Raising the Resistance of the Myocardium to Ischemia in a Chronic Model of Angina Pectoris

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The model of local reversible disturbances of the coronary blood flow in chronic experiments on nonanesthetized dogs or, in other words, a chronic model of angina pectoris [1,2] provides a methodological basis for seeking ways of raising the myocardial resistance to ischemia under the conditions most closely approaching the clinical ones.

The aim of the present study was to discover such methods, a task involving three stages. First, it is necessary to substantiate the experimental possibility of achieving an appreciable effect with low doses (not affecting the electrocardiogram, ECG) of pituitrin upon the zone of the ischemic focus in the myocardium (where the full-value coronary constrictive tone is absent). This problem has already been partially solved, since pretreatment with such doses of this hormone have been shown to cause a marked reduction of the intensity of the ischemic shifts of the ECG following the mechanical disturbances of the blood flow in the coronary artery [3]. The results of further study of this problem are presented in the first part (1st series of experiments) of this publication. The second stage of the research was to study to what extent the drug-induced stabilization and enhancement of the shifts which arise spontaneously in the ischemic heart serve to raise the resistance to local ischemia. Primarily, these shifts include the development of spasms of the small arteries (usually determined by angiography), as well as a decrease of contractility in the focus of lesions and its simultaneous increase in the zones of compensation [4,6,7]. It has already been shown that complex therapy must involve pituitrin in low doses. The goal of the second stage (2nd series of experiments) was to determine to what extent the effect of this hormone, combined with nonuniform (positive and negative) inotropic effects on the organism, may lead to the above beneficial changes of the local myocardial activity and, as a result, to a reduction of the intensity of ischemic shifts in the ECG. And, finally, the third stage, comprising the 3rd series of experiments, entailed studying the actual possibility and the effect of combining the methods of complex therapy developed by us with drugs traditionally used in maintaining cardiac activity during local disturbances of the coronary blood flow.

MATERIALS AND METHODS

The experiments were carried out on specially pretreated dogs (without anesthesia) fixed in stands with belts. A total of 99 experiments on 53 animals were performed in three series. Two to three weeks prior to the experiments, a preliminary operation was performed, during which we implanted a remote-control device making it possible (without repeating the thoracotomy) to arrest and then to restore the blood flow in the circumflex branch of the left common coronary artery at the site of its origin from beneath the left auricle [1]. Dur-

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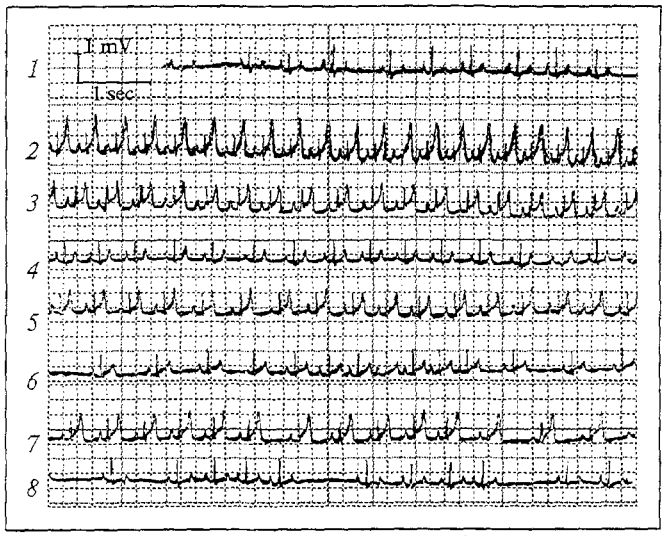

Fig. 1. Phase changes of ECG in standard lead II from extremities for reversible disturbance of coronary blood flow. ECG records: *1*) before myocardial ischemia, left: reference signals corresponding to 1 mV and 1 sec; *2*) 30 min after occlusion of lumen of coronary artery; *3*) 3rd min of myocardial ischemia; *4*) 5th min of myocardial ischemia; the loop on the coronary artery remains tightened; *5, 6, 7*) 6th, 7th, and 11th min of ischemia, respectively; *8*) 10 min after restoration of disturbed blood flow.

