· Original article ·

Moxonidine-induced transient pressor response is mediated by both I_1-imidazoline receptors and α_2-adrenoceptors in anesthetized spontaneously hypertensive rats

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[**ABSTRACT**] **Objective**: Clonidine, by activating peripheral α-adrenoceptors, produces transient pressor response after *i. v.* injection in anesthetized animals. Moxonidine, with at least 40-fold higher affinity to I_1-imidazoline receptors than to α_2-adrenoceptors, produces also a transient pressor response. This work was designed to investigate whether I_1-imidazoline receptors are involved in this pressor effect of moxonidine. **Methods**: Female spontaneously hypertensive rats (SHRs, aged 14-16 weeks) were anesthetized with urethane. To observe the transient pressor responses, moxonidine 0.1, 0.3, 1.0 mg/kg (intravenous, *i. v.*), 2.0 μg (intracerebroventricular, *i. c. v.*) and 1.0, 10.0 mg/kg (intragastric, *i. g.*) were administrated in different groups of rats. To evaluate the roles of α_1-adrenoceptors, α_2-adrenoceptors and I_1-imidazoline receptors in the transient pressor responses to moxonidine, prazosin (10.0 μg/kg), yohimbine (2.0 mg/kg), phentolamine (0.2 mg/kg), idazoxan (1.0 mg/kg) or yohimbine + idazoxan (2.0 mg/kg + 1.0 mg/kg) were intravenously given to the animals before moxonidine 0.3 mg/kg (*i. v.*). **Results**: It was found that *i. v.* moxonidine produced a greater pressor response than clonidine when producing a similar reduction of blood pressure. This effect of moxonidine was not influenced by prazosin, but was partly inhibited by yohimbine, phentolamine or idazoxan, and completely blocked by the combination of yohimbine and idzaxon. Neither *i. c. v.* injection nor *i. g.* administration of moxonidine induced transient pressor responses. **Conclusion**: The transient pressor response of *i. v.* moxonidine is mediated by both peripheral I_1-imidazoline receptors and α_2-adrenoceptors.

[**KEY WORDS**] moxonidine; clonidine; imidazoline; hypertesion; blood pressure

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Most of centrally acting antihypertensive drugs, such as clonidine and related imidazoline derivatives, moxonidine, mediate peripheral sympathoinhibition and reductions in blood pressure by central nervous system[1-4]. It is well known that intravenous (*i. v.*) clonidine elicits usually a biphasic blood pressure response, i. e. a transient pressure increase followed by a long lasting decrease[5-6]. Moxonidine, a second-generation central hypotensive agent, was also demonstrated to produce similar response when injected intravenously into conscious rabbits[7]. Both moxonidine and clonidine are I_1-imidazoline receptor agonists and possess different affinities for α_2-adrenoceptor. Moxonidine shows at least a 40 times higher affinity to I_1-receptor than to α_2-adrenoceptor, while there are only a few folds preferences for binding at the imidazoline I_1-receptor for clonidine, which has much higher affinity for α_2-adrenergic receptors than moxonidine. The transient pressor response of clonidine was ascribed to vasoconstriction induced by peripheral α-adrenoceptor[5-6]. However, little is available about the mechanisms of moxonidine involved in transient pressor response. In view of the fact that moxonidine has lower affinity for α_2-adrenoceptors and higher affinity for I_1-imidazoline receptors, we assumed that I_1-receptors might contribute to the pressor response of moxonidine. The present study was therefore designed to elucidate the role of I_1-imidazoline receptors and α-adrenoceptors in the pressor response of moxonidine in anesthetized SHRs.

1 MATERIALS AND METHODS

1.1 Animals and drugs Female SHRs, aged 14-16 weeks, provided by the Animal Center of the

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Second Military Medical University (Shanghai, China), were used in this study. The rats were housed with controlled temperature (23-25℃) and lighting (8:00-20:00 light, 20:00-8:00 dark) with free access to food and water. All the animals used in the experiment received humane care in compliance with institutional guidelines for health and care of experimental animals.

