SYMPATHETIC AND PARASYMPATHETIC REGULATION OF THE HEART DURING TRANSIENT CORONARY INSUFFICIENCY

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The writer previously [2, 3, 5, 7] argued in support of the concept of transient coronary insufficiency (TCI) as a combination of two cardiogenic syndromes: due to ischemia and perfusion. The latter is the result of the combined reparative and pathogenic action of reperfusion factors on the myocardium, and also of its prolonged ischemic damage. The pathogenic effects of reperfusion, especially on the mycardium in prolonged ischemia, are associated with additional (due to reperfusion) changes in the membrane apparatus and enzymes of the cardiomyocytes, and also with aggravation of the disturbance of their energy supply, especially in the stages of transport and utilization of the energy of ATP [2, 4, 5, 7].

The aim of this investiation was to study the principles and role of changes in sympathetic and parasympathetic mechanisms of regulation in the development of the adaptive responses of the heart to its local ischemia, of varied duration, and also in the period of subsequent reperfusion.

EXPERIMENTAL METHOD

Experiments were carried out on 480 noninbred male albino rats weighing 200 ± 20 g and 60 male chinchilla rabbits weighing 3-4 kg. TCI was produced in conscious and anesthetized animals by the methods described previously [3, 7]. The duration of the period of coronary occulsion was 10, 40, or 120 min. During reperfusion observations were made for 40-60 min. Concentrations of noradrenalin (NA) and dihydroxyphenylalanine (DOPA) in the myocardial tissue were determined by the method in [6]. The adrenergic properties of the heart were evaluated on the basis of changes in blood pressure (BP) in the left ventricle in response to injection of NA hydrotartrate into the jugular vein in a dose of 1.5 μmole/kg, and also by recording the degree of changes in heart rate (HR) at the maximum of the fall of BP in response to injection of acetylcholine chloride (ACh) into the jugular vein in a dose of 2.5 μmoles/kg, with calculation of the coefficient of sensitivity of the baroreflex as the ratio of the change in HR to the change in BP. The concentration of the free ACh fraction [1] and of the reserve pool of acetylcholine-like substances (AChLS) also was determined in the heart tissue [8]. The cholinergic properties of the heart were evaluated by recording changes in BP in the left ventricle in response to injection of ACh in a dose of 2.5 μmoles/kg, and also recording changes in the coefficient of sensitivity of the baroreflex after injection of NA in a dose of 1.5 μmole/kg.

EXPERIMENTAL RESULTS

Analysis of the data in Figs. 1 and 2 reveals regular alternation of a period of activation of sympathetic and parasympathetic influences on the heart in the early stage of the ischemic period of TCI (during its first 10 min) with a period of activation predominantly of parasympathetic influences, as the duration of cornary inclusion increased and also in the period of reperfusion. This was shown by alternation of a period of a considerable rise of the NA level in different regions of the heart accompanied by simultaneous increase in the ACh concentration with a period of lowering of the NA level, associated with preservation of a raised ACh concentration. Fluctuation of the neurotransmitter concentrations is the result of a change in the intensity of NA and ACh biosynthesis and, to a certain degree, of the processes of their inactivation. Evidence in support of the first factor is given by

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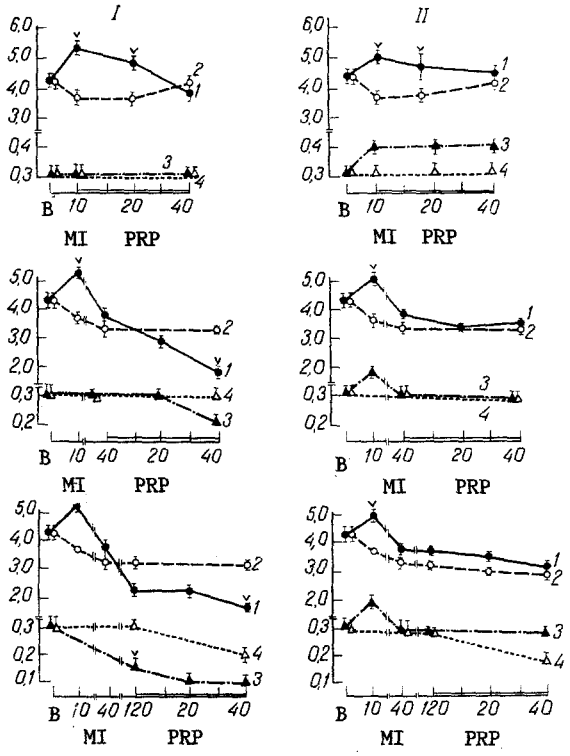

