ROLE OF ADRENERGIC MECHANISMS IN THE DEVELOPMENT OF CEREBROVASCULAR DISTURBANCES IN ACUTE MYOCARDIAL ISCHEMIA

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KEY WORDS: myocardial ischemia; cerebral circulation; adrenergic structures.

In the modern view the heart is a powerful reflexogenic zone, stimulation of whose receptors, by compression of the coronary arteries, leads to reflex excitation of the sympathetic nervous system [8, 10, 13, 14] and to acute cardiac failure, giving rise to considerable disturbances of the circulation and metabolism of the brain [11]. The increased activity of the sympathetic system in turn may lead to cerebrovascular disturbances [9].

The object of this investigation was to study the state of the cerebral circulation and the role of adrenergic structures in the development of cerebrovascular pathology in acute myocardial ischemia.

EXPERIMENTAL METHODS

Experiments were carried out on 45 anesthetized (pentobarbital sodium 50-70 mg/kg) cats of both sexes weighing 2.3-4 kg and artificially ventilated. The volume velocity of the blood flow in the carotid arteries was measured by a flowmeter [3] after preliminary ligation of all extracranial branches. The local blood flow in the cerebral cortex was determined by the hydrogen clearance method [5]. Cardiac output was determined by the thermodilution method [4]. The perfusion pressure (PP) in the blood vessels of the brain and hind limb was recorded by means of a resistograph connected to the common carotid artery. The arterial pressure (BP) was measured in the carotid artery by a mercury manometer. Blood clotting was prevented by intravenous injection of heparin.

Acute myocardial ischemia was produced by occluding the blood flow in the descending branch of the left coronary artery for 3-30 min.

Adrenolytics (phentolamine 0.5 mg/kg and inderal 1 mg/kg) were injected intravenously.

EXPERIMENTAL RESULTS

Myocardial ischemia led to a fall in the volume velocity of the blood flow in the carotid arteries and in BP by 11.9 ± 2.1 and 13.7 ± 3.2% respectively ($P < 0.001$). The effect was observed immediately after occlusion of the coronary artery and it increased in intensity with the passage of time (Fig. 1). After a temporary fall BP gradually returned to its initial level and after 15 min of myocardial ischemia it was only 4.8% below the initial level ($P > 0.1$), whereas the cerebral blood flow was reduced by 17.5 ± 2.3% ($P < 0.001$). The local blood flow in the cerebral cortex changed in various directions during the first 15 min, with an overall tendency to decrease. In the course of myocardial ischemia the cerebral circulation was progressively disturbed and at the 30th minute the total and local cerebral blood flow was reduced by 20.3 ± 4.2% ($P < 0.001$) and 28.9 ± 11% ($P < 0.05$) respectively.

Significant changes also were observed in the systemic hemodynamics. At the 15th minute of myocardial ischemia the cardiac output and stroke volume were 23 ± 10.5 and 27.2 ± 12.7% less respectively than initially ($P < 0.05$).

Consequently, one cause of disturbance of the cerebral circulation could be a decrease in functional activity of the myocardium. However, BP still remained adequately high under these circumstances. Possibly in myocardial ischemia the functional state of the cerebral vessels changes and this leads to cerebrovascular disorders.

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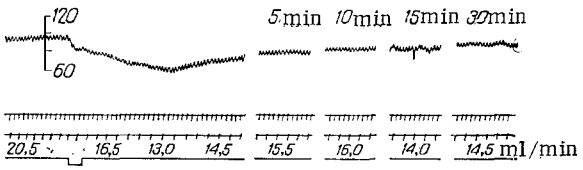

Fig. 1. Changes in total cerebral blood flow in myocardial ischemia. From top to bottom: arterial pressure; time marker 5 sec; total cerebral blood flow; marker of occlusions of coronary artery.