ing the course of ECG-monitored experiments the blood flow in the coronary artery was arrested for 1-3 min or, if the development of a pronounced ischemic response could be prevented, for a longer period lasting 20-30 min or more. In the 1st series of experiments, the effect of reversible disturbances of the coronary blood flow was studied in the absence of additional effects of drugs or (after 15-65 min) following intramuscular or intravenous administration of one of the coronary-active substances: the dilators difryl (10 mg/kg) and 0.5% curantil (0.03 ml/kg), or the constrictor pituitrin (0.25-0.5 IU/kg). In the 6 experiments of series 2, pituitrin (0.25 IU/kg), digoxin (0.003 mg/kg), and propranolol (0.015 mg/kg i.v. or 0.15 mg/kg i.m.) were similarly administered. In the 6 experiments of series 3, these three drugs were injected in combination with sustac (0.09 mg/kg) and 0.1% morphine (1.0 ml/kg subcutaneously).

RESULTS

As was noted earlier [1], the data obtained in the 1st series of experiments show that disturbances of the blood flow in the coronary artery cause a rise of the ST interval over the ECG isoline and increase the amplitude of the positive T wave in the leads directed toward the focus of lesions (for the vertical position of the heart in dogs: in the standard leads II and III from the extremities). It

TABLE 1. Therapeutic Effect during Stages of Complex Therapy of Ischemized Myocardium in Three Series of Experiments

Characteristics of effects	Specificities of adjunct drug administration in experiments with disturbed coronary blood flow		
	1st series: separate administration of low doses of pituitrin	2nd series: same as 1st, but involving propranolol and digoxin	3rd series: same as 1st and 2nd, but involving sustac and morphine
Frequency of total absence of ischemic shifts of ECG after disturbance of blood flow, %	8.3	16.6	83.3
Effect of reduction of ischemic shifts of ECG for a majority of observations following disturbances of coronary blood flow	Reduction does not lead to complete normalization of ECG; reduction of shifts of ECG is stable (without remissions)	Complete normalization of ECG is periodically attained during 25-30% of duration of ischemia (remission effect)	Normal ECG is preserved discontinuously until 10th-20th min of ischemia and longer (not intermittent effect)
Probable cause of therapeutic effect: myocardial activity decreases in zone of lesions and increases in zones of compensation, this being variously achieved. Here, the effects of realization of different mechanisms may probably be summed	Low doses of pituitrin strengthening normal constrictive tone in zone of ischemic coronary dilation (and spasm of small arteries disrupted by ischemia) are evidently too small to produce effect on myocardium in zones of compensation	Simultaneous manifestation of both positive and negative inotropic effects on heart causes intermittent (if above effects are balanced) activation of myocardium in zone of ischemia or in zones of compensation	Strengthening of parasympathetic effects on heart is attended by development of coronary inotropic effect predominantly manifested in zones of compensation, since nitrites are largely unable to dilate damaged arteries of small diameter

Note. After injection of pituitrin and subsequent disturbance of the coronary blood flow, ischemic shifts of ECG, namely ST_{II-III} and T_{II-III}, dropped 0.22±0.08 and 0.44±0.13 mV, respectively (vs. control observations, $p<0.05$).

