rate of $10\,ml \cdot kg^{-1} \cdot h^{-1}$ throughout the induction procedure. Induction was started with an i.v. bolus of $3\,\mu g \cdot kg^{-1}$ fentanyl, $0.6\,mg \cdot kg^{-1}$ atracurium, and then $5\,mg \cdot kg^{-1}$ thiopental over 1 min. After intubation, all the patients were mechanically ventilated with 100% oxygen at a proper frequency to keep end-tidal CO_2 within 30–35 mmHg (Datex, Helsinki, Finland). In the patients treated with urapidil, a dose of $0.6\,mg \cdot kg^{-1}$ [14] was injected i.v. over 15 s following thiopental administration. In the control patients, the equivalent volume of saline was injected i.v. instead. It is known that atracurium may cause release of 5-HT that may induce hypotension, as does as urapidil. However the incidence of hypotension with atracurium is rare and we used it in both groups to eliminate such influence. The intubation was successfully finished within 30 s by the same anesthesiologist, who was blinded to the agents used. None of the patients could recall the feeling of neuromuscular paralysis and mechanical ventilation after the operation. The arterial systolic, diastolic, and mean blood pressure and the heart rate were recorded in each patient before induction, 1, 2, 3, 4, and 5 min after induction, at intubation, and 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10 min after intubation. The product of the systolic blood pressure and the heart rate was calculated. As a measure of stable induction and intubation, the coefficient of variance (CV) of these observed variables was also calculated, with their standard deviations divided by their means. Only variables before intubation, at the time of intubation, and 1, 2, and 3 min after intubation were used for calculating the CV of systolic, diastolic, and mean blood pressure, the product of systolic pressure and heart rate, and the heart rate itself. The changes in these variables against time within the same group were analyzed by two-way ANOVA and the changes at time-matched points between the two groups were analyzed with the group t-test. P values less than 0.05 were considered statistically significant. Data are expressed as means ± SD.

Results

No differences were found between the two groups in age, body weight, height, and the sex ratio (Table 1).

Systolic blood pressure

Systolic blood pressure (SBP) values in patients 1, 2, 3, and 4 min after treatment with urapidil were significantly lower than those in control patients (Fig. 1). However, 5 min after urapidil administration and at the time of intubation, there were no significant differences in SBP between the two groups. SBP values at 1, 8, and 10 min after intubation were significantly lower in patients receiving urapidil than in control patients. SBP values at other time points varied little between the two groups. In general, SBP was below the level of induction at more time points in the urapidil group than in the control group.

Diastolic blood pressure

Diastolic blood pressure (DBP) values at every time point following administration of urapidil decreased much more than did those in the control group (Fig. 2). At the time of intubation and 1, 2, and 3 min thereafter, DBP increased with intubation, but not significantly

Table 1. Characteristics of patients in the two groups treated with urapidil or saline as control

Group	Age (yr)	Height (cm)	Weight (kg)	Male/female
Control	49.5 ± 12.7	163.0 ± 8.9	60.6 ± 9.3	6/9
Urapidil	49.4 ± 11.9	164.3 ± 8.9	58.1 ± 12.4	8/7

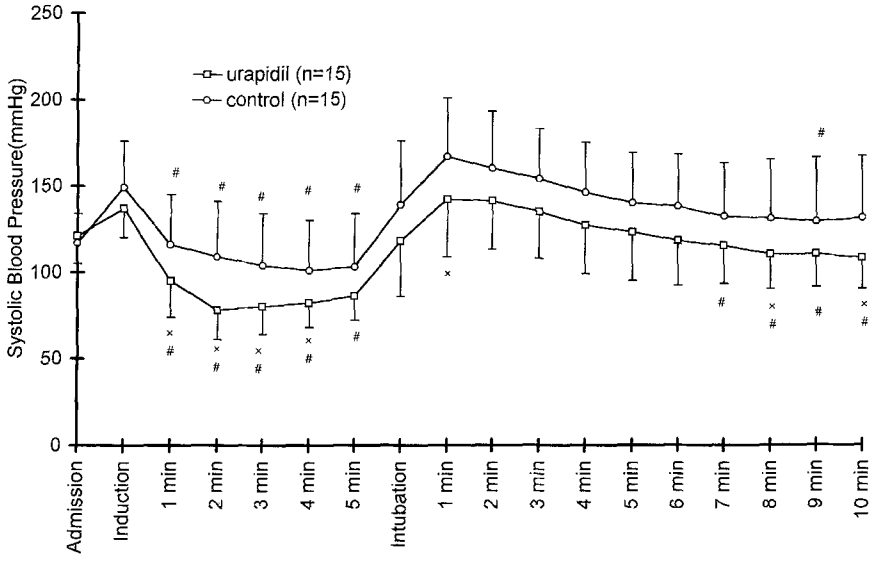

Fig. 1. Effect of urapidil on systolic blood pressure before and after intubation. $^{\times}P < 0.05$ *vs* the value at the same time between the two groups. $^{\#}P < 0.05$ *vs* the value at induction within the same group

