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Adrenergic mechanism of femoral arterial constriction during carotid occlusion in dogs[1]

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ABSTRACT The adrenergic mechanism of femoral vascular constriction (FVC) elicited by bilateral carotid occlusion (BCO) was studied in 17 anesthetized dogs. When the perfusion pressure was kept constant the femoral resistance increased, which was different from that when the perfusion pressure was allowed to rise. Plasma NE increased at 60 and 120 s of BCO. The elevation of systemic blood pressure occurred before the change of NE. Yohimbine (Yoh, α_2 antagonist) and indoramin (Ind, α_1 antagonist) caused the reduction of femoral vascular resistance (FVR)

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by 24 and 27%, respectively, and the combination of the two drugs by 38%. In the presence of Ind and Yoh, the dose-response curves (DRC) of phenylephrine shifted rightward as the equipotent doses increased 25-30 folds, respectively; the DRC for azepexole shifted rightward as well but the equipotent dose increased 6 folds only in the presence of Ind, and almost 30 folds in the presence of Yoh. Thus it is concluded that BCO appears to result in neurally mediated stimulation of both postsynaptic α_1 and α_2 adrenergic receptors.

KEY WORDS yohimbine; indoramin; norepinephrine; alpha adrenergic receptors; carotid arteries; femoral artery; vascular resistance

The marked vasoconstriction in response to bilateral carotid occlusion (BCO) has been shown to be abolished after alpha blockade[1,2]. Since the finding of postsynaptic adrenergic α_2 receptors in peripheral resistance vessels, the question has been emerged that which subtypes of the adrenergic α receptors is involved in the mechanism of the increase of vascular resistance induced by BCO. This paper was designed to study the neurohumoral machanism of BCO, to define the subtypes of α adrenergic receptors responsible to neural and circulating norepinephrine (NE) stimulation and the relative role of the receptors.

MATERIALS AND METHODS

Yohimbine (Yoh, Sigma), indoramin (Ind, Sigma), azepexole (Boehinger Ingelheim), sodium pentobarbital (Sigma), phenylephrine (PE, Winthrop) were freshly dissolved in saline.

17 mongrel dogs, 20 ± SD 6 kg, were anesthetized with iv sodium pentobarbital 15 mg/kg and subsequent doses of 4-7 mg/kg given hourly. The dogs were ventilated with a respirator. Femoral arteries from inguinal ligaments to the distal 1/3 of the legs, two branches of medial saphenous artery originated from both femoral arteries were dissected. A small catheter connected with pressure transducer (Statham P 23 ID) and another small polyvinyl catheter were introduced into the 2 branches for monitoring the intra-arterial blood pressure (BP) and intra-arterial injection or infusion of drugs separately. An electromagnetic blood flow probe was placed on the proximal part of the femoral artery with a hydraulic occluder around the artery nearby. Femoral artery blood flow (FBF) as well as the BP were monitored. The hemodynamic data were recorded with a Hewlett-Packard Model 8800 direct writing oscillograph.

Carotid arteries of both sides were dissected. Umbilical tapes were placed loosely around the arteries in such a manner that by lifting and clamping these tapes occlusion could be obtained. BCO was performed for 2 min each time.

Blood plasma NE was measured by the radioenzymatic assay using Cat-a-Kit (Upjohn). Duplicate determination yielded a coefficient of variation of 8.3%. Blood samples were collected before 20, 60 and 120 s after the outset of BCO separately.

The dogs were infused with normal saline 1 ml/(kg·min) via femoral artery for 2 min as control. Thereafter, the following studies were taken:

1. BCO were made on 13 dogs when the perfusion pressure of femoral artery were allowed to rise, the effect of BCO of the femoral artery vascular resistance (FVR) and the blood NE level were measured.

2. BCO were made when the hydraulic occluder was inflated manually to keep the femoral BP constant in order to investigate the effect of BCO on FVR at constant perfusion pressure.

3. Antagonists Yoh or Ind 1 μg/(kg·min) were started before and during BCO.

4. Doses of PE 0.003, 0.01, 0.03, 0.1 μg/kg and azepexole 0.1, 1, 3, 10 μg/kg were given in the presence of Yoh or Ind, to verify the selectivities of antagonists in femoral artery.

The hemodynamic data before and after BCO, PE, azepexole, Yoh, and Ind were evaluated by paired *t* test.

RESULTS

Normal saline 1 ml/(kg·min) intra-arterial infusion for 2 min did not cause any changes in FBF.

(1) BCO induced an elevation of BP from 14.0 ± 0.8 to 18.8 ± 1.3 kPa ($n=13$, $p<0.01$). When the perfusion pressure was allowed to rise, 5 dogs showed significant increases of FBF over 30 ml/min, 5 showed moderate increases (11-30 ml/min) and <10 ml/min were seen in 3. However, the FVR showed no substantial changes: from 0.24 ± 0.02 before BCO to 0.21 ± 0.03 kPa/(ml·min) during the BCO.