should be mentioned that the disturbance of the blood flow in this artery and its recovery per se (following the 2-min or longer occlusion) lead to the development of myocardial fibrillation in the majority of observations. In addition, in the experiments on one and the same animal in which the coronary blood flow was redisturbed at 1-3-day intervals, restoration of the flow elicited one or several waves of intermittent shifts of the ECG during 1-5 min of the postocclusion period following 1-2-min myocardial ischemia, these shifts being similar to the above-mentioned manifestations of ischemia (i.e., the appearance of the ST rise over the isoline and an increase of the positive T wave). And, finally, for the same disturbances of the coronary blood flow in the same animal, repeated during a single experiment (duration 30-60 min) at intervals lasting one or several minutes, the amplitude of ischemic ECG shifts caused by occlusion of the vessel proved to be higher during the first disturbance of the blood flow and markedly lower during the repetitions of the disturbances [1]. The pharmacological analysis performed by us showed significant differences between the sequelae of disturbances of the coronary blood flow following pituitrin injection and against the background of each of the above coronary dilators. After injection of pituitrin (in the dose mentioned above) the ST_{II-III} rise over the isoline was 0.22±0.08 mV ($p<0.05$), and the amplitude of the positive T_{II-III} wave proved to be 0.44±0.13 mV lower ($p<0.01$) than that for control occlusions of the same arteries in the same dogs in the absence of adjunct drug administration. When the coronary dilators were administered, such a reduction of the ECG shifts was never noted for disturbed coronary blood flow in similar experiments. Following pituitrin injection, the development of myocardial fibrillation in response to restoration of the disturbed coronary blood flow was observed in just 9.09% of cases, while after administration of one of the coronary dilators this was manifested in 71.4% of cases. A postocclusion rise of ST_{II-III} and an increase of T_{II-III} were noted in only one out of 6 tests against the background of pituitrin and in 6 out of 7 experiments following injection of coronary dilators ($p<0.05$). At the same time, in the majority of observations the number of separate waves of transient ischemic ECG shifts increased to 5-7 (vs. 1-3 in the control). Lastly, the frequency of a decrease of the amplitude of ischemic shifts also proved to be different for redisturbances of the blood flow in the same coronary artery over the 30-60 min of the follow-up: 16.6% with the use of coronary dilators

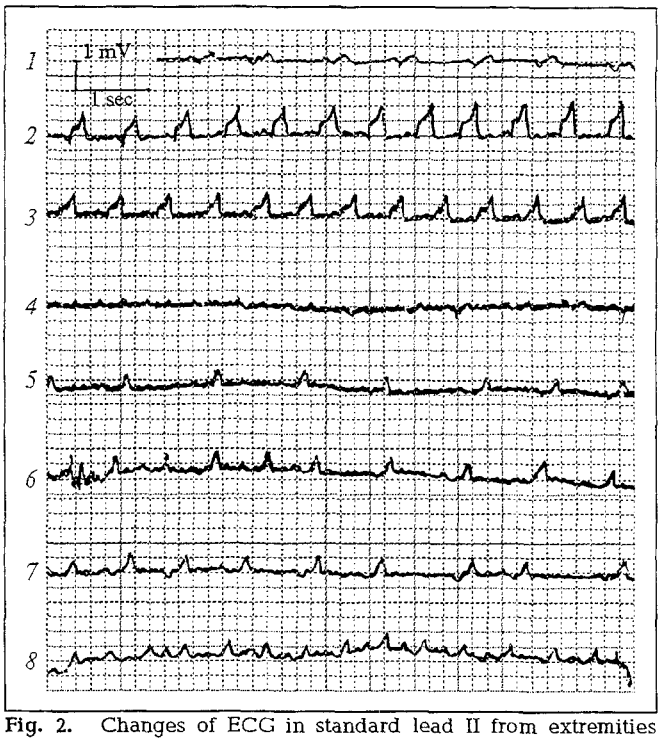

Fig. 2. Changes of ECG in standard lead II from extremities during chronic experiment with redisturbances of blood flow in circumflex branch of left common coronary artery in a dog. ECG records: *1*) initial record, left: reference signals corresponding to 1 mV and 1 sec; *2*) 2 min after first arrest of blood flow; *3*) effect of 2nd arrest of blood flow in the same artery (2nd min of myocardial ischemia); *4*) after restoration of blood flow in the artery; *5*) after injection of the 5 indicated preparations; *6* and *7*) 2–3 and 10–11 min after third arrest of blood flow in the artery; *8*) directly after restoration of disturbed blood flow.

and 100% (6 experiments) in the case of pituitrin injection ($p<0.05$). Thus, in our experimental model, the administration of coronary dilators does not elicit any therapeutic effect or any reduction of the ischemic damage to the myocardium. On the other hand, low doses of pituitrin do produce such an effect, providing a basis for the development of a multicomponent scheme of therapy aimed at boosting the resistance of the heart to local ischemia.

