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Influence of Mild Hypothermia on Clonidine-Induced Cardiovascular Responses in the Pentobarbital-Anesthetized Rat

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This study was carried out to determine whether the effects of an α_2-adrenoceptor agonist, clonidine, on mean arterial pressure (MAP) and heart rate (HR) are influenced by mild hypothermia. Experiments were performed in respiration-controlled and spontaneously breathing pentobarbital-anesthetized rats. Rectal temperature was maintained at $37.5 \pm 0.3^{\circ}C$ for normothermic groups or at $35.2 \pm 0.3^{\circ}C$ for mild hypothermic groups. Intravenous injection of clonidine (1 and 2 μg/kg) produced depressor and bradycardic responses in spontaneously breathing rats under both normothermic and mild hypothermic condition: a decrease in MAP was not altered but bradycardic response was significantly augmented in the mild hypothermic group as compared with the normothermic group. Under the respiration-controlled condition, the hypotensive effect of clonidine (2 μg/kg) was reduced, whereas the bradycardic effect was increased in mild hypothermic rats as compared with normothermic rats. Both hypotensive and bradycardic effects of clondine (2 μg/kg) were blocked by pretreatment with an α_2-adrenoceptor antagonist, yohimbine (0.5 mg/kg), in both thermal conditions. Yohimbine (0.5 mg/kg, i.v.) alone produced signifcantly an increase in heart rate in the mild hypothermic group than in the normothermic group. Pretreatment with a muscarinic receptor antagonist, atropine methylnitrate (1 mg/kg, i.v.), attenuated the bradycardic effect of clonidine in the mild hypothermic group but not in the normothermic group. These results suggest that clonidine-induced bradycardia is amplified by mild hypothermia probably through an increased parasympathetic activity.

Key Words: Clonidine, Mild hypothermia, Heart rate, Blood pressure, Perioperative period

INTRODUCTION

It is well-known that classical α_2-adrenoceptor agonists, such as clonidine, produce both hypotension and bradycardia (van Zwieten, 1997). Several lines of evidence have demonstrated that hypotensive effect of the α_2-adrenoceptor agonist is mediated by supraspinal mechanisms (Timmermans et al, 1981; Punnen et al, 1987; MacMillan et al, 1996).

α_2-Adrenoceptor agonists are now being used clinically for perioperative indications. Since sedation and anxiolysis are necessary attributes of premedication for general anesthesia, administration of α_2-adrenoceptor agonists suits this purpose well (Wright et al, 1990; Carabine et al, 1991; Kumar et al, 1992). Also, clonidine reportedly has the postoperative analgesic effect (Hayashi & Maze, 1993). Moreover, it has been suggested that α_2-adrenoceptor agonists might be effective in blunting the perioperative stress response, including tachycardia and hypertension (Flacke et al, 1987; Ghignone et al, 1987) and that clonidine may have perioperative antiischemic effects (Dorman et al, 1993). Therefore, the clinical application of α_2-adrenoceptor agonists during anesthesia will be steadily increased.

Unintended perioperative mild hypothermia occurs in approximately one-half of all surgical patients (Slotman et al, 1985; Frank et al, 1997). Mild hypothermia which frequently occurs in perioperative

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patients may be due to (1) exposure to cold operating environment; (2) impaired thermoregulatory function during anesthetic state; (3) vasodilation induced by some anesthetics (Frank et al, 1992; Sessler et al, 1993). It is well known that body temperature can influence responses to many drugs (Weihe, 1973). In vitro studies using isolated blood vessels also suggest that temperature may alter responses to α_2-adrenoceptor stimulation. For an example, lowering of the bath temperature from 37°C to 24°C augmented the contractile responses of isolated human or canine cutaneous veins to α_2-adrenoceptor agonists, presumably because of an increased receptor affinity (Gantzos & Neubig, 1988; Roberts et al, 1989; Arner & Hogestatt, 1990). Taken together, these results suggest that pharmacological effects of α_2-adrenoceptor agonists may be augmented during hypothermia. This hypothesis is supported by a previous finding showing that the bradycardic effect of a selective α_2-adrenoceptor agonist, mivazerol, was amplified during mild hypothermia (Kim et al, 1997).