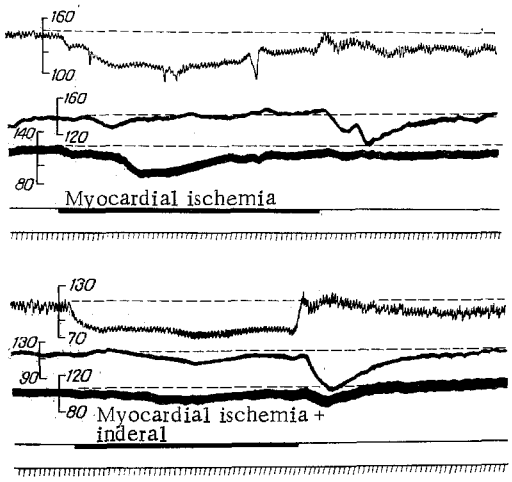

Fig. 2. Reaction of blood vessels of hind limb and brain during myocardial ischemia before and after injection of inderal. From top to bottom: arterial blood pressure; perfusion pressure in blood vessels of hind limb and brain; marker of occlusion of coronary artery; time marker 5 sec.

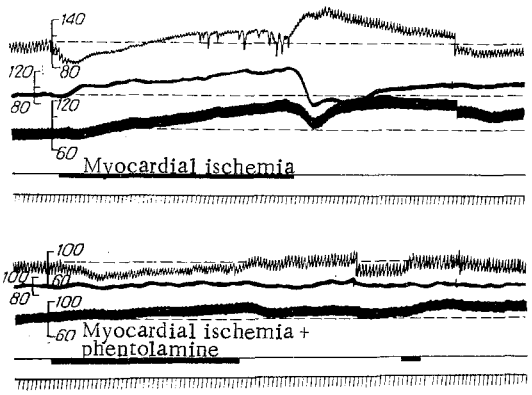

Fig. 3. Reaction of blood vessels of hind limb and brain during myocardial ischemia before and after injection of phentolamine. Legend as to Fig. 2.

To test this hypothesis, autoperfusion of the hemodynamically isolated brain was carried out by means of a constant delivery pump. Blood vessels of the hind limb were perfused at the same time for comparison.

In 53% of the 21 experiments occlusion of the coronary artery caused a fall of BP in blood vessels of the brain and hind limb by 15.2 ± 2.6% ($P < 0.001$) and 10.8 ± 3.9% ($P < 0.05$), respectively. BP was lowered by 35.3 ± 5.7% ($P < 0.001$). The effect was observed after 5-10 sec and was maximal after 2 min (Fig. 2). After 3-5 min of myocardial ischemia PP returned to its initial level in the blood vessels of both these regions. In the other experiments PP was unchaged or increased; on average after 2 min of occlusion PP in vessels of the brain and hind limb was increased by 6.6 ± 3% ($P < 0.05$) and 8.1 ± 4.1% ($P > 0.05$) respectively.

BP fell by 27.8 ± 6.3% ($P < 0.01$). The constrictor response increased with the course of time (Fig. 3) and after 5 min the resistance to the blood flow in vessels of the brain and hind limb was increased by 22.6 ± 7.4 and 26.2 ± 7.4% respectively ($P < 0.05$). BP remained 12.6 ± 7.2% below its initial level ($P > 0.05$).

In all experiments PP in the vessels of the brain and hind limb was initially reduced, although not statistically significantly, by 7.1 ± 3.6 and 4.3 ± 4% respectively, but BP was significantly reduced by 31.2 ± 4.3% ($P < 0.001$). After 5 min PP in these vessels was the same amount higher than the initial level.

Consequently, in myocardial ischemia brief vasodilatation is followed by a prolonged vasoconstrictor reaction, which intensifiies with the course of time.

After removal of the ligature from the coronary artery in the overwhelming majority of experiments PP fell during the first minute (Fig. 3) in the vessels of the brain and hind limb by 8.9 ± 1.6% ($P < 0.001$) and 9.2 ± 5.5% ($P > 0.05$) respectively. The changes in BP after restoration of the coronary blood flowwere as a rule pressor in character.

In the experiments with myocardial ischemia in which a definite vasodilator reaction was observed, β-adrenoreceptor blockade led to a marked weakening of that reaction. In seven cases, for instance, occlusion of the coronary artery caused PP in the cerebral vessels to fall by 16.8 ± 3.8% ($P < 0.01$) and in the vessels of the hind limb by 9.5 ± 7.5% ($P < 0.1$); against the background of inderal PP fell by 4.1 ± 1.6% ($P > 0.05$) and 8.4 ± 4.1% ($P < 0.05$) respectively (Fig. 2). A 0.05 level of statistical significance was adopted.