Moxonidine hydrochloride (Ya-Hu Pharm Ltd, Shanghai); clonidine hydrochloride, prazosin hydrochloride, yohimbine hydrochloride, phentolamine hydrochloride and idazoxan hydrochloride (Sigma Chemical Co., St Louis, MO, U. S. A.). All of them were dissolved with sterile saline and stored at 0-4℃. The antagonists were prepared fresh daily.

1.2　Surgical procedure　Rats were anesthetized with urethane (1.3-1.5 g/kg, *i. p.*). The level of anesthesia was determined by monitoring the response to toe or tail pinch, and further injections of the anesthetic were administered when necessary to guarantee an anesthetic state during the whole experimental procedure[8-9].

To investigate the transient pressor response induced by *i. v.* injection, a floating polyethylene catheter was inserted into the lower abdominal aorta *via* the femoral artery for blood pressure measurement; another catheter was placed into the femoral vein for drug administration. Instead of the femoral venous catheter, a stomach catheter was inserted when intragastric (*i. g.*) administration was given[10].

For intracerebroventricular (*i. c. v.*) injection, a stainless steel cannula (0.7 mm O. D.) was stereotaxically (coordinate: 1.0 mm posterior to bregma; 1.6 mm lateral from the midline; 4.0 mm below the surface of the skull) implanted into the lateral cerebral ventricle of the rat after the implantation of femoral arterious catheter. The cannula was secured to the skull with two jeweler's screws and dental cement. At the end of the experiment, the animals were killed with aeroembolism and 2 μl Evans blue solution was injected *via* the stainless steel cannula. The brains were removed for verification of the placement of the *i. c. v.* cannula. Only data from animals with the dye distributed in the lateral, third, and fourth ventricles were used[11-12].

1.3　Groups and determination of pressor response

Totally 83 SHRs, randomly divided into 14 groups, were used in this study. That is, 11 groups of *i. v.* injection: moxonidine (0.1, 0.3 and 1.0 mg/kg); clonidine (3.0, 10.0 and 30.0 μg/kg); moxonidine (0.3 mg/kg) after pretreatment with either 10.0 μg/kg prazosin[13], or 2.0 mg/kg yohimbine[14], or 0.2 mg/kg phentolamine[15], or 1.0 mg/kg idazoxan[14], or 2.0 mg/kg yohimbine plus 1.0 mg/kg idazoxan. Two groups of *i. g.* administration: moxonidine (1.0 and 10.0 mg/kg). One group of *i. c. v.* injection: moxonidine (2 μg/2 μl). There were 5 rats in *i. c. v.* injection group and 6 rats in the other groups. The *i. v.* doses of moxonidine (0.1, 0.3 and 1.0 mg/kg) and clonidine (3.0, 10.0 and 30.0 μg/kg) were chosen in order to achieve a similar blood pressure reduction.

After the surgery, blood pressure was continuously recorded using a technique described previously[16-17]. Briefly, the aortic catheter was connected to a blood pressure transducer. After about 1h habituation, blood pressure was continuously recorded for 30 min and digitized by a microcomputer. Systolic blood pressure (SBP), diastolic blood pressure (DBP) and heart period (HP) during the last 10 min were calculated and served as values of pre-drug administration. Then drugs were administered as designed groups. The antagonists were given 10 min (prazosin) or 5 min (the other antagonists) before moxonidine was administered intravenously. In all cases, a small *i. v.* volume (0.5 ml/kg) of drug solution was given to avoid the influence of blood volume increase induced by *i. v.* injection to pressor response. Pressor response was observed and blood pressure was continuously recorded for over 2 h or 6 h (*i. g.* administration) until a stable hypotensive state was reached. Pressor area, selected as the index to evaluate the transient pressor response, was calculated with analysis software (MPA 2000, Shanghai, China). The mean values of SBP, DBP and HP during a period of 10 min with the maximal blood pressure reduction after moxonidine or cloni-

dine injection were calculated and served as values of post-drug administration. To determine the effect of antagonists on blood pressure and HP, the mean values of SBP, DBP and HP during a period of 10 min (prazosin) or 5 min (the other antagonists) after the antagonists administration were calculated.

1.4 Statistical analysis All data were expressed as $\bar{x}\pm s$. Differences in SBP, DBP and HP before and after drug administration were tested for significance by paired Student's t-test. In all cases, $P<0.05$ was considered statistically significant.