The present study was, therefore, designed to determine whether mild hypothermia influences the effects of clonidne, an α_2-adrenoceptor agonist, on mean arterial pressure (MAP) and heart rate (HR) in pentobarbital-anesthetized rats. In the present study rectal temperature of rats was maintained at 37.5±0.3°C for normothermia and at 35.2±0.3°C because mild perioperative hypothermia (approximately 2°C below the normal body temperature) is common in

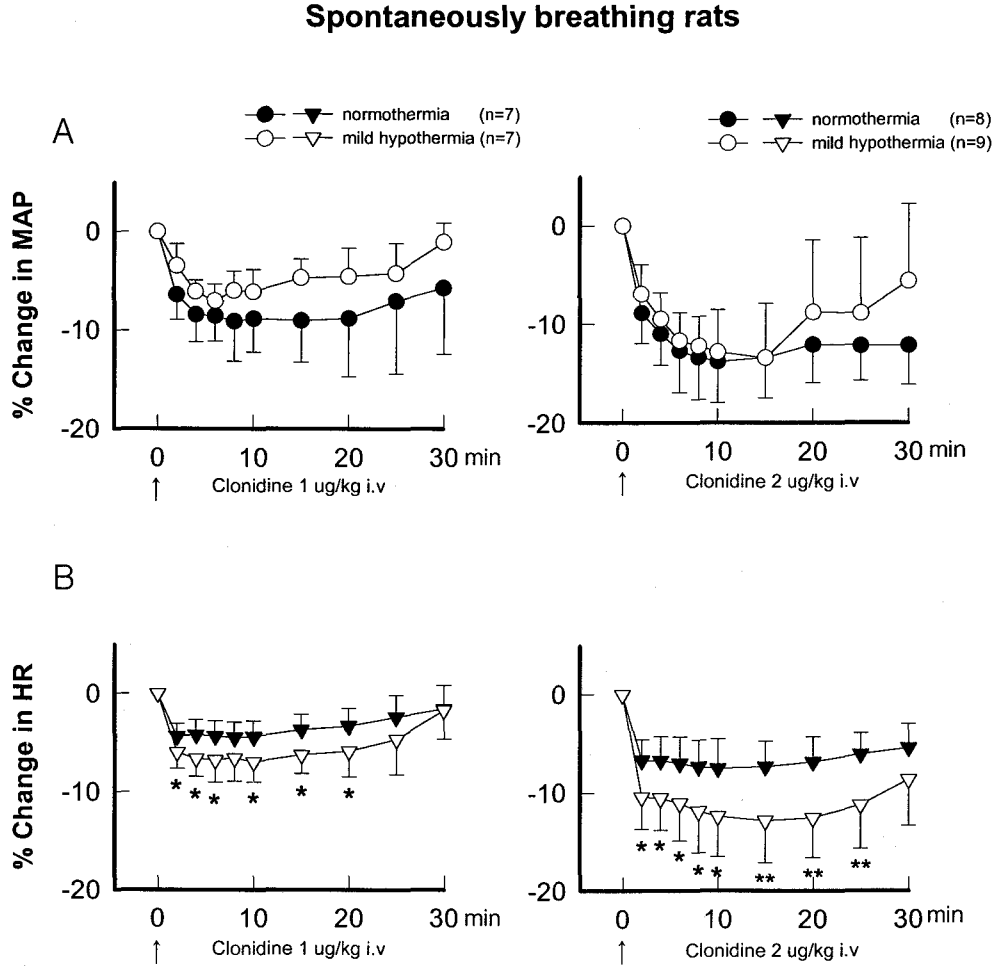

Fig. 1. Effects of intravenous clonidine on mean arterial pressure (MAP) between the normothermic and mild hypothermic groups in spontaneously breathing pentobarbital-anesthetized rats. Results are expressed as mean±SD. $*P<0.05$ and $**P<0.01$ vs. the normothermic group.

general surgical patients (Frank et al, 1992; Kurz et al, 1996).

