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# Changes of the Efficacy of Vasoconstrictive Stimuli in Acute and Chronic Hypotension in the Microcirculatory Bed of Rat Skeletal Muscle

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UDC 616.12-008.331.4-06:616.16-008.1-031:611.73]-092.9-07

Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny*, Vol. 116, № 8, pp. 139-142, August, 1993
Original article submitted January 26, 1993

**Key Words:** *microcirculation; arterioles; myogenic tone; sympathetic nervous system; hypotension*

Changes of intravascular pressure may modulate the sensitivity and responsiveness of blood vessels to constrictive stimuli. An increase in the perfusion pressure to 140 mm Hg raises the sensitivity and responsiveness of the small vessels of dog kidneys to norepinephrine [5]. According to the data obtained by us earlier, the responses to stimulation of the sympathetic tract in the microcirculatory bed of rat skeletal muscle become weaker in acute and chronic hypertension [1,2]. One may assume that regional hypotension elicits the opposite effect. For instance, in experiments performed on the mesentery of rats, a decrease of perfusion pressure to 30 mm Hg caused an enhancement of constrictive responses to angiotensin II and phenylephrine [6]. At the same time, it has been demonstrated on the perfused extremities of rats with hypotension lasting 1-2 months that vascular responses to neuroergic stimuli, as well as the blood supply of the tissues (but not the perfusion pressure) initially drop and recover later on [3].

In the present work we studied vasoconstrictive responses of the microcirculatory bed of rat skeletal muscle to stimulation of the sympathetic tract in control (sham-operated) rats and in rats with chronic regional hypotension lasting 1-2 months, as well as these responses against the background of a short-term decrease of perfusion pressure in the posterior part of the rat body.

## MATERIALS AND METHODS

The experiments with a short-term decrease of the arterial pressure (AP) were carried out on 11 male Wistar rats weighing 250±35 g. Pretreatment of the animal, preparation of the muscle (*m. extensor hallucius proprius*) on the left hind paw, and biomicroscopy were performed as in the previous investigation [1]. The AP was recorded in the right femoral artery with the aid of an RE-10 catheter hooked up to a manometer. The perfusion pressure in the posterior part of the body was reduced by occluding the abdominal aorta with a hydraulic

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0007-4888/93/0008-0926$12.50 

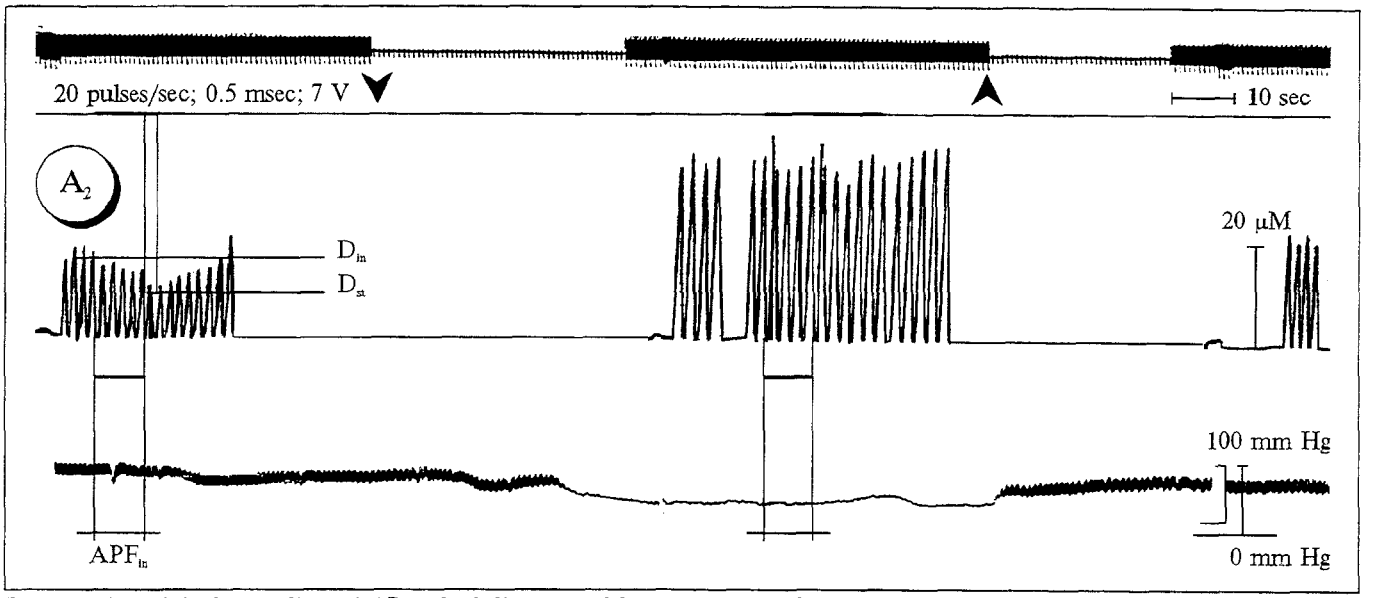


Fig. 1. An original recording of AP and of diameter of lumen for arteriole of 2nd branching order ($A_2$). From top to bottom: marks of time and of the moment of application and removal of occlusion of the aorta. Mark of period of stimulation. Diameter of lumen of vessel (height of peaks is proportional to diameter of lumen): $D_{in}$ is initial diameter, $D_{st}$ is minimal diameter during stimulation. Curve of AP in femoral artery: $APF_{in}$ is initial pressure level.

