CORRELATION BETWEEN ENDOTHELIUM-DEPENDENT RELAXATION OF THE AORTA AND BLOOD PRESSURE IN RATS WITH MYOCARDIAL INFARCTION

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The endothelium plays an important role in the regulation of vascular reactivity. Its damage in various diseases and pathological situations, such as atherosclerosis [13], diabetes [8], hypertension [6], toxic concentrations of catecholamines [1], and anoxia [4] leads to weakening or even reversal of endothelium-dependent vascular relaxation under the influence of endogenous and exogenous vasodilators. Ultimately vascular tone is disturbed, and this is reflected in increased peripheral resistance to the blood flow and spasm of the coronary arteries [14]. Meanwhile we know that acute myocardial infarction is often accompanied by a marked lowering of vascular tone and of blood pressure (BP). It was accordingly decided to study whether potentiation of endothelium-dependent relaxation, along with other factors, can play a role in the development of such disturbances.

The aim of this investigation was to study endothelium-dependent relaxation of the rat aorta and to compare it with the trend of BP after experimental myocardial infarction.

EXPERIMENTAL METHOD

Experiments were carried out on male Wistar rats weighing 200-230 g. Experimental myocardial infarction was induced by the method in [11] by ligating the descending branch of the left coronary artery at the boundary between the left auricle and the trigone of the pulmonary artery. Intact animals and rats undergoing a mock operation served as the control. The mock operation consisted of thoracotomy and placing a ligature beneath the artery, without tying it. BP was measured 1, 3, 5, 9, and 24 h after creation of the experimental myocardial infarction by an indirect bloodless method in the caudal artery, by means of a DMP 4F Physiograph ("Narco Bio-Systems," USA). BP was measured in the control animals simultaneously, so as to exclude any effect of circadian rhythms. The animals were killed by decapitation and the thoracic aorta was removed and freed from adipose and connective tissue. A ring preparation of the aorta 3 mm wide was placed in a constant-temperature (37°C) working chamber, filled with oxygenated (95% O_2 ± 5% CO_2) Krebs' solution, with an initial stretching load of 1200 mg. The preparations were kept under these conditions for 1 h before recording began (period of stabilization). Simultaneous recordings were obtained from a preparation with intact endothelium and a de-endothelized preparation. The endothelium was removed mechanically with the aid of a special catheter. Endothelium-dependent relaxation was induced by cumulative addition of acetylcholine (ACh) to the chamber in concentrations of 10^{-8}-10^{-5} M against a background of contraction, induced beforehand by noradrenalin (NA, 5×10^{-7} M). Under these conditions the de-endothelized preparations did not relax. The amount of endothelium-dependent relaxation was expressed as a percentage of contraction on the plateau of the response to NA. Isometric contractions were recorded on a Gemini two-channel recorder (Ugo Basile, Italy). The results were subjected to statistical analysis by Student's t test and determination of the coefficient of correlation r.

EXPERIMENTAL RESULTS

During the first hour after creation of a myocardial infarct a marked fall of BP was observed, which was greatest 3 h after the operation when BP fell from 110 to 70-75 mm Hg (Fig.

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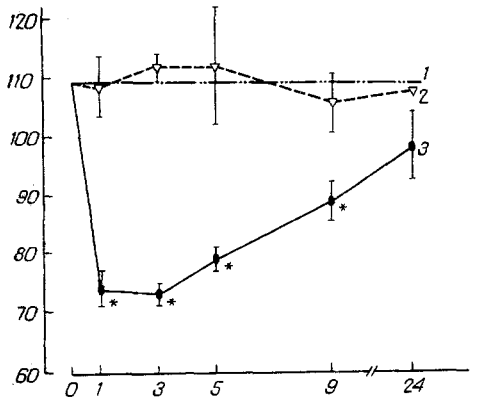

Fig. 1

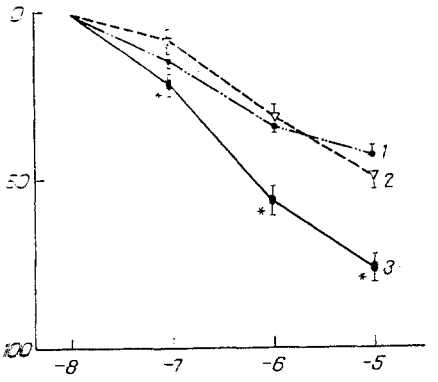

Fig. 2

Fig. 1. Effect of experimental myocardial infarction on trend of BP in rats. Abscissa, time after experimental operation, in h; ordinate, BP, mm Hg. 1) Control; 2) mock operation; 3) myocardial infarction; *$p < 0.01$ indicates significance of differences from control.