METHODS

The experiments were performed on male Sprague Dawley rats weighing between 250 and 300 g. Rats were anesthetized with sodium pentobarbital; initially with 60 mg/kg i.p and then, 30 minutes later, supplementally with 15 mg/kg i.p to maintain anesthesia throughout the experiments. The trachea was cannulated with a polyethylene tube. Femoral artery and vein were cannulated for the measurement of blood pressure and heart rate, and drug administration respectively. Experiments were performed on respiration-controlled and spontaneously breathing pentobarbital-anesthetized rats. Under respiration-controlled condition, the rats were maintained under assisted air respiration by a ventilator (Model 683, Harvard, England). Rectal temperature was monitored by a body temperature controller (CMA150, Carnegie Medicin, Sweden) and maintained with a heating lamp at $37.5 \pm 0.5^{\circ}C$ for normothermia. The hypothermic rats cooled spontaneously and were then maintained at $35.2 \pm 0.3^{\circ}C$ by intermittent use of a heating lamp.

Blood pressure and heart rate were continuously monitored via the femoral artery catheter connected to a transducer of a BP analyzer (Digi-Med Model 400, Micro-Med, USA). The femoral vein catheter was connected to a syringe mounted on a syringe pump (Model 361, Sage, USA) to inject drugs continuously. Clonidine, atropine methylnitrate and yohimbine were obtained from Sigma chemical company (USA). Clonidine and atropine were dissolved in saline (0.9% NaCl).

Data were expressed as mean $\pm$ SD. An unpaired t-test was used to evaluate differences between the normothermic and the mild hypothermic groups. Statistical significance was accepted for $P<0.05$.

RESULTS

Baseline MAP and HR

Under the spontaneously breathing condition, the resting MAP of the normothermic rats was 137.0 ± 8.0 mmHg (n=15) and of the mild hypothermic rats was 119.8 ± 7.5 mmHg (n=16). These values were significantly different ($P<0.01$). And the resting level of HR in the normothermic and mild hypothermic rats averaged 411.8 ± 17.5 bpm (beats per min; n=15) and 339.7 ± 24.1 bpm (n=16), respectively. These values were significantly different ($P<0.01$).

Under the respiration-controlled condition, the resting MAP of normothermic rats was 145.0 ± 7.4 mmHg (n=24) and of the mild hypothermic rats was 140.1 ± 7.9 mmHg (n=24). There was no significant difference between the normothermic and mild hypothermic rats in terms of resting MAP. The resting level of HR in the normothermic and mild hypothermic rats averaged 393.6 ± 20.2 bpm (n=24) and 354.3 ± 28.9 bpm (n=24), respectively. These values were significantly different ($P<0.01$).