Fig. 1

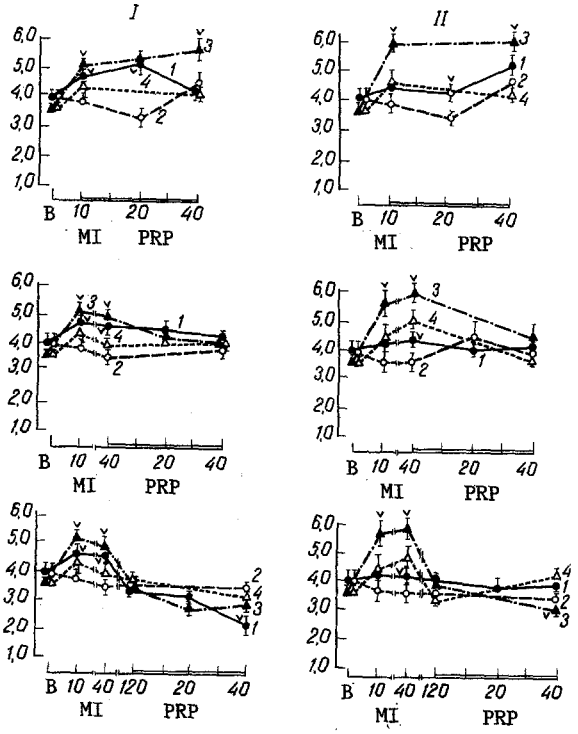

Fig. 2

Fig. 1. Time course of NA and DOPA concentrations in the heart in transient coronary insufficiency (M ± m). Abscissa, duration (in min) of periods of myocardial ischemia (MI) and postischemic reperfusion (PRP); ordinate, NA and DOPA concentrations (in mmoles/g). I) Zone of MI and PRP; II) areas of myocardium at a distance from it; B) background values. 1, 3) NA and DOPA levels in I and II, respectively; 2, 4) NA and DOPA levels in myocardium after mock operation. ν) Significant difference between values and those after mock operation ($p < 0.05$); n = 8 (at each point of the graph).

Fig. 2. Time course of levels of free ACh fraction and bound AChLS in heart during transient coronary insufficiency (M ± m). Ordinate, concentrations of ACh (in mmoles/g) and AChLS (in mg/g). 1,3) ACh and AChLS concentrations of I and II, respectively; 2, 4) ACh and AChLS concentrations respectively in myocardium after mock operation. Remainder of legend as to Fig. 1.

data showing, as a rule, parallel changes in the concentrations of DOPA, a precursor of NA synthesis (Fig. 1), in the myocardium and in the value of a parameter of ACh replenishment, namely the reserve fraction of AChLS (Fig. 2), whereas support for the second factor is given by the opposite changes in cholinesterase activity compared with the ACh concentration [7]. The time course of neurotransmitter concentrations in the myocardium described above was accompanied by simultaneous alternation of the hyperkinetic response of the heart (during the first 5-10 min of the ischemic period) with a hypokinetic mode of working. The hyperkinetic cardiac response in this case must be regarded as adaptive, so far as the body as a whole is concerned, for it was aimed at emergency compensation of disorders arising in the heart tissue and in the microhemocirculation due to exclusion of the ischemic part of the heart from the contractile process. The formation of the hypokinetic mode of working of the myocardium with an increase in the duration of its local ischemia and potentiation of that mode in the initial stage of the reperfusion period of TCI are adaptive from the point of view of the heart, for they help to reduce the load on the heart and thus to prevent the development of heart failure or to reduce its severity.