Fig. 2. Effect of experimental myocardial infarction on endothelium-dependent relaxation of isolated rat aorta. Abscissa, ACh concentration (on logarithmic scale, M); ordinate, relaxation (% of contraction in response to 5×10^{-7} M NA). Remainder of legend as to Fig. 1.

1). Mortality of the animals undergoing coronary ligation, it will be noted, was maximal at this time. Later, BP began to rise gradually and after 24 h it did not differ significantly from the control. The mock operation caused no significant changes in BP. In intact animals it amounted to 109 ± 1.0 mm Hg and remained virtually constant throughout the period of the experiment.

To study endothelium-dependent relaxation of the aorta, time points were chosen after myocardial infarction at which the greatest changes were observed in BP: 3 and 24 h after ligation of the coronary artery.

The curves shown in Fig. 2 indicate that cumulative addition of ACh to the perfusion solution against the background of NA-induced contraction led to relaxation of aortic rings with intact endothelium in all series of experiments. However, preparations of aorta from animals developing myocardial infarction relaxed by a much greater degree under the influence of ACh than preparations of aorta from animals of the control and mock operation series. After addition of ACh to the perfusion solution in a concentration of 10^{-5} M the aorta of the control animals relaxed by 43 ± 2.7%, whereas the aorta of animals developing an infarct relaxed by 76 ± 4.2% ($p < 0.01$). The degree of relaxation of the aorta in response to addition of ACh, 24 h after ligation of the coronary artery, was virtually the same as in the control, which coincided in time with recovery of BP. The mock operation induced no significant changes in endothelium-dependent relaxation.

Experimental myocardial infarction thus leads to potentiation of endothelium-dependent relaxation of vascular smooth muscle.

When the possible mechanism of the increased effect of the endothelium on vascular smooth muscle is evaluated, it must be recalled that an important component of stress-induced damage is realization of the "lipid triad," composed of activation of lipid peroxidation, activation of lipid peroxidation, activation of lipases and phospholipases, and elevation of the blood level of free fatty acids [2]. Certain products on free-radical oxidation such as, for example, the hydroxyl radical, induce release of endothelial relaxation factor (EDRF) or potentiate its release under the influence of endothelial-dependent vasodilators [9, 10]. An important role in the formation of EDRF is also played by the release of free fatty acids, which enhance the endothelium-dependent relaxation. Meanwhile, phospholipase inhibitors prevent the endothelium-dependent vascular relaxation [12]. The most likely precursor of EDRF is arachidonic acid [5], whose metabolism is potentiated by the action of catecholamines [15]. It has recently been suggested that EDRF is identical with nitric oxide (NO) [7]. The role of each of these factors for stress-induced potentiation of endothelium-dependent relaxation has not been explained.

TABLE 1. Correlation between Degree of Endothelium-Dependent Relaxation of the Aorta and BP (M ± m)

Experimental conditions	BP, mm Hg	Relaxation, % of force of contraction in response to NA	r
Control (intact animals; n = 10)	109±1,0	43±2,7	−0,87
Infarct:			
3 h (n = 9)	73±1,4*	76±4,2*	−0,93
24 h (n = 9)	99±6,5	47±5,7	−0,78
Mock operation:			
3 h (n = 8)	112∓2,3	49±3,6	−0,78
24 h (n = 8)	108±1,6	39±3,0	−0,56

Legend. n) Number of animals in series. *$p < 0.01$.

Since, according to data in the literature, weakening of endothelial function may cause a disturbance of vascular relaxation, which may go on to the development of vasospasm [14], it can be tentatively suggested that potentiation of endothelium-dependent relaxation, like that observed in the present experiments, may be due, on the other hand, to a reduction of vascular tone, with a sharp fall of BP, and may thus facilitate the development of cardiogenic shock in patients with myocardial infarction.

To test this hypothesis we compared the degree of endothelium-dependent relaxation of the aorta with the level of BP in animals of all the experimental groups (Table 1).

Table 1 shows that in all series of experiments lowering of BP was accompanied by potentiation of endothelium-dependent relaxation and, conversely, on recovery of BP to the control level, there was simultaneous weakening of endothelial functions. In this case, as Table 1 shows, a sufficiently high degree of negative correlation exists between these parameters. These results are evidence in support of the view that the endothelium has a role in the regulation of the systemic BP.

The experiments showed that experimental myocardial infarction leads to marked potentiation of endothelium-dependent relaxation of the vascular wall, which is accompanied by a sharp fall of BP. Considering the high degree of correlation between these two parameters, it is suggested that excessive activation of endothelial function can play an important role in the development of cardiogenic shock in patients with myocardial infarction, in the same way as an excess of opioid peptides plays a role in the development of shock states [3]. Of course this hypothesis requires comprehensive verification and, in particular, a study of the effect of stress and infarction on endothelium-dependent relaxation not only of the aorta, which is a conducting vessel, but also of arterioles, which play the principal role in formation of the peripheral resistance.

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