2 RESULTS

2.1 Transient pressor response induced by *i. v.* clonidine or moxonidine *i. v.* clonidine (3.0, 10.0 and 30.0 μg/kg) produced pressor responses immediately after injections of clonidine; the pressor areas were 1.3±0.3, 2.1±0.6 and 5.6±1.3 mmHg·ks, respectively (Fig 1). Both SBP and DBP were significantly decreased (SBP: −11±3, −19±10, −34±12 mmHg; DBP: −9±4, −13±4, −20±12 mmHg), and HP was significantly prolonged dose-dependently.

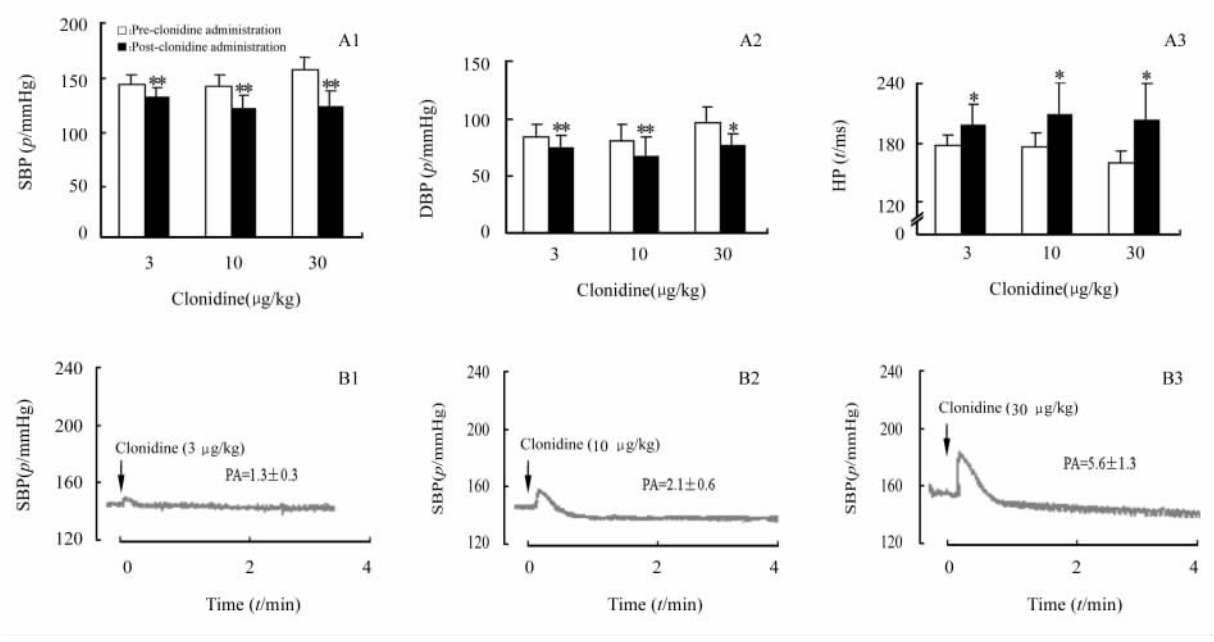

Fig 1 Transient pressor responses and the subsequent depressor effects of intravenous clonidine in anesthetized SHRs

A1-A3: Effects of clonidine on SBP, DBP and HP; B1-B3: Representative tracings of SBP showing the transient pressor effects induced by intravenous clonidine. SBP: Systolic blood pressure; DBP: Diastolic blood pressure; HP: Heart period; PA: Pressor area (mmHg·ks). 1 mmHg=0.133 kPa. $^*P<0.05$, $^{**}P<0.01$ *vs* pre-clonidine administration ($n=6$ in each group)

Compared with clonidine, moxonidine (0.1, 0.3, and 1.0 mg·kg^{-1}) produced much stronger pressor responses when inducing a similar reduction of blood pressure (Fig 2). The pressor areas of the three doses were 4.3±0.8, 26.4±4.6 and 97.1±12.6 mmHg·ks, respectively, which were about 3, 13 and 17 times of those induced by clonidine. The pressor amplitude was increased and pressor duration was prolonged when a larger dose was administrated. After the pressor phase, moxonidine produced significant and dose-dependent SBP reductions (−13±12, −18±9 and −33±13 mmHg). Moxonidine 0.1 mg/kg did not change DBP and HP. However, both moxonidine 0.3 and 1.0 mg/kg significantly decreased DBP (−7±4 and −17±7 mmHg) and prolonged HP (21%±14% and 35%±10%).