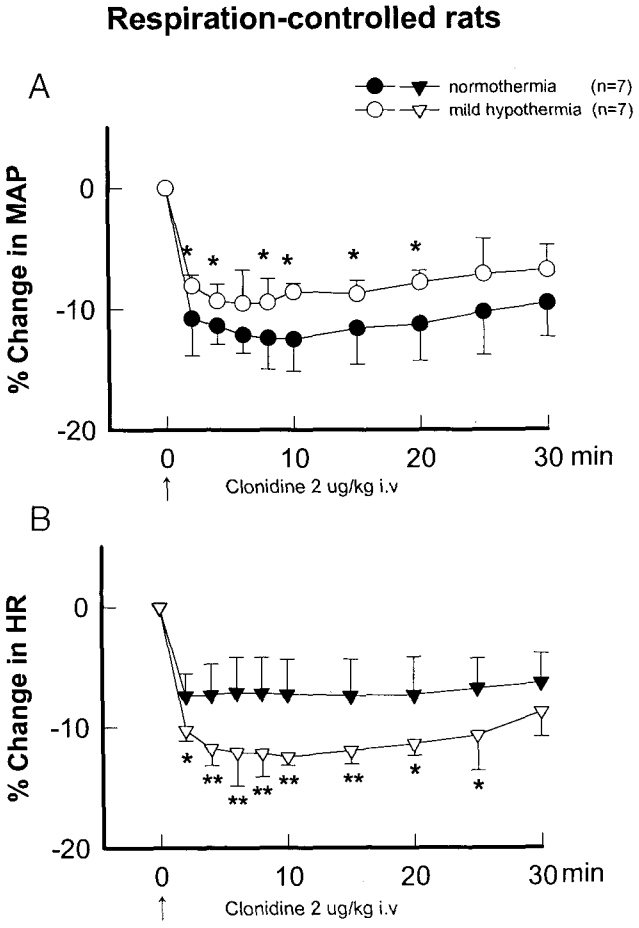

Fig. 2. Effects of intravenous clonidine (2 μg/kg) on mean arterial pressure (MAP; A) and heart rate (HR; B) between the normothermic and mild hypothermic groups in respiration-controlled rats anesthetized with pentobarbital. Results are expressed as mean $\pm$ SD. $^{*}P<0.05$ and $^{**}P<0.01$ vs. the normothermic group.

Effects of clonidine on MAP and HR in spontaneously breathing rats

Intravenous injection of clonidine (1 and 2 μg/kg) produced a profound reduction of MAP and HR in both normothemic and mild hypothermic rats. There was no significant difference in terms of the clonidine-induced decrease in MAP between the normothermic and mild hypothermic groups (Fig. 1A). However, the decrease in HR evoked by clonidine was significantly greater in mild hypothermic rats than in normothermic rats ($P<0.01$, Fig. 1B).

Effects of clonidine on MAP and HR in respiration-controlled rats

To exclude secondary change in MAP which can be derived from the breathing pattern, we performed next experiments under the respiration-controlled condition. Intraveous injection of clonidine (2 μg/kg) caused depressor and bradycardic responses in both normothermic and mild hypothermic rats. The de-