sleeve applied to the aorta below the site of origin of the renal arteries. Stimulation of the sympathetic tract was performed on the $L_{VI}$-$S_I$ level. The sympathetic tract was not transected. The experimental protocol involved the following (Fig. 1). The initial values of AP (mean or diastolic) in the femoral artery ($APF_{in}$) and the diameter of the arteriole lumen ($D_{in}$ averaged for several peaks) were recorded; the branching order of the vessels ($A_1$, $A_2$, etc.) was noted. The power of the stimulation current was chosen for each vessel so that the degree of occlusion of the lumen constituted 30-40% of $D_{in}$ (minimum 3 V, maximum 21 V, 20 pulses per sec, duration of one pulse 0.5 msec, total duration 10 sec). During stimulation, the minimal diameter of the vessel ($D_{st}$) and the time of attainment of this value were registered. The contractile response was calculated as $\Delta D_{st}=(D_{in}-D_{st})/D_{in}\times 100\%$. The aorta was then occluded by means of a sleeve to cause a decrease of APF to within 50%, the blood flow in the vessel examined being preserved. The degree of decrease of APF was varied so as to make it possible to perform correlation analysis; its minimum and maximum decrease constituted 8.3% and 54.5% of $APF_{in}$, respectively. After 1 min of stabilizing the APF (this time being indicated by Morff et al. [7]), stimulation of the sympathetic tract was performed once again using the same parameters of stimulation pulses, and the contractile response was recorded in the same vessel. The duration of stimulation was sometimes increased to analyze alterations in the time characteristics of the responses. After that the blood supply of the muscle was restored. The intervals between individual observations constituted 4-5 min. The experiments with chronic hypotension were carried out on 8 male rats weighing 250-500 g, in which the abdominal aorta was occluded with the aid of a metal spiral 1-2 months (38-68 days) before, as in the previous report [4]. The group of sham-operated rats consisted of 4 animals operated on days 41-

TABLE 1. Mean Values of Changes of APF, of Diameter of Vessel Lumen, and of Efficacy of Vasoconstrictive Stimuli in Acute Stenosis of the Aorta ($M\pm m$)

| Group of vessels | Type of vasomotor response | $n$ | ΔAPF, % | ΔD, % | Stimulation | | |
|---|---|---|---|---|---|---|---|
| | | | | | $n_r/n_e$ | ΔD, % | $\Delta D_{in}$, % |
| 1st | Dilation of lumen | 19 | 19.98±2.73* | 18.68±5.68* | 15/3 | −15.71±2.01* | +3.41±1.56 |
| 2nd | Constriction of lumen | 20 | 21.31±2.72* | 7.73±1.89* | 17/3 | −21.07±4.04* | +9.73±4.18 |
| 3rd | Absence | 6 | 27.1±7.06* | – | 3/3 | −26.63±5.11* | +21.13±9.06* |

**Note.** Here and in Table 2: $n$ is number of vessels; ΔAPF: changes of pressure in left femoral artery as compared with initial state for acute stenosis of aorta; ΔD: changes of diameter of vessel lumen; $n_r/n_e$: number of vessels exhibiting reduced and enhanced constrictive responses to a drop of APF; ΔD and $\Delta D_{in}$: decrease (−) and increase (+) of the efficacy of vasoconstrictive stimuli for a drop of APF. Asterisk indicates reliable differences ($p<0.05$) (paired $t$ test).

TABLE 2. Diameter of Lumen of Vessels, APF, and Efficacy of Vasoconstrictive Stimuli for Acute Stenosis of the Aorta and in a Sample of Experimental Data on Acute Stenosis ($M \pm m$)

| Experimental group | $n$ | D | APF | ΔD, % |
|---|---|---|---|---|
| Sham-operated | 39 | 15.2±0.4 | 108±2.7 | 11.6±1.3* |
| Chronic stenosis | 42 | 15.6±0.4 | 85.4±1.8 | 10.4±0.9* |
| Acute stenosis | 13 | 14.6±0.7 | 82.3±3.9 | [21.4±4.4*] |

Note. The value of $\Delta D_{ini} - \Delta D$ is shown in brackets.

56 before the experiment. Pretreatment of the animals and biomicroscopy were the same as in the acute experiments. Stimulation of the sympathetic tract was performed with a current of a constant amplitude (4 mA, 0.5 msec, 20 pulses per sec, during 10 sec), as described elsewhere [2], in order to compare the two animal groups.

