Adrenergic mechanism of femoral arterial constriction during carotid occlusion in dogs

CHEN Da-Guang, Peter CARLYLE, Wenda CARLYLE, Patricia EEEKOFF, Jay N COHN

(Department of Medicine, University of Minnesota, Minneapolis MN 55455, USA)

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2 Now in Nanjing Railway Medical College, Nanjing 210009, China

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, α₂ antagonist) and indomethacin (Ind, α₁ antagonist) caused the reduction of femoral vascular resistance (FVR).
by 24 and 25%, respectively, and the combina-
tion of the two drugs by 35%. In the presence of Ind and Yoh, the dose-response curves (DRC) of
phentolamine shifted rightward as the equipro-
tant dose increased 25-50% dose, respectively; the
DRC for norepinephrine shifted rightward as well but the equipotent dose increased 4-5 folds only in
the presence of Ind, and almost 40% folds in the
presence of Yoh. Thus it is concluded that BCO
appears to react in essentially mediatel stimulation
of both post synaptic a1 and a2 adrennergic
receptors.

KEY WORDS yohimbine; indoramin; norepi-
nephrine; alpha adrenergic receptors; carotid
arteries; femoral artery; vascular resistance

The marked vasocostriction in response to bilateral carotid occlusion (BCO) has been shown to be abolished after alpha blockade. Since the finding of post synaptic adrenergic a2 receptors in peripheral resis-
tance vessels, the postion has been emerged that which subtypes of the adrennergic a receptors is involved in the mechanism of the increase of vascular resistance induced by BCO. This paper was designed to study the neurohumoral mechanism of BCO, to define the subtypes of adrenergic receptors responsible to neural and circulating norepi-
nephrine (NE) stimulation and the relative role of the receptors.

MATERIALS AND METHODS
Yohimbine (Yoh, Sigma), indoramin
(Ind, Sigma), azepoxol (Boehinger Ingel-
haim), sodium pentobarbital (Sigma),
phenylephrine (PE, Winthrop) were freshly dissolved in saline.
17 mongrel dogs, 20 ± 2 SD 6 kg, were
anesthetized with IV sodium pentobarbital
30 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 internal (a) and external arteries 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 monitor-
ing the intra-arterial blood pressure (BP) and intra-arterial injection of 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
tying and clamping these tapes occlusion could be obtained. BCO was performed for 2 min each time.

Blood plasma NE was measured by the radioimmunometric assay using Cat-s-Kit (Upjohn). Duplicate determinations yielded a
coefficient of variation of 8.3%. Blood sam-
ples were collected before 20, 60 and 120 s
after the onset 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 intravenous
occluder was inflated manually to keep the
femoral BP constant in order to investigate the
effects of BCO on FVR at constant perfusion pressure.
3. Antagonists Yoh or Ind 1 µg/(kg-
min) were stanced before and during BCO.
4. Doses of PE 0.003, 0.01, 0.03,
0.1 µg/kg and azepoxol 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, azepoxide, 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 ± 0.6 to 18.8 ± 1.2 kPa (n = 13, p < 0.05). 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 0.31 ± 0.03 kPa/(ml·min) during the BCO.

2. Among the 7 measurements carried out in 4 dogs, BCO caused the decrease of FBF in 3 when the perfusion pressure of femoral artery was kept constant. 5 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 4.9 ± 1.7 pg/ml before BCO. 20 h after the start of BCO, when the BP was elevated, the NE remained at no marked change (p > 0.05). NE increased to 118 ± 26 pg/ml (+26.5%, p < 0.01) at 60 s and to 216 ± 26 pg/ml (+43.5%, p < 0.01) at 120 s. The elevation of BP occurred definitively 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 a1 adrenoceptors. During BCO, BCO increased from 16.0 to 20.5 kPa (+27%, p < 0.01). Because of the further increase of FBF to 17 ± 17 ml/min, the infused side

FVR decreased by 24%. As compared to the control side of +11.5%, it is demonstrated that Yoh can effectively prevent FVC induced by BCO (Tab 1). Before BCO, Ind is infusion alone increased FBF significantly from 07 ± 8 to 92 ± 12 ml/min (n = 11, p < 0.01), when no systemic pressor response was noted, indicating blockade of a1 adrenoceptors by Ind can produce vasodilation of femoral artery. During BCO, the FBF increased furthermore to 116 ± 24 ml/min (+73%), thus the FVR of infused side decreased from 0.35 ± 0.03 to 0.18 ± 0.02 kPa/(ml·min) (−47%). In comparison to the control side of −6.8%, 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).