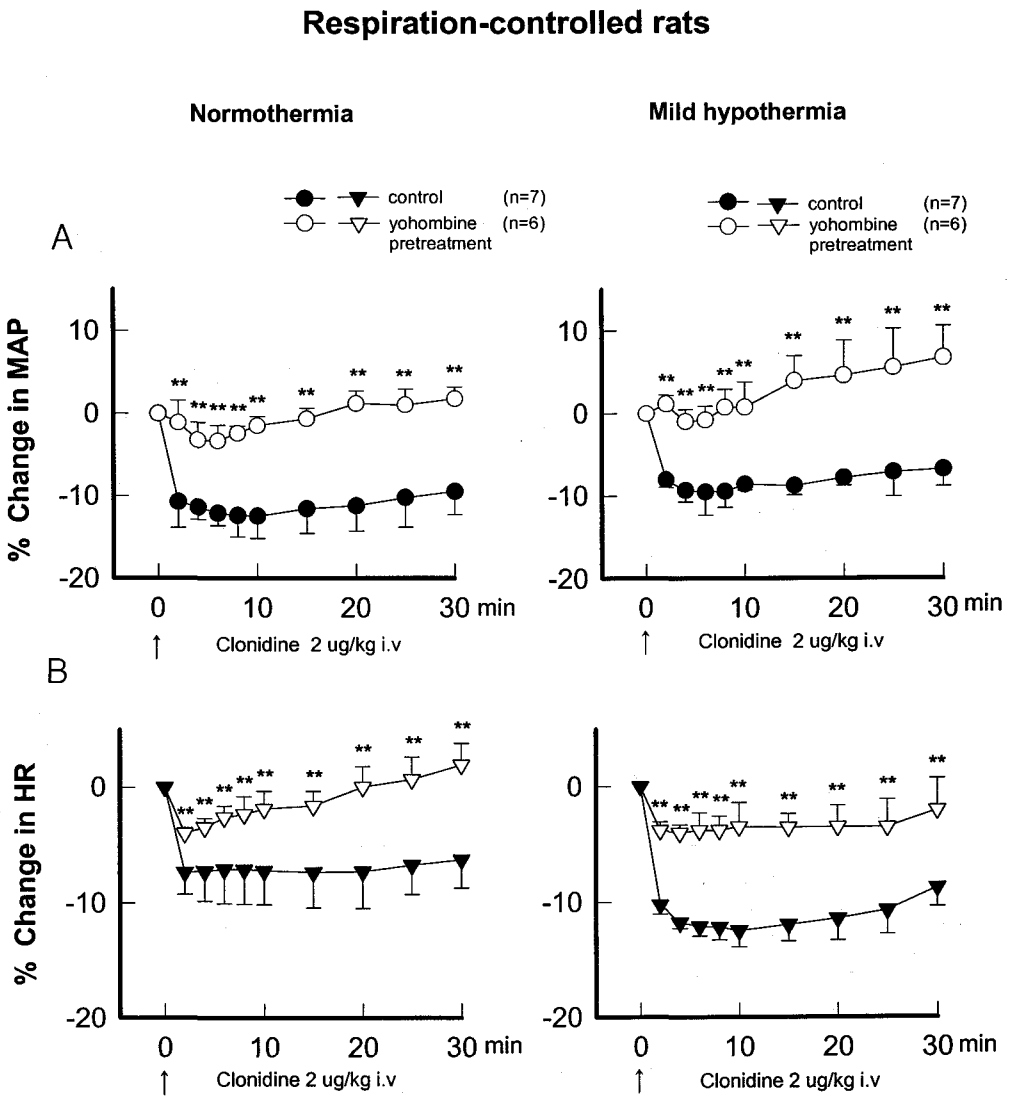

Fig. 3. Effects of yohimbine (0.5 mg/kg, i.v) on hypotensive and bradycardic responses to clonidine (2 μg/kg) between the normothermic and mild hypothermic groups in respiration-controlled rats anesthetized with pentobarbital. Results are expressed as mean± SD. $^{**}P<0.01$ vs. control group.

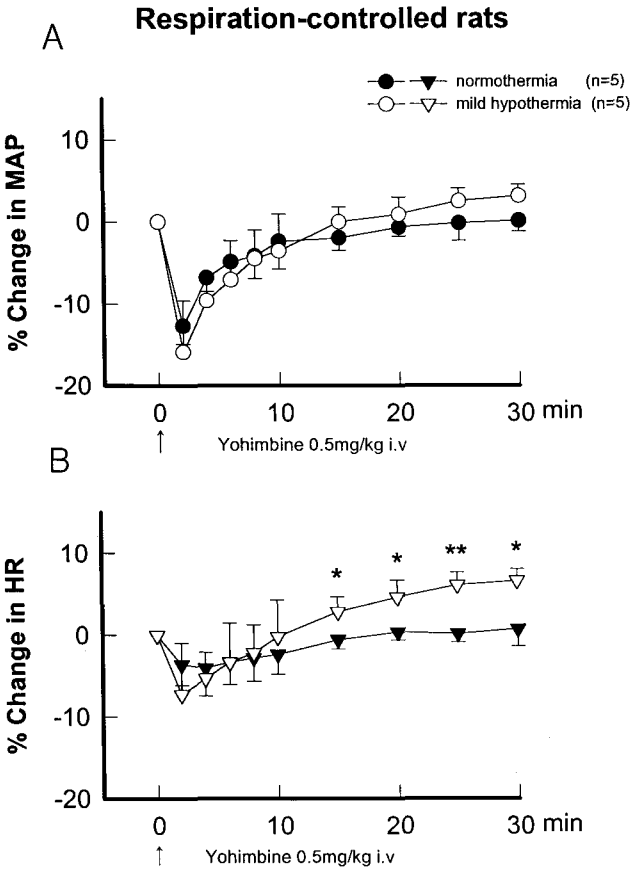

Fig. 4. Effects of yohimbine (0.5 mg/kg, i.v.) on mean arterial pressure (MAP; A) and heart rate (HR; B) between the normothermic and mild hypothermic groups in respiration-controlled rats anesthetized with pentobarbital. Results are expressed as mean ± SD. $*P<0.05$ and $**P<0.01$ vs. the normothermic group

pressor response of clonidine was significantly greater in mild hypothermic rats than in normothermic rats ($P<0.05$, Fig. 2A). In contrast, the bradycardic effect of clonidine was significantly greater in mild hypothermic rats than in normothermic rats ($P<0.05$ or $P<0.01$, Fig. 2B).