(2) Among the 7 measurements carried on 4 dogs, BCO caused the decrease of FBF in 2 when the perfusion pressure of femoral artery was kept constant. 2 decreased moderately, while no changes were observed in 3. When the BP increased during BCO, the FVR rose from 0.31 ± 0.03 to 0.78 ± 0.10 kPa/(ml·min).

(3) The plasma NE concentration was 149 ± 17 pg/ml before BCO; 20 s after the start of BCO, when the BP was elevated, the NE remained no marked change ($p>0.05$). NE increased to 188 ± 26 pg/ml (+26%, $p<0.01$) at 60 s and to 214 ± 26 pg/ml (+43%, $p<0.01$) at 120 s. The elevation of BP occurred definitely before the increase of NE (Fig 1).

(4) Before BCO, Yoh infusion alone increased FBF from 64 ± 14 to 91 ± 24 ml/min ($n=9$, $p<0.01$). Since no appreciable pressor changes occurred by the intra-arterial infusion of Yoh, the increase of FBF should be considered as proportional to the vasodilation of femoral artery due to the blockade of α_2 adrenoceptors. During BCO, BP increased from 16.9 to 20.5 kPa (+27%, $p<0.01$). Because of the further increase of FBF to 108 ± 17 ml/min, the infused side

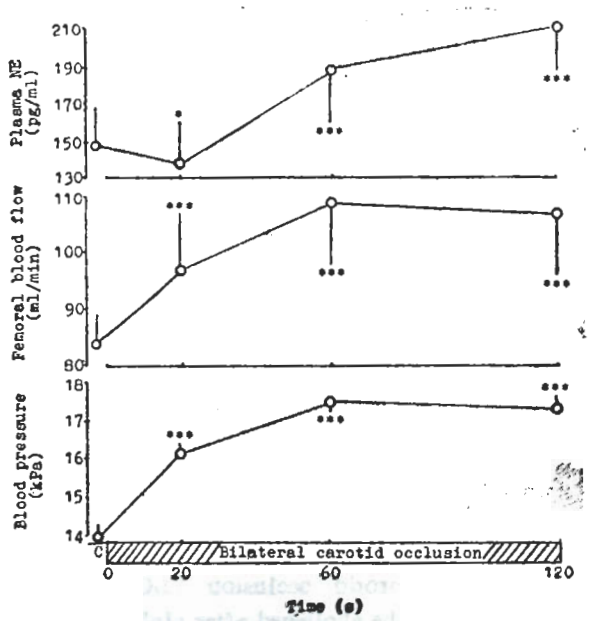

Fig 1. Plasma norepinephrine, femoral blood flow and mean arterial blood pressure during bilateral carotid occlusion (BCO) in 13 dogs. C means before BCO. $\bar{x}\pm SD$, *$p>0.05$, **$p<0.05$, ***$p<0.01$

FVR decreased by 24%. As compared to the control side of +11%, it is demonstrated that Yoh can effectively prevent FVC induced by BCO (Tab 1). Before BCO, Ind ia infusion alone increased FBF significantly from 67 ± 8 to 93 ± 12 ml/min ($n=11$, $p<0.01$), when no systemic pressor response was noted, indicating blockade of α_1 adrenoceptors by Ind can produce vasodilation of femoral artery. During BCO, the FBF increased furthermore to 116 ± 14 ml/min (+73%), thus the FVR of infused side decreased from 0.25 ± 0.03 to 0.18 ± 0.02 kPa/(ml·min)(−27%). In comparison to the control side of −6.9%, the difference was highly significant. It seemed that Ind can prevent the increase of FVC induced by BCO.

Before BCO, combined Yoh and Ind infusion increased FBF markedly ($n=8$, +43%). During BCO, the combined infusion decreased the FVR by −38%, which was significantly lower than the case by Yoh ($p<0.01$) or Ind alone ($p<0.01$).

Tab 1. Effects of antagonists on femoral vascular resistance ($kPa \cdot ml^{-1} \cdot min^{-1}$) before and during bilateral carotid occlusion in dogs. $\bar{x} \pm SD$. $^{**}p < 0.05$, $^{***}p < 0.01$ *vs* control or noninfused side

	Yohimbine (9 dogs)	Indoramin (11 dogs)	Yohimbine + indoramin (8 dogs)
Control	0.30±0.04	0.27±0.03	0.19±0.03
Infused	0.22±0.04**	0.18±0.02***	0.13±0.02***
During bilateral carotid occlusion			
Noninfused	0.33±0.05	0.25±0.03	0.19±0.02
Infused	0.22±0.02***	0.18±0.02***	0.13±0.02***

(5) Dose-response curve for PE and azepexole: PE 0.003, 0.01, 0.03, 0.3 μg/kg induced dose-dependent FVC ($n = 8$). In the presence of Ind, the dose-response curve shifted rightward significantly: PE 0.3 μg/kg produced a decrease of FBF which was almost equivalent to that of 0.01 μg/kg prior to the Ind. However, in the presence of Yoh, only 6-10 folds increases were seen (Tab 2).

