Role of Endothelium-Dependent Mechanism in Formation of Systemic Hemodynamic Responses to Hypervolemia

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Blockade of NO synthesis in anesthetized rats significantly potentiated pressor responses to Polyglucin (by 70%) and considerably increased total peripheral resistance. It was concluded that vasodilatation induced by increased systemic blood flow (cardiac output) modulates pressor responses under conditions of increased blood volume.

Key Words: *blood volume*; *cardiac output; arterial blood pressure*; *blockade of nitric oxide synthesis*

Experiments on isolated and intact blood vessels [2,6, 8] demonstrated that synthesis endothelium-derived relaxing factor (NO) [7] is a fundamental mechanism of regulation of the vascular tone. It is accepted that enhanced synthesis of NO by the endothelium can be induced by changes in mean arterial blood pressure (BP), pulse pressure, blood flow, and any other mechanical events, which increase shear stress at the inner surface of the vascular wall [1,2,6,9]. Inhibition of NO-synthase leads to vasoconstriction and arterial hypertension [2], which suggests that NO-related mechanisms play an important role in the regulation of not only local, but also systemic circulation. However, in a great number of systemic responses to various physiological stimuli the role of endothelium-dependent dilatation is still unclear. The aim of this study was to elucidate the role of NO-based mechanism in systemic hemodynamic responses to increased cardiac output (CO) and BP. The hemodynamic responses were studied on a rat model of acute hypervolemia, which induced increases in CO and BP. It should be noted that the role of endothelium-dependent mechanisms in the reaction of systemic hemodynamics to physiological stimuli is poorly studied.

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MATERIALS AND METHODS

Experiments were performed on 9 adult male Wistar rats weighing 220-340 g anesthetized with urethane (1.2-1.5 g/kg). The rats were heparinized (500 U/kg) and ventilated using a Vita apparatus. Systolic, diastolic, and mean BP were recorded in the femoral artery via a PDP-400 transducer. Cardiac output (blood flow in the ascending aorta) was recorded by an RKE-2 electromagnetic flowmeter using a 2-mm gage and recorded with an N-3021 ink-pen recorder. The total peripheral resistance was calculated as the ratio of mean BP and CO measured at the same time interval.

Acute hypervolemia (7% increase in blood volume) was produced by infusion of plasma-substituting solution (Polyglucin) into the femoral vein over 3 min at a flow rate of 0.3 ml/min using an NP-1M pump.

N^{ω}-nitro-L-arginine methyl ester (L-NAME), an inhibitor of NO-synthase, was injected into the femoral vein in a dose of 1mg/100 g body weight. Infusion of plasma-substituting solution was performed before and 15 and 30 min after injection of L-NAME.

The data were stored and processed using a computer. The results were statistically analyzed using Student's *t* test.

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RESULTS

The initial BP and CO were 87.2±3.7 mm Hg and 63.4±6.6 ml/min, respectively (Table 1, Fig. 1).

Infusion of plasma-substituting solution under the conditions of NO-synthase blockade increased BP and total peripheral resistance, which was the most important result obtained in this series of experiments. Although inhibition of NO synthesis considerably increased the baseline BP and total peripheral resistance, their shifts in response to Polyglucin infusion were statistically significant (Table1, Fig. 1). Under these conditions, CO increase in response to infusion of Polyglucin potentiated pressor responses by 70%. The total peripheral resistance underwent similar changes.

Initially, the growth of CO by 20% was accompanied by 25% increase in BP. After inhibition of NO synthesis, these parameters increased by 14 and 28%, respectively. This attests to an important role of the flow-dependent vasodilatation caused by NO secretion in response to systemic blood flow increase in the formation of the pressor response to Polyglucin.

It is noteworthy that Polyglucin was infused against the background of increased BP (result of NO synthase blockage): 136 *vs*. 87 mm Hg.

It was previously demonstrated that the increase in BP diminishes the pressor responses to Polyglucin infusion [1]. It can be hypothesized that in parallel to events associated with changes in mechanical properties of the vascular wall, BP rise stimulated synthesis of NO by endothelium, which led to attenuation of the pressor responses.

In the present work, the lower baseline level of NO due to inhibition of NO-synthesis was the major factor responsible for reversal of changes in pressor responses during NO-synthase blockade.