Fig. 1. Plasma norepinephrine, femoral blood flow and mean arterial blood pressure during bilateral carotid occlusion (BCO) in 13 dogs, C means before BCO, *p<0.05, **p<0.01, ***p<0.01.
Tab. 1. Effects of antagonists on femoral vascular resistance (ΔP/Δt·min⁻¹) before and during bilateral carotid occlusion in dogs. Y±SD, "p<0.05, "p<0.01 vs control or noninjected side.

<table>
<thead>
<tr>
<th>Yohimbine</th>
<th>Indomethacin</th>
<th>Yohimbine + indomethacin</th>
</tr>
</thead>
<tbody>
<tr>
<td>(9 dogs)</td>
<td>(11 dogs)</td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>0.30±0.04</td>
<td>0.27±0.03</td>
</tr>
<tr>
<td>Infused</td>
<td>0.22±0.04</td>
<td>0.18±0.05</td>
</tr>
<tr>
<td>During bilateral carotid occlusion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Noninfused</td>
<td>0.33±0.05</td>
<td>0.29±0.03</td>
</tr>
<tr>
<td>Infused</td>
<td>0.22±0.02</td>
<td>0.18±0.02</td>
</tr>
</tbody>
</table>

Tab. 2. Decrease of femoral blood flow (ml/min) produced by the antagonists in the presence of antagonists, n=8. Y±SD, "p<0.05, "p<0.01.

<table>
<thead>
<tr>
<th>Phenytoin</th>
<th>0.005</th>
<th>0.01</th>
<th>0.03</th>
<th>0.03</th>
<th>0.12</th>
<th>0.3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concentration (mg/kg)</td>
<td>10</td>
<td>20</td>
<td>50</td>
<td>100</td>
<td>200</td>
<td>500</td>
</tr>
<tr>
<td>Decrease of femoral blood flow (ml/min)</td>
<td>8.7±2.1**</td>
<td>18.4±2.3***</td>
<td>32.5±3.5**</td>
<td>32.5±3.5**</td>
<td>32.5±3.5**</td>
<td>32.5±3.5**</td>
</tr>
</tbody>
</table>

Azoxyphene and | 31.2±4 | 52.3±8*** | 63.1±14** | 63.1±14** | 63.1±14** | 63.1±14** |
| 1 | 20 | 40 | 80 | 160 | 320 | 640 |
| Decrease of femoral blood flow (ml/min) | 8.7±2.1** | 18.4±2.3*** | 32.5±3.5** | 32.5±3.5** | 32.5±3.5** | 32.5±3.5** |

In the mechanism of the responses of skeletal blood flow to BCO, autoregulation may not be important in the vasomotor reaction induced by BCO, since the response of femoral artery to BCO dose not follow the typical time course of the change of blood flow observed in kidney, mesenteric artery, etc.¶. Skeletal muscle vascular autoregulation occurs only within a relatively narrow pressure range of 8–12 kPa.† 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 21±4±6 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 exccss of 1.8 ng/ml was required to produce hemodynamic and/or metabolic effects.‡ The plasma NE concentration rapidly 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 PVC 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.¶. Yoh iv 0.02–3 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 predominately mediated via a-adrenergic receptors. Our study provided the strong evidence that not only Ind but also Yoh in prevented the PVC caused by BCO, when both a1 and a2 adrenergic receptors were blocked, the inhibition effect was much more significant than the antagonist infused, respectively.
Thus the stimulation of both α₁ and α₂ 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 interrelated 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 α₁ in addition to α₂ adrenoceptors antagonists are more effective in prevention from vasoconstriction induced by increased sympathetic tone suggests that inclusion in the current vasoconstrictor therapy with α₂ adrenoceptors antagonists would be appropriate.

REFERENCES

2. Ziegler D, Gribins PS. Effect of cardiac adrenoceptor stimulation upon the forearm vascular bed of the dog. Circ Res 1964; 14: 393

大动脉脉冲动引起胶动脉收縮的腎上腺素能作用机理

陈远光1, Peter CARLYLE, Wenda CARLYLE, Patricia EEKHOFF, Jay N COHN

(Deperment of Medicine, University of Minnesota, Minneapolis MN 55445, USA)

摘要 17只棉耳犬不做动脉脉冲动引起胶动脉收縮，当动脉脉脉冲波出现时，动脉脉脉力加大，脉冲在起始时，动脉脉脉力变大。在其去甲腎上腺素(NB)合量对脉冲脉冲时 66与120 s时增加，血压并反复出现于 NB 测量之前。用 α₁内肽阻断剂(α₁内肽阻断剂)与 α₂内肽阻断剂(α₂内肽阻断剂)分别注入脉冲脉力增加，高脉压时脉力最大，脉压低可，脉压低与脉压低的脉力增加，去甲腎上腺素的脉力增加，去甲腎上腺素的脉力增加，去甲腎上腺素的脉力增加，去甲腎上腺素的脉力增加，去甲腎上腺素的脉力增加，去甲腎上腺素的脉力增加。