2.2 Effects of different receptor blockers on transient pressor response to moxonidine Fig 3 illustrated the influences of 4 antagonists on the transient pressor response induced by *i. v.* moxonidine (0.3 mg/kg) in anesthetized SHRs. Transient pressor response of moxonidine was not affected by prior injection of prazosin. The pressor area of prazosin-pretreated group (25.6±7.1 mmHg·ks) was similar to that without prazosin pretreatment

(26.4±4.6 mmHg · ks, Fig 2). Transient pressor response to moxonidine was attenuated by yohimbine, phentolamine or idazoxan; the pressor areas were 7.7±1.2, 12.3±2.7 and 8.1±1.3 mmHg · ks, respectively. However, pretreatment with the combination of yohimbine and idazoxan completely blocked the transient pressor response of *i. v.* moxonidine. These results indicated that both I_1-imidazoline receptors and α_2-adrenoceptors were involved in the transient pressor response of *i. v.* moxonidine.

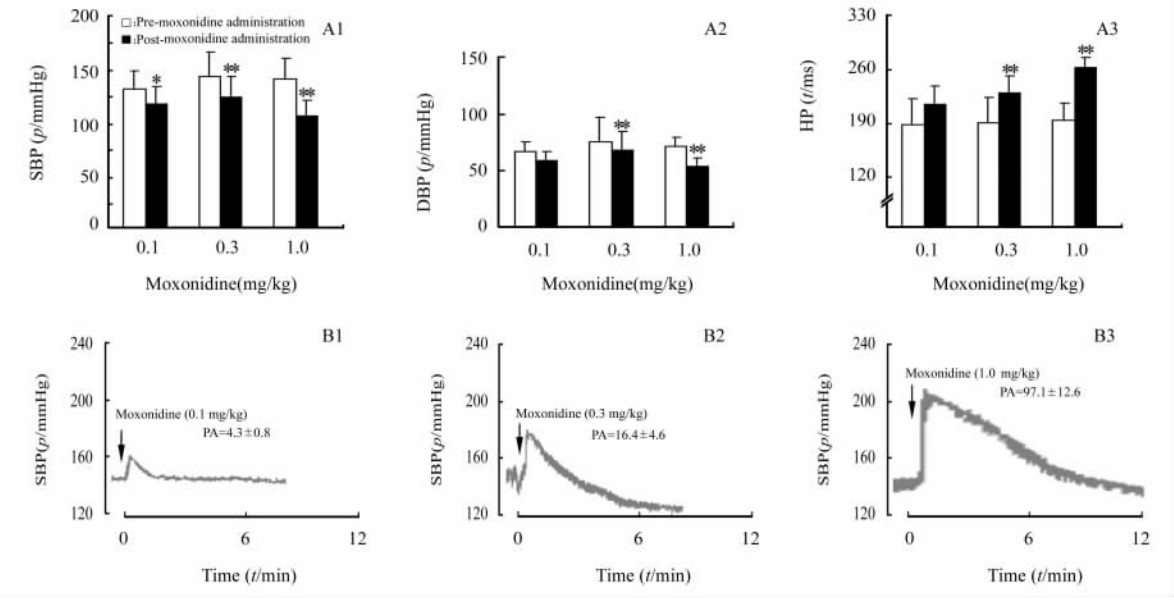

Fig 2　Transient pressor responses and the subsequent depressor effects of intravenous moxonidine in anesthetized SHRs

A1-A3: Effects of moxonidine on SBP, DBP and HP; B1-B3: Representative tracings of SBP showing the transient pressor effects induced by intravenous moxonidine. SBP: Systolic blood pressure; DBP: Diastolic blood pressure; HP: Heart period; PA: Pressor area (mmHg · ks). 1 mmHg=0.133 kPa. $^*P<0.05$, $^{**}P<0.01$ *vs* pre-moxonidine administration ($n=6$ in each group)

Effects of the 4 antagonists on blood pressure and HP were shown in Fig 4. SBP and DBP were significantly decreased by all the injections of antagonists. HP was significantly shortened by *i. v.* yohimbine and not influenced by other antagonists.