Effects of yohimbine-pretreatment on MAP and HR responses to clonidine under respiration-controlled condition

Yohimbine, an α_2-adrenoceptor antagonist, was pretreated in the normothermic and mild hypothermic rats 10 min before i.v. injection of clonidine. Both depressor and bradycardic effects of clondine (2 μg/kg) were significantly blocked by pretreatment with yohimbine (0.5 mg/kg, i.v) in both normothermic and mild hypothermic rats (Fig. 3). Yohimbine (0.5 mg/kg, i.v) alone did not induce a significant difference in MAP between the normothermic and mild hypothermic rats. The significant time-dependent difference in HR between two thermal conditions was observed from 10 min after yohimbine administration (Fig. 4).

Effects of atropine-pretreatment on MAP and HR responses to clonidine under respiration-controlled condition

Atropine, a muscarinic receptor antagonist, was pretreated in both normothemic and mild hypothermic rats 10 min before clonidine administration. In normothermic rats, clonidine-induced decrease in MAP and HR was not blocked by preteatment with atropine (1 mg/kg, i.v.). In mild hypothermic rats, atropine-pretreatment did not influence clonidine-induced decrease in MAP but significantly attenuate the decrease in HR ($P<0.05$, Fig. 5).

DISCUSSION

In the present study, we have determined whether the effects of clonidine, an α_2-adrenoceptor agonist, on MAP and HR were influenced by mild hypothermia. Experiments were carried out in spontaneously breathing and respiration-controlled rats. It has been observed that the baseline values of MAP and HR are lower in the mild hypothermic group than normothermic group under spontaneously breathing condition. These results are consistent with previous findings that hypotension and bradycardia were induced in anesthetized animals if the body temperature was not maintained normally by external heating (Estima-Martins, 1975). They showed that progressive bradycardia in the moderately hypothermic dog was due, among other factors, to the enhanced cholinergic action. This results was confirmed by our findings that the i.v. pretreatment with atropine, a muscarinic receptor antagonist, increased the baseline values of HR in mild hypothermic rats, which resulted in the reduction of the difference in the baseline values of HR between the normothermic and mild hypothermic groups. Tiveito et al (1991) demonstrated that changes in the peripheral vascular function and the myocardial metabolism during hypothermia in pentobarbital-anesthetized rats may lead to