The ischemic period of TCI was characterized by a decrease in the severity of the direct hypodynamic response of the heart to ACh (Fig. 1, I, b). This led to an increase in the stability of its function in the presence of acute local ischemia. Reperfusion of the previously ischemic region of the myocardium led to comparatively rapid normalization (or a tendency toward it, during the first 10-40 min of the period) of the intensity of the hyper- and hypodynamic responses of the heart to neurotransmitters. This was combined with restoration

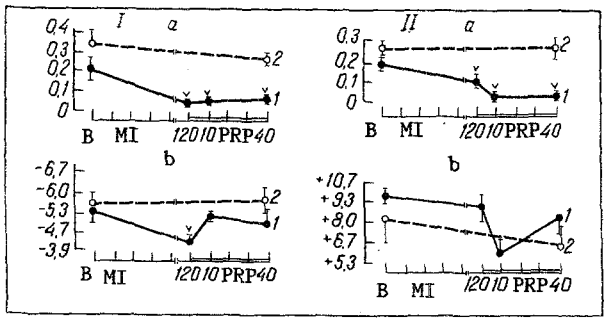

Fig. 3. Changes in BP in left ventricle and coefficient of sensitivity of baroreflex during transient coronary insufficiency with a duration of coronary occlusion of 120 mn (M ± m). Ordinate: a) coefficient of sensitivity of baroreflex (in pulses·min^{-1}·kPa) in acute hypertension induced by NA (I, a) and acute hypotension, induced by ACh (II, a); b) value of deviation of BP (in kPa) in response to injection of ACh (I, b) or NA (II, b). 1) Transient coronary insufficiency; 2) mock operation. Remainder of legend as to Fig. 1.

of the NA and ACh concentrations in the myocardium to near-control values or with cessation of their fall, mainly outside the zone of reperfusion, with consequent matching of the level of heart function to the course of sympathetic and parasympathetic regulatory influences on the heart.

TCI also was characterized by restriction of involvement of the heart in reflex response of the cardiovascular system to efferent excitatory (Fig. 3, I, a) and inhibitory (Fig. 3, II, a) stimuli of sympathetic and cholinergic nature. The intensity of this phenomenon increased with an increase in the duration of coronary occlusion. In the initial stage of the reperfusion period, a further reduction (Fig. 3, II, a) or maintenance (Fig. 3, I, a) of the depressed chronotropic response of the heart to acute hyper- or hypotension was recorded. Weakening of sympathetic and parasympathetic reflex influences on the heart, combined with a decrease in the degree of its hyperdynamic response to catecholamines, facilitates the regulatory limitation of function of the myocardium and reduction of the degree of its alternation by ischemic and reperfusion factors.

The results of this study are evidence of the regular development of the phenomenon of "limitation" of involvement of the heart in direct and reflex responses of the circulatory system at stages of TCI fraught with the risk of considerable or irreversible myocardial damage. The development of the "limitation" phenomenon, which is realized with the participation of sympathetic and parasympathetic mechanisms of regulation, reduces the severity of damage to the heart during its local ischemia and potentiates repair processes in it during the reperfusion period of TCI.

LITERATURE CITED

1. K. B. Vinnitskaya, Lab. Delo, No. 2, 89 (1970).
2. P. F. Litvitskii, A. Kh. Kogan, A. N. Kudrin, et al., Byull. Éksp. Biol. Med., No. 3, 271 (1981).
3. P. F. Litvitskii, Byull. Éksp. Biol. Med., No. 8, 120 (1982).
4. P. F. Litvitskii, A. Kh. Kogan, A. N. Kudrin, and L. O. Luk'yanova, Kardiologiya, No. 7, 94 (1982).
5. P. F. Litvitskii, Kardiologiya, No. 6, 11 (1984).
6. É. Sh. Matlina and V. V. Men'shchikov, Clinical Biochemistry of Catecholamines [in Russian], Moscow (1967).
7. L. I. Ol'binskaya and P. F. Litvitskii, Coronary and Myocardial Insufficiency [in Russian], Moscow (1986).
8. S. Hestrin, J. Biol. Chem., 180, No. 1, 249 (1949).