2.3　Transient pressor response induced by *i. c. v.* or *i. g.* moxonidine　Effects of *i. c. v.* moxonidine were shown in Fig 5 A. Compared with *i. v.* injection of 0.3 mg/kg moxonidine, *i. c. v.* injection (2 μg) caused a similar blood pressure reduction. HP was also prolonged significantly. However, *i. c. v.* moxonidine did not produced transient pressor response.

Effects of *i. g.* moxonidine on blood pressure and HP in anesthetized SHRs were shown in Fig. 5 B and Fig 5 C. Moxonidine at 1.0 mg/kg did not produce significant effects on blood pressure and HP. But 10 mg/kg moxonidine significantly decreased blood pressure (SBP: 25 ± 13 mmHg; DBP: 21±10 mmHg) and prolonged HP. However, neither dose of moxonidine caused transient pressor response after *i. g.* administration.

3　DISCUSSION

The main finding of this work was that transient pressor response induced by *i. v.* injection of moxonidine was mediated by both peripheral I_1-imidazoline and α_2-adrenoceptors.

From the first suggestion of the existence of imidazoline receptors, there has been a continuing debate over the hypotensive mechanism of clonidine and moxonidine, which were originally exclusively attributed to activation of central α_2-adrenoceptors and subsequent decrease of sympathetic nerve activity[18]. It is now widely recognized that both moxonidine and clonidine exerted their antihypertensive effects not only *via* activation of centralner-

vous α_2-adrenoceptors but also *via* I_1-imidazoline receptors[19]. Studies also suggested that peripheral presynaptic inhibition contributed to the overall reduction in sympathetic tone produced by these drugs and that the central action was perhaps not sufficient for the blood pressure decrease[20-22]. Besides the hypotensive effect, there are interesting phenomena after moxonidine or clonidine injection, i. e. the biphasic blood pressure responses, which were extensively confirmed[5-6]. However, up to now, no special researches focused on the transient pressor response itself.

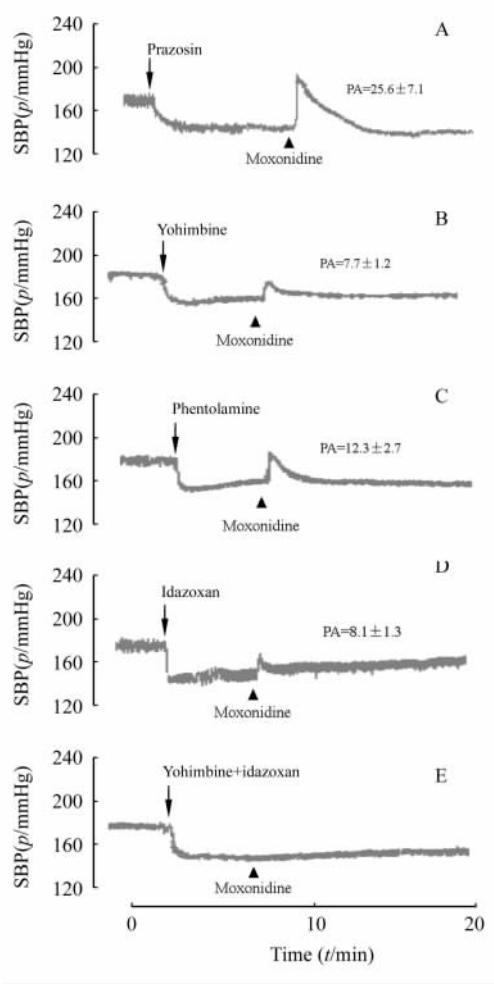

Fig 3 Representative tracings of SBP showing the effects of 4 antagonists on the transient pressor responses induced by moxonidine (0.3 mg/kg) in anesthetized SHRs

A: Effect of prazosin; B: Effect of yohimbine; C: Effect of phentolamine; D: Effect of idazoxan; D: Effect of yohimbine+idazoxan. The doses were 10.0 μg/kg for prazosin, 2.0 mg/kg for yohimbine, 0.2 mg/kg for phentolamine and 1.0 mg/kg for idazoxan. All drugs were given intravenously. PA: Pressor area (mmHg · ks)