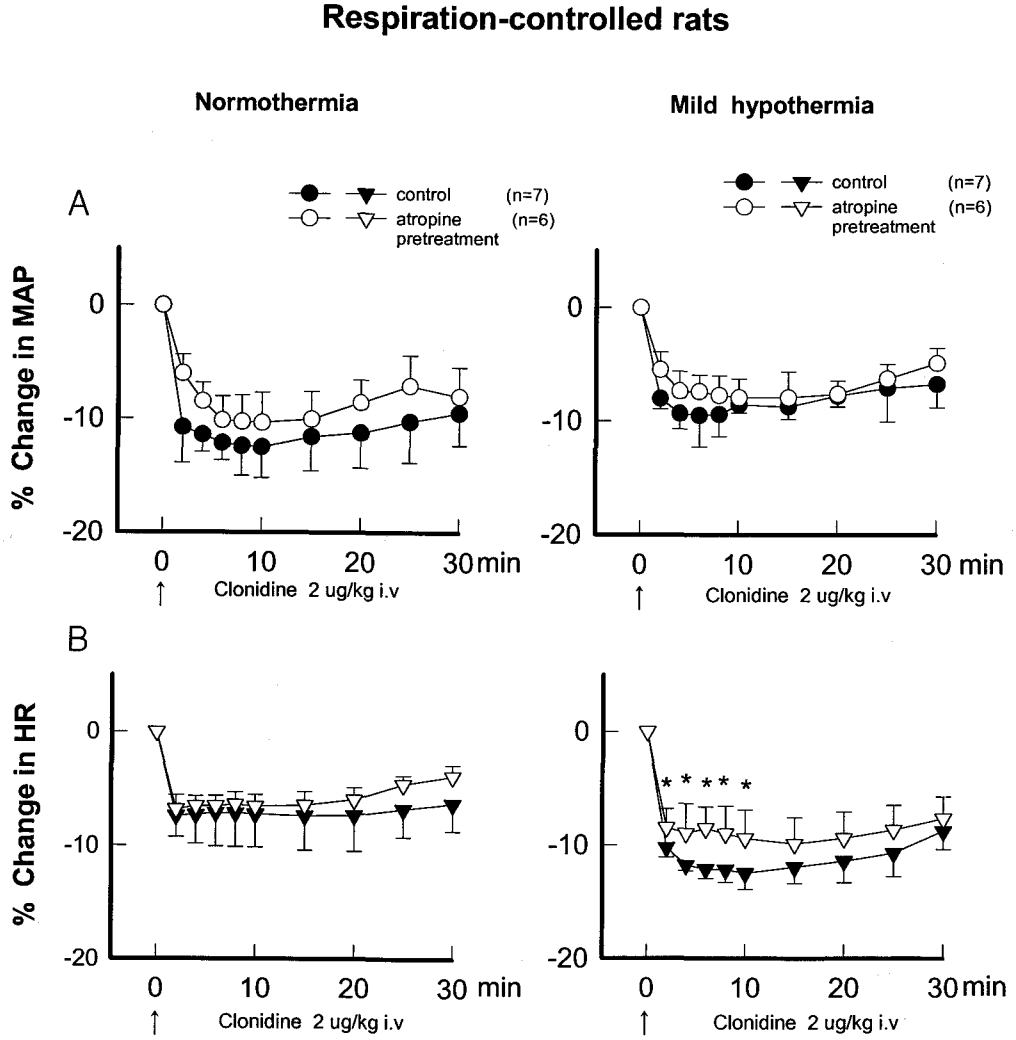

Fig. 5. Effects of atropine (1 mg/kg, i.v) on hypotensive and bradycardic responses to clonidine (2 μg/kg, i.v.) between the normothermic and mild hypothermic groups in respiration-controlled rats anesthetized with pentobarbital. Results are expressed as mean ± SD. $^*P<0.05$ vs. control group.

decreases in MAP and HR. Therefore, it could be thought that both the reduced cardiovascular function and the enhanced cholinergic activity could be at least partly responsible for decreases of the baseline values of MAP and HR under the mild hypothermic condition.

It is well-known that clonidine produces centrally mediated hypotensive and bradycardic effects. Stimulation of central α_2-adrenoceptor with clonidine reduced central sympathetic outflow, leading to a decrease in BP (van Zwieten et al, 1984). Several lines of evidence indicate that clonidine-induced bradycardia is caused by complex combination of following three phenomena: (1) the centrally induced reduction of peripheral sympathetic tone, which involves central α_2-adrenoceptors (Kobinger, 1978); (2) the enhancement of vagal reflex bradycardia initiated at the level of central α_2-adrenoceptors (Kobinger & Wallard, 1973); (3) the stimulation of presynaptic α_2-adrenoceptors in the heart (Jonge et al, 1981). Collectively, clonidine-induced bradycardia which accompanies the hypotensive effect is assumed to be the result of both a decreased sympathetic and an increased parasympathetic activities (Timisjärvi et al, 1984; van Zwieten, 1984; Punnen et al, 1987; Ruffolo et al, 1993).