Enhanced pressor reactions to Polyglucin infusion against the background of NO-synthase blockade attests to involvement of NO-related vasodilatation cau-

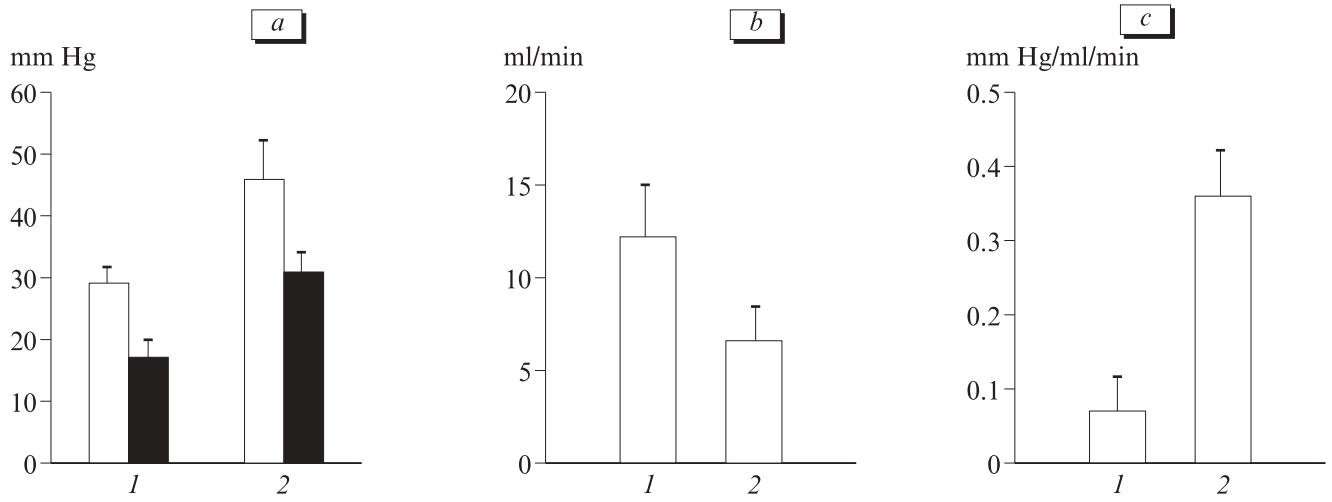

Fig. 1. Changes in systemic hemodynamic parameters induced by infusion of plasma-substituting solution (Polyglucin) before (*1*) and during NO-synthase blockade in rats. *a*) systolic (light bars) and diastolic (dark bars) pressure; *b*) cardiac output; *c*) total peripheral vascular resistance.

TABLE 1. Effects of NO-Synthase Inhibition on Systemic Hemodynamic Responses Induced by Infusion of Plasma-Substituting Solution (*M*±*m*)

Parameters	Before blockade		During blockade	
	baseline value	response to infusion	baseline value	response to infusion
Mean pressure, mm Hg	87.2±3.7	22.5±2.7	134.9±10.7*	38.8±6.5***
Systolic pressure, mm Hg	115.7±4.9	29.1±2.7	157.4±10.8**	45.9±5.3***
Diastolic pressure, mm Hg	69.3±3.6	17.1±2.7	118.4±10.5*	30.9±5.3***
Cardiac output, ml/min	63.4±6.6	12.2±2.7	46.0±4.7	6.6±1.7
Total peripheral resistance, mm Hg/ml/min	1.46±0.14	0.07±0.04	3.06±0.46*	0.36±0.08**

Note: *p<0.001; **p<0.01; ***p<0.05 compared to initial values (before blockade).

sed by CO increase and subsequent increase in systemic circulation.

Thus, the effect of blood flow changes on the basal level of NO synthesis established for local circulatory responses [1,2,8], can also play an important role in systemic hemodynamics. The evidence that inhibition of NO-synthesis diminishes distensibility of feline hindlimb arterial bed during increased perfusion flow [5] gives another confirmation of actual functioning of the flow-dependent vasodilatation mechanism.

The data obtained on isolated arteries demonstrate that NO is not a single factor involved in endothelium-mediated arterial dilatation in response to increased blood flow or shear stress [3].

Our findings confirm the view [10] that NO-related vasodilatation represents the second most important regulatory mechanism (after baroreflex) aimed at smoothing BP fluctuations induced by mechanical perturbations in the vascular bed and at the maintenance of optimal BP level. This is the physiological role of the flow-dependent vasodilatation based on ability of endothelium to enhance NO synthesis in response to shear stress.

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