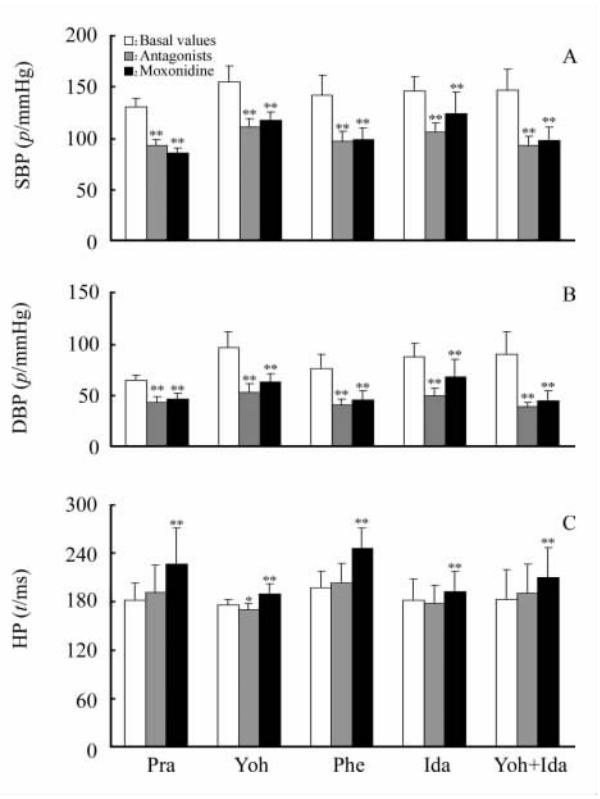

Fig 4 Effects of different antagonists and moxonidine on SBP(A), DBP(B) and HP(C) in anesthetized SHRs

The doses were 10.0 μg/kg for prazosin, 2.0 mg/kg for yohimbine, 0.2 mg/kg for phentolamine, 1.0 mg/kg for idazoxan and 0.3 mg/kg for moxonidine. All drugs were given intravenously. Pra: Prazosin; Yoh: Yohimbine; Phe: Phentolamine; Ida: Idazoxan; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; HP: Heart period. $^*P<0.05$, $^{**}P<0.01$ *vs* basal values ($n=6$ in each group)

In the present study, it was found that *i. v.* injection of moxonidine in anesthetized SHRs produced transient pressor response in a dose-dependent manner, which lasted 0.5-9.0 min with the magnitude from 20 to 80 mmHg. This pressor response of moxonidine was much obvious than that induced by clonidine, which lasted about 30 s with the magnitude from 10 to 35 mmHg. As far as we know, this is the first report to describe in detail the characteristics of transient pressor response by *i. v.* moxonidine. *i. c. v.* moxonidine did not produce transient pressor response, indicating that central mechanism was not involved in this effect. Transient pressor responses were also not found after intragastric administrations of moxonidine (1.0 mg/kg and 10.0 mg/kg). Clinically, moxonidine is

mostly administered orally. As moxonidine has a greater pressor effect, it should not be administered intravenously.