Under the spontaneously breathing condition, there was no difference in the hypotensive response of

clonidine between the normothermic and mild hypothermic groups, but the bradycardic response of clonidine was greater in mild hypothermic rats than in normothermic rats. It is possible that the secondary change in MAP caused by several factors, such as an acid-base imbalance, could occur under the spontaneously breathing condition. Therefore, to clarify the effect of clonidine on cardiovascular responses during mild hypothermia, other experiments were carried out in the respiration-controlled condition. Under the respiration-controlled condition, intravenous pretreatment with yohimbine, an α_2-adrenergic antagonist, significantly blocked the hypotensive response to intravenous clonidine in both normothermic and mild hypothermic rats. Intravenous pretreatment with atropine methylnitrate, however, did not alter clonidine-induced decrease in MAP in both thermal groups. Thus, it appears that the hypotensive effect of clonidine in respiration-controlled rats may be mediated by stimulation of central α_2-adrenoceptor in both thermal conditions. In addition to the hypotensive effect, clonidine produced bradycardic effect in both two groups. The bradycardic effect of clonidine was blocked by the pretreatment with an α_2-adrenoceptor antagonist, yohimbine, in both thermal conditions, whereas the pretreatment with a muscarinic receptor antagonist, atropine methyl nitrate, attenuated the bradycardic effect of clonidine only in the mild hypothermic group. In previous studies, clonidine is found to increase the parasympathetic tone through an increase in the spontaneous firing of the carotid sinus nerve (Laubie et al, 1976) and the central activation of vagal activity (Johansson et al, 1981). There is an interesting finding showing that a dose-related bradycardic response to i.v. injection of acetylcholine in anesthetized rats was greater in a temperature-uncontrolled group (average rectal temperature, 32.1°C) than in a temperature-controlled group (average rectal temperature, 34.8°C) (Vidrio & Garcia-Marquez, 1987). In addition, potentiation of effects of acetylcholine and other cholinergic agonist by lower temperature had been observed in a variety of effector systems in vitro (Graham et al, 1971; Ishii & Shimo, 1985). Taken together, it can be suggested that the hypothermia-induced augmentation of the bradycardic response to clonidine may result from the reduction of sympathetic tone by central α_2-adrenoceptor activity as well as by a clonidine-induced increase in the parasympathetic activity during mild hypothermia. However, there are two other possibilities that can explain hypothermia-induced augmentation of the bradycardic response to clonidine.

Firstly, there is a possibility that the peripheral α_2-adrenoceptor binding affinity for clonidine is enhanced during mild hypothermia. In vitro studies using isolated blood vessels suggested that decreases in temperature of the organ bath increase the potency of α_2-adrenoceptor agonists, presumably because of an increased receptor affinity (Gantzos & Neubig, 1988; Roberts et al, 1989; Arner & Hogestatt, 1990). In addition to a centrally mediated hypotensive response, clonidine can produce the contraction of the peripheral vasculature via a mechanism mediated by α_2-adrenoceptors on the smooth muscle (Richard et al, 1996). The present results show that the hypotensive effect of clonidine is greater in mild hypothermic rats than in normothermic rats. This result seems to be due to an increase in peripheral α_2-adrenoceptor binding affinity to clonidine by mild hypothermia. In addition, in the present study, i.v. pretreatment with yohimbine increased the baseline value of HR in mild hypothermic rats, thereby reducing the difference in baseline values between two thermal groups.

Secondly, we can not rule out a possibility that mild hypothermia can influence the pharmacokinetics of clonidine because it has been suggested that this is the case for some drugs (Leslie et al, 1995). Potential pharmacokinetic phenomena which mild hypothermia can produce include: (1) the reduction of hepatic blood flow, leading to a decrease in drug metabolism (Karen et al, 1987; Leslie et al, 1995); (2) the reduction of biliary or urinary excretion of drugs (Miller et al, 1978); (3) the reduction of clearance and volume of distribution of drugs (Miller et al, 1978; Karen et al, 1987; Leslie et al, 1995). Since data on pharmacokinetics of α_2-adrenoceptor agonists during mild hypothermia have not been available so far, thus more studies on the pharmacokinetics of α_2-adrenoceptor agonists including clonidine remain to be performed.

This study shows that (1) the hypotensive effect of clonidine which might be due to an decrease in central sympathetic activity was attenuated during mild hypothermia; (2) the bradycardic effect of clonidine was amplified during mild hypothermia, probably an increase in parasympathetic activity. Our results suggest that effects of clonidine on cardiovascular responses are influenced by mild hypothermia, a condition that occurs frequently in periopera-

tive patients.

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