## RESULTS

The mean APF in the rat group with a short-term decrease of APF was 105±5.1 mm Hg. Arterioles of the 1st, 2nd, and 3rd branching order were observed; the maximum diameter of the lumen was 88 m, the minimum was 7.8 μ. In the majority of cases a decrease of APF during occlusion of the aorta was accompanied by a vasomotor response (Table 1). The vessels were divided into three groups, and their response to stimulation of the sympathetic tract was analyzed. The mean decrease of APF proved to be approximately equal, at least in the first two groups; but although the dilation of the vessels in the 1st group correlated (albeit insignificantly, $r$=0.34) with the decrease of AP, in the 2nd group of vessels this correlation was not observed at all, that is, the vessels of this group may be regarded as passively shrinking. No correlation was noted between the branching order of the vessels and the degree of myogenic response of the microvessels.

During stimulation of the sympathetic tract all the vessels examined contracted in the initial state as well as when the APF was reduced. In the majority of cases (35 vessels out of 45) the degree of vasoconstriction was lower when the APF was reduced, 9 vessels contracted more strongly, and in a single case the degree of vasoconstriction was unchanged. In all three groups the efficacy of vasoconstrictive stimuli dropped 19.1±2.1%. It is more convenient in this case to assess the efficacy of vasoconstrictive stimuli by studying the relative diameter of the vessel lumen, which remained open against the background of stimulation. For example, such assessment yields a value of 68.8±2.5% for the initial APF and 99.1±6.9% for the reduced APF in the vessels of group 1 (active). In group 2 and 3 vessels such significant differences among the diameters of the lumen remaining open were not observed: their values constituted 69.4±2.4% for the initial APF and 74.7±2.9% for the reduced APF.

Thus, activation of the myogenic mechanisms underlying autoregulatory maintenance of the blood flow markedly inhibits neuroergic vasoconstriction, at least in the vessels less than 100 μ in diameter, although a heterogenity of this process is observed.

In experiments with chronically reduced APF the mean systolic APF in sham-operated rats was approximately 20% higher than APF in the rats with chronic regional hypotension (Table 2). In this series of experiments only arterioles of the 2nd branching order with a diameter of 10-20 μ (mean value 15.6±0.4 μ) were examined. The ratio between the thickness of the vascular wall and the radius of the lumen (w/r) was approximately equal in the rats with stenosis and in sham-operated animals and constituted 0.44±0.02 and 0.43±0.01, respectively. A similar value of w/r was obtained in the previous experiments on rats with chronic stenosis of the aorta [4]. The APF in rats with stenosis was 20% lower than in sham-operated rats, but at the same time, APF of the latter was the same as the initial APF in the series of experiments on acute stenosis of the aorta. During stimulation of the sympathetic tract all the vessels contracted, but the degree of vasoconstriction in sham-operated animals and in the rats with chronic stenosis did not differ (between the groups $p$>0.05). The data derived from a sample of 13 vessels of the experimental series with acute stenosis, in which the drop of APF was comparable to that observed under conditions of chronic hypotension, are presented in Table 2. Vessels of an equal diameter were chosen. The data provide evidence that the degree of vasoconstriction drops both in this sample and in the whole aggregate of data obtained in the experiments with acute stenosis; however, it should be mentioned that $\Delta D_{in}$ was more pronounced in these vessels and constituted 30% (vs. 10% in experiments with chronic stenosis; Table 2).

Thus, it was established that after 1-2 months of chronic regional hypotension the initially reduced efficacy of vasoconstrictive stimuli is restored, at least in arterioles with a diameter of about 20 μ.

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# Enhancement of Nitric Oxide Synthesis in the Aorta Wall in Experimental Myocardial Infarction

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UDC 616.127-005.8-092.9]-092-07

Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny*, Vol. 116, № 8, pp. 142-144, August, 1993
Original article submitted March 10, 1993

**Key Words:** *nitric oxide; aorta; endothelium-dependent relaxation; myocardial infarction*

It is well known that the post-infarction drop of arterial pressure (AP) may be a function not only of the reduction of the minute heart volume, but also of the decrease of the vascular tone [6]. The progressive drop of the vascular tone may play an important role in the development of cardiogenic shock accompanying extensive myocardial infarctions [6]. Another clinical situation, which is also accompanied by a decrease of the vascular tone, frequently takes place in myocardial infarction in hypertensive patients, in whom the AP may plunge from hypertensive to a subnormal level for several weeks or months [4]. In a study of the regulatory mechanisms of the post-infarction drop of AP, a certain role in this phenomenon was ascribed to the increase of acetylcholine-induced endothelium-dependent relaxation of the vascular wall [3]. This led us to assume that the actual factor participating in the post-infarction decrease of the vascular tone might be an enhanced generation of NO by the endothelial wall.

The present study aimed to verify of this assumption by directly measuring the NO production by the aorta wall after experimental myocardial infarction.

## MATERIALS AND METHODS

The experiments were conducted on Wistar male rats weighing 220-250 g. Experimental myocardial infarction was produced after Selye [7] by ligating the left coronary artery. Intact animals served as the control. Three hours after infarction the animals were killed by decapitation, because this is the time of the maximal drop of arterial pressure [3]. The thoracic aorta was removed and freed of fatty and connective tissue. An aorta ring 3 mm wide was placed in a thermostatically controlled (37°C) working bath containing an oxygenated (95% $O_2$+5% $CO_2$) Krebs solution, the initial rest-

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0007-4888/93/0008-0929$12.50 