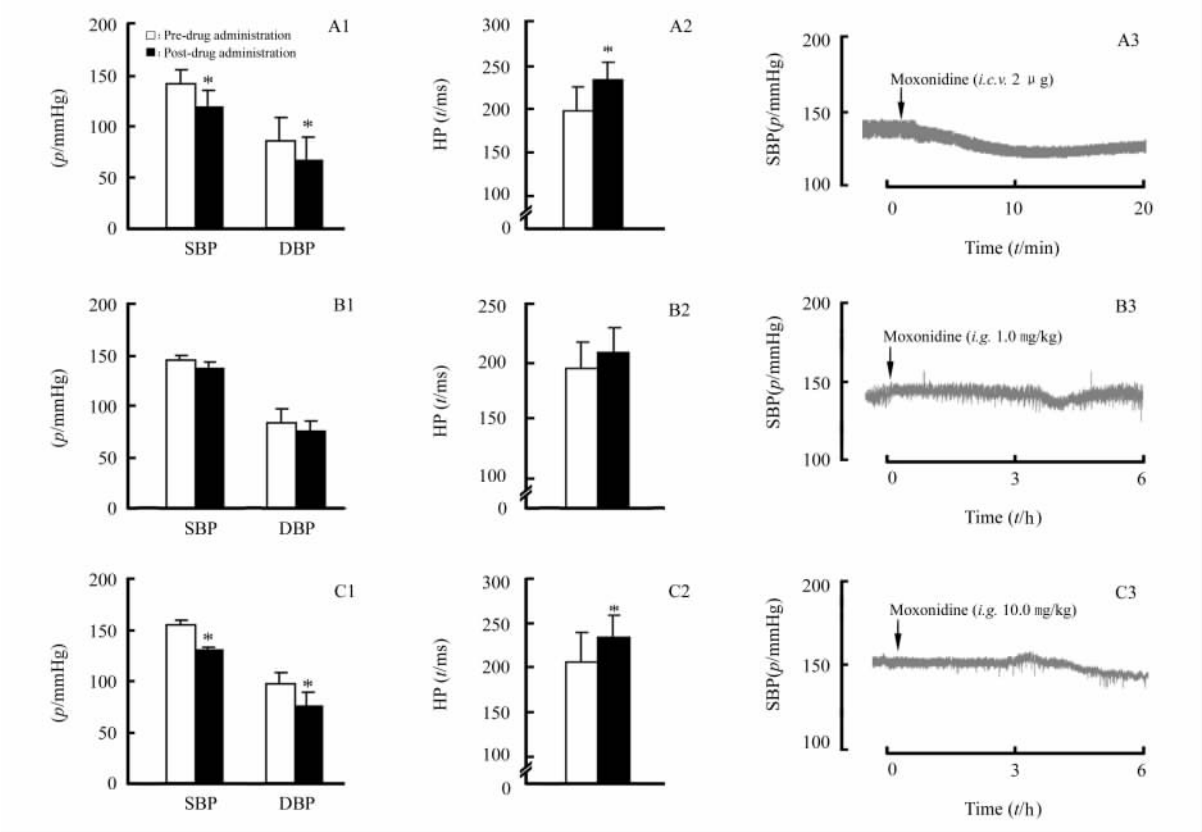

Fig 5　Intracerebroventricular (*i. c. v.*) and intragastric (*i. g.*) moxonidine did not produce transient pressor response in anesthetized SHRs

A1-A3: *i. c. v.* moxonidine (2 μg; 2 μl); B1-B3: *i. g.* moxonidine (1.0 mg/kg); C1-C3: *i. g.* moxonidine (10.0 mg/kg); SBP: Systolic blood pressure; DBP: Diastolic blood pressure; HP: Heart period. * $P<0.05$ *vs* pre-moxomdine administration ($n=5$ in A1-A3; $n=6$ in B1-B3 and C1-C3)

Considering the higher affinity for I_1-imidazoline receptors and the larger pressor response of moxonidine than those of clonidine, we assumed that I_1-imidazoline receptor might be involved in the transient pressor response induced by moxonidine. The results that, prior injection of selective α_1-adrenoceptor antagonist prazosin did not affect the transient pressor response produced by *i. v.* moxonidine and pretreatment of α_1/α_2-adrenergic receptor antagonist phentolamine partly blocked it, indicated that it was α_2-adrenoceptors but not α_1-adrenoceptors that were involved in the pressor response. The findings that, prior injection of either α_2-adrenoceptor antagonist yohimbine or I_1-imidazoline receptor antagonist idazoxan partly blocked the transient pressor response of *i. v.* moxonidine and pretreatment with yohimbine plus idazoxan completely blocked this response, implicated that both I_1-imidazoline receptors and α_2-adrenoceptors were involved in this response. Furthermore, the result that *i. c. v.* moxonidine did not produce pressor response suggested that central I_1-imidazoline receptors or α_2-adrenoceptors were not involved in this response. These results indicated that transient pressor response induced by *i. v.* moxonidine in anesthetized SHRs was mediated by both peripheral I_1-imidazoline receptor and α_2-adrenoceptor.