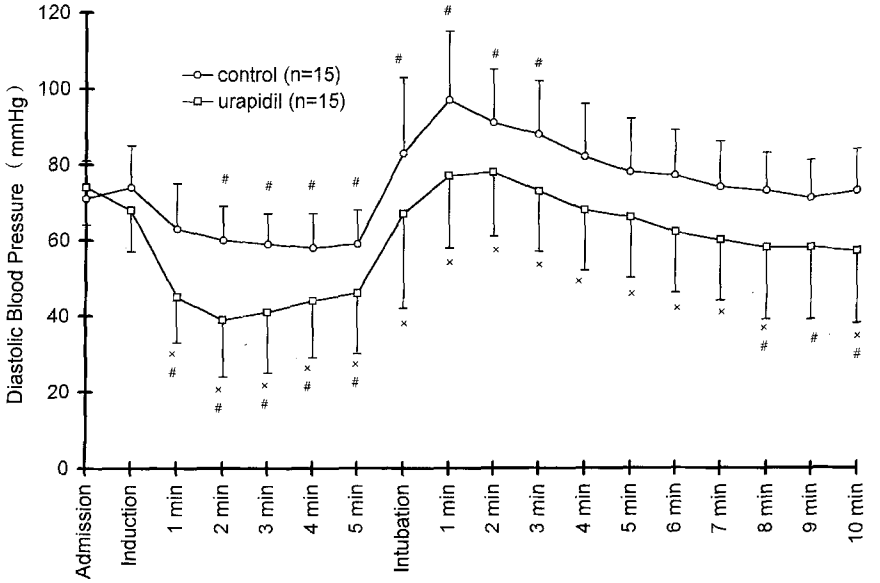

Fig. 2. Effect of urapidil on diastolic blood pressure before and after intubation. $^{\#}P < 0.05$ *vs* the value at induction within the same group. $^{\times}P < 0.05$ *vs* the value at the same time between the two groups

more than the level of induction in the urapidil group. However in the control group, DBP rose greatly after intubation and exceeded the level of induction at some points.

Mean blood pressure

The changes in mean blood pressure (MBP) were similar to those in DBP. MBP had significant lower values in the urapidil group than in the control group in the period between induction and intubation (Fig. 3). Following intubation, MBP rose to values significantly higher than the level of induction in the control group, but rose slightly in the urapidil group.

Heart rate

There were no significant differences in heart rate (HR) between the two groups throughout the duration of observation (Fig. 4). However, compared with the level of induction in the same group, HR rose significantly at intubation and 1, 2, and 3 min thereafter in the control group, but only rose 1 and 2 min after intubation in the urapidil group.

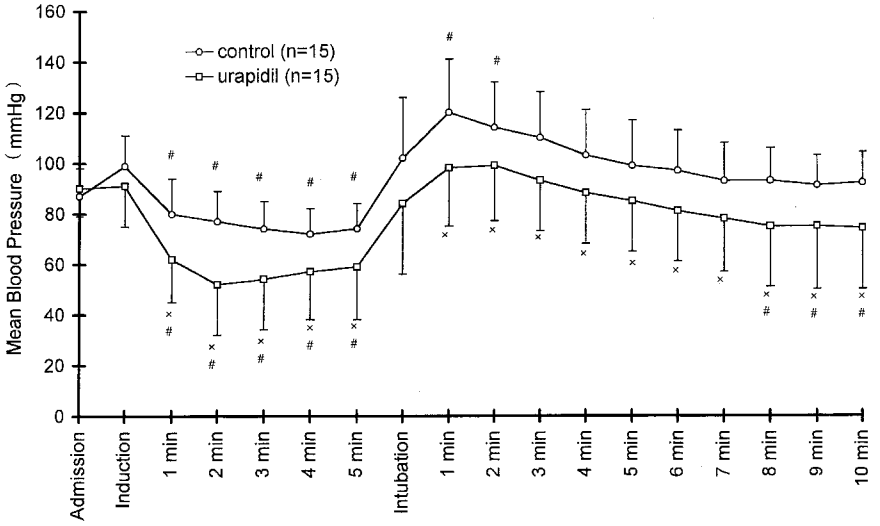

Fig. 3. Effect of urapidil on mean blood pressure before and after intubation. $^{\times}P < 0.05$ *vs* the value at the same time between the two groups. $^{\#}P < 0.05$ *vs* the value at induction within the same group