In six experiments myocardial ischemia caused an increase in PP in blood vessels of the brain and hind limb by 7.2 ± 1.7% ($P < 0.001$) and 8.7 ± 2.5% respectively ($P < 0.01$), whereas α-adrenoreceptor blockade led to a reduction of PP in the cerebral vessels by 3.3 ± 3.7% ($P > 0.1$) and in vessels of the hind limb by 5 ± 2.2% ($P < 0.05$; Fig. 3).

Analysis of these data shows that the reduction in the cerebral blood flow immediately after occlusion of the coronary arteries was associated with the fall in BP, for in most experiments at this time a vasodilator reaction was observed. Reactions of the peripheral vessels arising immediately after occlusion and restoration of the blood flow in the coronary arteries are neurogenic. This is confirmed by the short latent period of the reactions (5-10 sec). The action of humoral factors was ruled out by increasing the rate of flow of blood through the perfusion system (20-30 sec). The most likely source of reflex reactions was the receptors in the myocardium and coronary arteries, although a fall in BP modifies activity of sino-aortic baroreceptors [2, 8]. In the present experiments, however, PP in the carotid sinuses was stabilized.

The subsequent progressive decline in the cerebral blood flow while BP was raised is evidence of activation of the humoral stage of vasoconstriction. This is shown by the protracted character of the process and of the response and the strengthening of the vasoconstrictor or weakening of the vasodilator reactions with time after occlusion of the coronary artery.

Potentiation of the flow of afferent impulses from receptors of the heart may perhaps lead to activation of central adrenergic structures. In rats, for instance, myocardial ischemia led to an increase in the noradrenalin and dopamine concentration in various brain structures [12]. Consequently, the final link in the reflex chain is formed by adrenoreceptors of the cerebral vessels, for blocking them weakens or may even reverse the response of the cerebral vessels. It should be pointed out that in myocardial ischemia the dilator response is more marked in the cerebral vessels, the constrictor response is more marked in vessels of the hind limb. Peripheral vasoconstriction, developing in myocardial ischemia, prevents any considerable drop of BP.

Under conditions of acute myocardial ischemia complex interrelations are thus created between nervous-reflex and humoral factors, which may be realized in the cerebral vessels and may lead to the development of cerebrovascular disturbances such as are frequently observed in clinical practice [1, 6].

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CHOLINERGIC MECHANISM OF REGULATION OF CARDIAC FUNCTION IN ACUTE TRANSIENT CORONARY INSUFFICIENCY

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Cholinergic regulation of cardiac activity plays an essential role in the maintenance of homeostasis during hypoxia. It does so, in particular, by reducing the oxygen demand of the myocardium and its utilization of high-energy phosphates and glycogen and by reducing the degree of disturbance of the transmembrane ion distribution [10]. Collectively these effects increase the resistance of the heart to energy-deficient states of varied genesis. The writer previously found that disturbance of the contractile function and rhythm of the heart in local myocardial ischemia (MI) of coronary genesis and during subsequent reperfusion (RP), takes place in stages which are accompanied by phasic changes in the functional state of the adrenergic control mechanism of cardiac activity [4, 6]. Depression of the parameters of cardiac contractility in the early stages of local MI and during postischemic RP under these circumstances was combined with maintenance of a high functional reserve of the myocardium, reflected in the pressure difference in the left ventricle at rest and during isometric contraction. This fact suggests that the reduction in the contractile function of the heart may be the result not only of regional hypoxic changes, but also of activation of controlling, mainly parasympathetic, influences on the myocardium.

It was accordingly decided to study the state and the role of the cholinergic control mechanism of the heart in acute transient coronary insufficiency (ATCI) of varied duration.

EXPERIMENTAL METHOD

Experiments were carried out on 120 noninbred male albino rats weighing 200 ± 10 g, kept under animal house conditions on an ordinary diet. ATCI was produced by the method described previously [4, 5] under urethane anesthesia (1200 mg/kg) and with artificial ventilation of the lungs with atmospheric air. The duration of MI was 10, 40, or 120 min, and of subsequent RP 40 min. In the zone of MI and in the same zone during subdequent RP of the myocardium, and also in remote parts of the heart the acetylcholine (ACh) concentration was determined by a biological method on the dorsal muscle of the leech [1]; total and bound acetylcholine-like substances (ACLS) [3] and total cholinesterase (ChE) activity [7] also were determined. The response of the heart to ACh was assessed by the time course of the chronotropic reaction,

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