Tab 2. Decrease of femoral blood flow (ml/min) produced by the agonists in the presence of antagonists. $n = 8$, $\bar{x} \pm SD$. $^{*}p > 0.05$, $^{**}p < 0.05$, $^{***}p < 0.01$.

	μg/kg	Control	Decrease of femoral blood flow (ml/min) Yohimbine 1 μg/(kg·min)	Indoramin 1 μg/(kg·min)
Phenylephrine	0.003	49±23	57±21**	53±35*
	0.01	33±4	50±13***	52±22**
	0.03	26±3	38±8***	44±18***
	0.3	12±3	21±1**	32±8***
Azepexole	0.1	31±4	53±26***	43±14***
	1	16±5	40±7***	26±4**
	3	16±2	31±4***	20±2*
	10	12±4	15±1**	14±4*

Azepexole in the doses of 0.1, 1, 3, 10 μg/kg caused dose dependent vasoconstrictions. In the presence of Yoh, DRC for azepexole shifted rightward, as the equivalent doses increased almost 30 folds while Ind only increased 6 folds.

DISCUSSION

In the mechanism of the responses of skeletal blood flow to BCO, autoregulation may not be important in the vasoconstriction induced by BCO, since the response of femoral artery to BCO does not follow the typical time course of the change of blood flow observed in kidney, mesentric artery, etc[3,4]. Skeletal muscle vascular autoregulation occurs only within a relatively narrow pressure range of 8-12 kPa[5]. The pressure both before and during BCO in our study were in the range of 14-18 kPa.

The study demonstrated that during BCO, plasma NE increased very slightly to 214±26 pg/ml at 120 s after BCO. A time lag existed between the elevation of BP and the increase of plasma NE, suggesting that the increase of peripheral vascular resistance is not closely related to the increase of plasma NE. With NE infusion in normal human being, NE level in excess of 1.8 ng/ml was required to produce hemodynamic and/or metabolic effects[6]. The plasma NE concentration rarely exceeded 1.8 ng/ml in physiological condition except those of prolonged or maximal exercise as well as patients with major acute illness. Apparently, the increase of plasma NE could not be accounted for FVC during BCO.

Prazosin has been shown to be much more effective in inhibiting the pressor response to BCO than in inhibiting that to NE injection[7]. Yoh iv 0.03-0.3 mg/kg preferentially blocked the pressor response to NE, while iv 1.0 mg/kg inhibited both NE and BCO induced responses. It is suggested that the pressor response to BCO is predominantly mediated via α_1 adrenoceptors. Our study provided the strong evidence that not only Ind but also Yoh ia prevented the FVC caused by BCO; when both α_1 and α_2 adrenoceptors were blocked, the inhibition effect was much more significant than the antagonist infused, respectively.

Thus the stimulation of both α_1 and α_2 adrenoceptors locally by the increased sympathetic tone seems to be the principal mechanism of BCO, while the hormonal link of sympathetic system is of fairly subordinate importance so far as it concerns the excitatory influence on innervated cardiovascular effectors.

In the present study, we try to simulate a condition with elevated sympathetic tone which has been usually encountered in congestive heart failure, and to investigate the vasoconstriction produced by them. The fact that α_1 in addition to α_2 adrenoceptors antagonists are more effective in prevention from vasoconstriction induced by increased sympathetic tone suggests that inclusion in the current vasodilator therapy with α_2 adrenoceptors antagonists would be appropriate.

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犬颈动脉封闭引起股动脉收缩的肾上腺素能作用机理

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提要　17只麻醉犬双侧颈动脉封闭引起股动脉收缩。当股动脉灌注压维持恒定时，股动脉阻力加大；灌注压任其增高时，股动脉阻力变动较大。血浆中去甲肾上腺素(NE)含量在颈动脉封闭60 s与120 s时增加，血压升高发生于NE变化之前。育亨宾(α_2拮抗剂)与吲哚拉明(α_1拮抗剂)分别减低股动脉阻力24与27%，若两药同时使用，阻力减低38%。去氧肾上腺素的剂量-反应曲线(DRC)分别因吲哚拉明或育亨宾的影响右移，等效剂量分别增加30及6-10倍；上述2种拮抗剂使氮䓬克唑的DRC也发生右移，但吲哚拉明仅使氮䓬克唑的等效剂量增大6倍，育亨宾则使其增大30倍。上述结果说明颈动脉封闭引致股动脉收缩的机制是通过神经性刺激股动脉壁α_1与α_2肾上腺能受体。

关键词　育亨宾；吲哚拉明；去甲肾上腺素；α肾上腺素能受体；颈动脉；股动脉；血管阻力

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