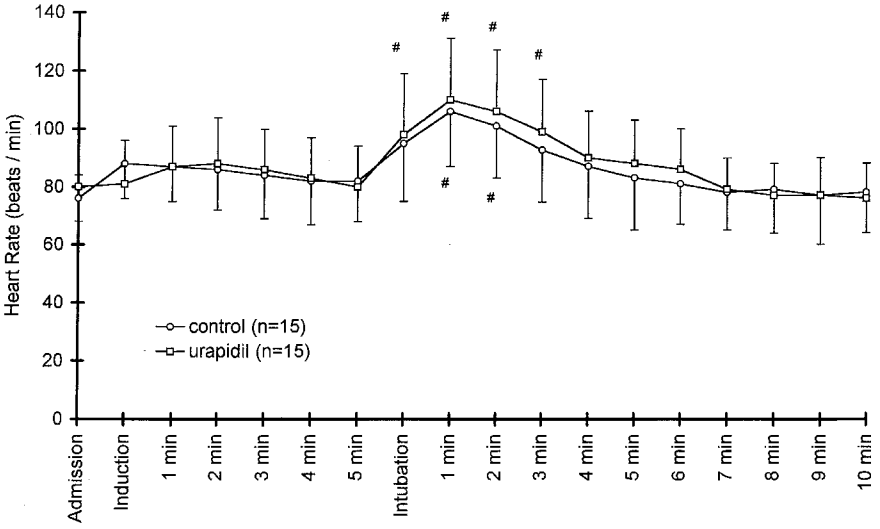

Fig. 4. Effect of urapidil on heart rate before and after intubation. $^{\#}P < 0.05$ *vs* the value at induction within the same group

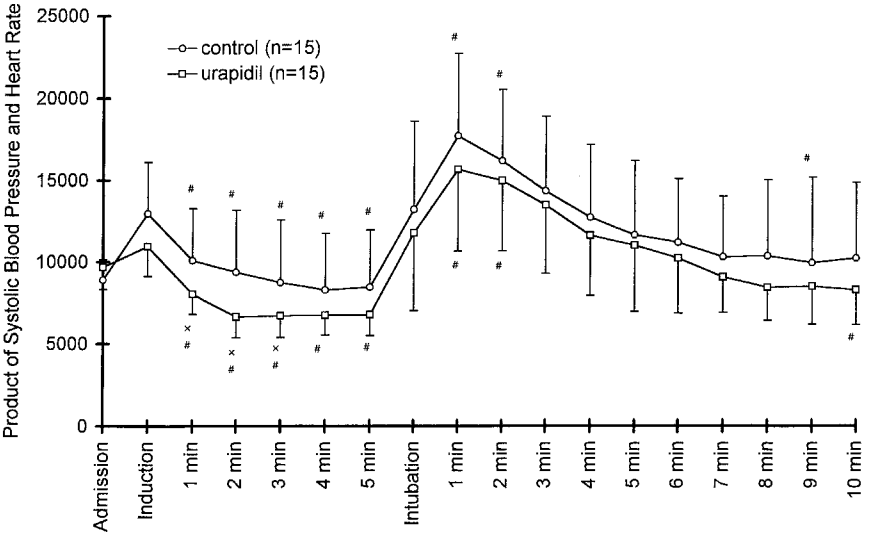

Fig. 5. Effect of urapidil on product of systolic blood pressure and heart rate before and after intubation. $^{\#}P < 0.05$ *vs* the value at induction within the same group. $^{\times}P < 0.05$ *vs* the value at the same time between the two groups

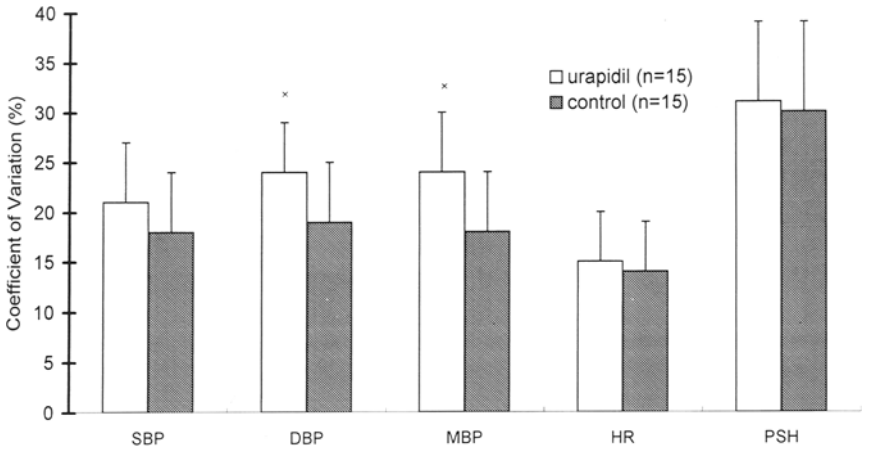

Fig. 6. Effects of urapidil on coefficients of variation of systolic blood pressure (SBP), diastolic blood pressure (DBP), mean blood pressure (MBP), Heart rate (HR), and product of systolic blood pressure and heart rate (PSH). $^{\times}P < 0.05$ between the two groups