Information about the effects of moxonidine on blood vessels is still inadequate. Zhu et al verified that moxonidine acted on α_2-adrenoceptors to mediate contraction of dog saphenous veins and α_1-adrenoceptors were not involved in the contractile re-

sponse[23]. In contrast, other studies have reported α_1-adrenoceptors contributed to the contractile response of rat-tail artery to moxonidine[24-25]. In the present work, it was demonstrated that peripheral α_2-adrenoceptors were involved in the transient pressor response induced by *i. v.* moxonidine in anesthetized SHRs and α_1-adrenoceptors did not participate in this effect. This was not consistent with previous reports that activation of α_1-adrenoceptors contributes to vasoconstrictive effects of moxonidine. The possible reasons may be: (1) these previous reports were *in vitro* studies and aimed on a certain organ or tissue; the present study was an *in vivo* experiment. (2) the difference at receptor level caused by different species. Langer et al demonstrated that α_2-adrenoceptors in smooth muscle mediated vasoconstrictor responses to a greater extent in SHRs than in the corresponding normotensive Wystar-Kyoto rats[26]. The present study was carried out in SHRs, and previous studies were performed with normotensive Sprague-Dawley rats. (3) the transient pressor response of moxonidine might be mediated by the contraction of small arteries. It was reported that in small arteries contractile responses were mediated by α_2-adrenoceptors, whereas in large arteries this effect was mediated more by α_1-adrenoceptors[27].

I_1-imidazoline receptors are mainly found in brainstem rostro-ventrolateral medulla, which plays an important role in the antihypertensive effect of clonidine-like agents[28-29]. In peripheral organs relevant to the blood pressure control, such as kidney and heart, the distribution of I_1-imidazoline receptors was also found[30]. Mukaddam-Daher and Gutkowska demonstrated that injections of moxonidine increased sodium and water excretion by selective activation of imidazoline receptors[31], which may help to decrease blood pressure. So it is not clear from which organ or organs, the activation of I_1-imidazoline receptors produces transient pressor response. Most probably, there is the distribution of I_1-imidazoline receptors in blood vessels, especially in small arteries, and activation of these receptors may produce vasoconstriction. This hypothesis remains to be confirmed.

In this study, pressor area but not pressor magnitude was used. These two parameters were consistent in evaluation of the transient pressor response. When pressor area was used, not only pressor amplitude but also pressor duration was considered.

In conclusion, this study demonstrated the transient pressor response induced by *i. v.* moxonidine in anesthetized SHRs was mediated by both peripheral I_1-imidazoline receptors and α_2-adrenoceptors.

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I_1-咪唑啉受体和 α_2 受体介导大鼠静脉注射莫索尼定的瞬时升压作用

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[**摘要**] **目的**:考察哪些受体参与了莫索尼定的瞬时升压作用。**方法**:雌性自发性高血压大鼠(SHR)采用乌拉坦麻醉。分别经静脉给予可乐定(3, 10, 30 μg/kg)、莫索尼定(0.1, 0.3, 1.0 mg/kg),经侧脑室给予莫索尼定或经胃管给予莫索尼定(1.0, 10.0 mg/kg),观察瞬时升压现象的发生情况;莫索尼定(0.3 mg/kg)静脉注射前预注射哌唑嗪(10.0 μg/kg)、育亨宾(2.0 mg/kg)、酚妥拉明(0.2 mg/kg)、咪唑克生(1.0 mg/kg)或育亨宾+咪唑克生(2.0 mg/kg+1.0 mg/kg),观察莫索尼定瞬时升压作用的变化情况,确定 α_1 受体、α_2 受体和 I_1-咪唑啉受体在莫索尼定瞬时升压中的作用。**结果**:在降压程度相当的情况下,静脉注射莫索尼定的瞬时升压作用比可乐定强大得多。莫索尼定的瞬时升压作用不受哌唑嗪的影响,但可被育亨宾、酚妥拉明或咪唑克生部分阻断,而被育亨宾+咪唑克生完全阻断。莫索尼定侧脑室和胃管给药不产生瞬时升压现象。**结论**:静脉注射莫索尼定引起的瞬时升压作用是由外周 α_2 受体和 I_1-咪唑啉受体共同介导的。

[**关键词**] 莫索尼定;可乐定;咪唑啉; 高血压;血压
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