In the 2nd series of experiments we attempted to realize the above possibilities by combining the effect of low doses of pituitrin with that of propranolol and digoxin (in the doses mentioned). The dynamics of the ECG shifts assumes a new character when myocardial ischemia is reproduced after administration of these drugs (Fig. 1). Discontinuous (intermittent) manifestations of the ECG shifts are observed for continuous occlusion of the lumen. In the experiment presented in Fig. 1, such specific remissions (periods of normalization of the ECG) appeared three times over the 11-min disturbance of the coronary blood flow. Two such periods are shown in Fig. 1, *4*, *6*).

Further modification of the scheme of complex therapy, involving two more drugs: morphine (which raises the tone of parasympathetic effects on the heart and prevents tachycardia) and nitrites (sustac) (which increases the blood flow in the heart arteries not damaged by ischemia) [5,9] enabled us to prevent outright the above ischemic shifts of ST in the ECG until the 10th-20th min of myocardial ischemia in 5 out of 6 experiments (3rd series). As is seen from Fig. 2, the control disturbances of the blood flow in the coronary artery (prior to injection of the drugs) twice led to the development of pronounced ischemic shifts in the terminal portion of the ventricular complex of the ECG, these shifts manifesting themselves during the first 15 sec of myocardial ischemia. The administration of the above drug combination altered the ECG: the heart rate dropped and the amplitude of the T wave (variable in dogs) attained the high normal level: 0.7-0.8 mV. The subsequent complete arrest of the blood flow in the coronary artery for a period lasting more than 11 min failed to cause marked changes in the ECG and, most importantly, did not cause the development of ischemic shifts of ST.

On the whole, all these findings are sufficiently illustrative of the fact that a sequential, well-founded scheme of complex therapy of the ischemized heart improves the efficacy of the multifaceted influence upon the organism (Table 1): at first (1st series of experiments), the effect of ECG normalization is not complete, but quite evident; then (2nd series) it becomes discontinuous; and only in the 3rd series of experiments did we succeed in normalizing the ECG over the whole period of myocardial ischemia in the majority (83.3%) of observations. Thus, there are grounds for assuming that the scheme of complex therapy of ischemic damage to the myocardium, which calls for the use of low (not affecting the ECG by themselves) doses of pituitrin, may clear the way for boosting the efficacy of some traditional and routinely used drugs (such as morphine and nitrites) in the treatment of certain forms of cardiac ischemia. Further improvement of antianginal therapy (within the scope of the above method) involves the analysis, identification, and drug correction of the pathophysiological mechanisms of ischemic damage to the myocardium which have not yet been taken into account when developing the present scheme of complex action. The phenomena which demand further study include the changes of tonic (not contractile) tension of the myocardium in the ischemic focus, the selective activation of neural structures in the ischemic heart, and the reflex changes of myocardial activity [8,10,12].

REFERENCES

1. V. M. Pozin, *Kardiologiya*, **6**, № 4, 29-35 (1966).
2. V. M. Pozin, I. V. Samokhvalova, T. G. Chumakova, *et al.*, *Krovoobrashchenie*, **15**, № 6, 46-48 (1982).
3. V. M. Pozin, S. G. Skuratovskaya, and G. A. Pocheptsova, *Fiziol. Zh. SSSR*, **38**, № 2, 19-25 (1992).
4. J. Amano, J. Thomas, C. Lavalee, *et al.*, *Amer. J. Physiol.*, **252**, № 1, Pt. 1, H110-H117 (1987).
5. W. Aronow, *Rev. Med.*, **16**, № 1-2, 37-41 (1975).
6. R. Bolli, J. Triana, and M. Jerondi, *Circulat. Res.*, **67**, № 2, 332-343 (1990).
7. A. Chu, D. Chabers, C. Lin, *et al.*, *Ibid.*, **66**, № 6, 1484-1490.
8. M. Cohen and J. Downey, *Amer. Heart J.*, **120**, № 2, 282-291 (1990).
9. R. Feldman, *Circulation*, **75**, Suppl. 5, V96-V117 (1987).
10. K. Gallagher, T. Kumada, J. Koziol, *et al.*, *Ibid.*, **62**, 1266-1274 (1980).
11. J. Parker, R. West, and S. Di Giorgi, *Amer. J. Cardiol.*, **27**, 59-65 (1971).
12. M. Thames and A. Minisi, *Circulation*, **80**, № 6, 1878-1885 (1989).