Product of systolic blood pressure and heart rate

Compared with the control group, the product of systolic blood pressure and heart rate (PSH) significantly decreased 1, 2, and 3 min after urapidil administration, but the values at other time points thereafter differed little between the two groups (Fig. 5). In both groups, PSH decreased significantly 1, 2, 3, 4, and 5 min after induction and increased markedly 1 and 2 min after intubation.

Coefficient of variance of the variables

The CV of DBP and MBP was significantly greater in the urapidil group than in the control group (Fig. 6). There were few differences between the two groups in the CV of SBP, HR, and PSH.

Discussion

This study revealed that urapidil has little effect on HR. This implies that urapidil cannot depress the increases in HR caused by intubation and has no effect on *HR*, although arterial blood pressure is significantly reduced by its administration. This result is similar to that obtained by other researchers [15] and supports the advantage of urapidil, which, unlike some antihypertensive agents, does not induce reflective tachycardia. The mechanism for this action may be explained by the centrally mediated reduction of peripheral sympathetic tone, probably by stimulation of central 5-HT_{1A} receptors and by a blunting of baroreflex activity through the blocking of central α_1 receptors [16]. In addition, urapidil does not provoke blockade of the presynaptic α_2 receptors [15] and thus does not accelerate the release of noradrenaline.

In the urapidil group, SBP, DBP, and MBP changed in a manner similar to that in the control group, and they differed between the two groups only in amplitude. This phenomenon implies that urapidil can reduce but not eliminate the cardiovascular response to endotracheal intubation.

The SBP was reduced significantly by urapidil compared to that in the control group, and this effect was most marked within 4 min after its administration. However, this hypotensive effect was not strong enough to depress the elevations in SBP caused by the intubation, showing small intergroup differences at most time points after intubation.

Although the reducing effect of urapidil on SBP is weak in general, its effect on DBP was prominent, attenuating significantly the elevations in DBP caused by the intubation. This effect was also revealed by comparison of the time points with those at induction within the same group. The specific effect of urapidil on DBP has been also verified by other research [17]. As the blood supply to the left ventricle is principally determined by DBP [18], the marked decrease in DBP may readily lead to myocardial ischemia, especially in patients with ischemic cardiac disease.

MBP was reduced by urapidil similarly to SBP, but only slightly. Such an action on MBP may be attributed to its relatively mild action on SBP.

CV is a statistical concept describing the variation of a series of numbers against the mean. In this study, the CV of each variable was used to scale the fluctuations in the cardiovascular system, reflecting the degree of stability of induction. Small values of CV indicate a smooth induction. This index was first used in this study, and is surely helpful in evaluating the overall effect of urapidil. The CV values of DBP and MBP in the urapidil group were greater than those in the control group, and the values of other variables were also greater than those in the control group, although the differences were not statistically significant. Such results suggest that the hemodynamics during intubation with urapidil are not

more stable than those with saline as control. The severe fluctuations in arterial blood pressure with urapidil should be considered when used simply for the control of hypertension due to intubation. To attenuate such fluctuations by urapidil, intubation at the appropriate time, 2 min after urapidil administration, when the lowest hypotension occurred in the present study, might be helpful. The moment is also optimum for intubation, since the maximum muscle relaxation from atracurium was also obtained. Intubation at this time might avoid the compromise of sustained hypotension to patients. In fact, the time after urapidil administration that intubation is performed is so important that it may contribute to the discrepancy between our results and Quere's [13], who showed that at 3 min after urapidil administration, the elevations in both SBP and DBP due to intubation were significantly attenuated.

In summary, this study indicated that the effects of urapidil on reducing SBP, DBP, and MBP were different in potency. Generally, its effect on reducing the cardiovascular response to intubation is mild. It can hardly suppress elevations in SBP and has no effect on the increased HR due to intubation. As urapidil mainly decreases DBP, an important determinant of cardiac blood supply, and makes SBP, DBP, and MBP fluctuate strongly during induction, we should be alert to its latent detrimental effect on patients, especially those with ischemic heart disease.

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