greatly intensified. The dynamics of the number of large, medium, and small lymphocytes suggests a probable change in the rate of cell differer tiation.

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PATHOLOGICAL PHYSIOLOGY AND GENERAL PATHOLOGY

Changes in Rhythmoinotropic Reactions of the Myocardium in Chronic Ischemia: Pathology or Adaptation?

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Changes in the organization of the Ca^+-transporting systems but not disturbances in the contractile apparatus of cardiomyocytes are shown to occur in chronic coronary heart disease. During a certain stage of CHD the change in rhythmoinotropic relations may reflect adaptive changes induced by functioning of the myocardium under conditions of ischemia.

Key Words: *myocardium; rhythmoinotropic activity; ischemia*

The pumping function of the heart depends first of all on its contractility and on the rhythmic pattern of heart-beats. These two properties are acted upon by regulatory influences which adjust heart functioning to adequately meet the physiological requirements of the organism.

Whereas the gross and often irreversible changes in the myocardium during acute ischemia are almost always pathological in nature, chronic ischemic heart disease (IHD) is characterized by the parallel development of hypoxemic damage and adaptation to it [4]. However, current approaches to the study of myocardial ischemia and to the search for protective measures are unable to reveal the first step in the development of adaptive reactions in cardiomyocytes [6].

The aim of the present study was to investigate the effect of chronic IHD on the character of the rhythmoinotropic function of the human heart in comparison with the analogous reaction of intact myocardium of guinea pigs and rats.

MATERIALS AND METHODS

The study was carried out on biopsy material (auricular trabecula of the right atrium) obtained dur-

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ing either bypass surgery or operative correction of UPW syndrome (in the last case the material was considered as intact). Patients were 40-55 years old. The excised material was placed in cold Krebs-Henseleit solution [10], and after the necessary preparation of the trabeculae it was fixed in a 1-ml thermocontrolled flow chamber (31°C). Contractile activity was evaluated with a 6MKh 1S mechanotron in an isometric regime at a stimulating frequency of 0.5 Hz. The rhythmoinotropic reaction was studied by lowering or elevating the rate of stimulating pulses in each experiment after adaptation to 0.1 and 1 Hz, respectively. The stimulation mode was switched through the baseline frequency. The next switch of the stimulation mode was made after restoration of the contractility to the baseline level. During all changes of the stimulation frequency a plateau of the contractile response of the muscle preparation was reached. Analogous experiments were performed on the papillary muscles of guinea pigs and rats. The methods of isolation and preparation of these muscles were described earlier [2,9]. The force of contraction and its first derivative were recorded. The maximal developed tension (T_{max}) and the maximal rate of its increase and decrease (T'_{max} and T'_{min}) were calculated. The value of each parameters in each experiment was expressed as a percentage with respect to that obtained at baseline frequency and processed statistically using the Student *t* test.

RESULTS

The changes in contractile activity of muscle preparations from the heart in response to modulation of the stimulation frequency are presented in Table 1. In muscles isolated from the heart of UPW patients an increase in the stimulation frequency led to the development of a positive inotropic effect. The changes in the studied parameters were expressed as follows: $T'_{max}>T'_{min}>T_{max}$. On the other hand, a decrease of the stimulating frequency induced a negative inotropic effect, and the order of changes in the studied parameters was: $T'_{min}>T'_{max}>T_{max}$.

Similar changes in response to an increase or decrease of the stimulation frequency were observed in muscle preparations from the heart of guinea pig (Table 1). This verifies the well-known similarity in the organization of electromechanical coupling in the myocardium of man and guinea pig, on the one hand, and, on the other, enables us to categorize the biopsy material from UPW patients in a separate group and to consider the parameters obtained for it as characteristic for intact human myocardium.

The obtained responses of the muscle preparations to modulation of the stimulation frequency are usually attributed to a greater Ca^{2+}-accumulating capacity of the sarcoplasmic reticulum, which enable cardiomyocytes to accumulate a considerable amount of Ca^{2+} in response to an increased stimulation frequency for utilization during the subsequent contraction [11].

The muscle preparations isolated from the biopsy material of the IHD patients were also susceptible to changes in the stimulation mode. However, this manifested itself in a fundamentally different manner. Namely, after increasing the stimulation frequency to 1 Hz, we observed a marked negative inotropic effect, which manifested itself virtually to the same extent in both a drop of T_{max} and a more than 40% decrease of the rate parameters T'_{max} and T'_{min} in comparison with their initial values. After returning the stimulation frequency to the baseline value (0.5 Hz), we observed a complete restoration of the recorded pa-

TABLE 1. Inotropic Reactions of Myocardium in UPW and IHD Patients, and in Guinea Pig and Rat in Response to Modulation of Stimulation Frequency ($M\pm m$)

Parameter	Modulation of frequency	Experimental series			
		guinea pigs (n=4)	patients		rats (n=4)
			UPW (n=6)	IHD (n=14)	
Maximal developed tension, T_{max}		119±3	128±4	58±7	61±4
Rate of increase of tension, T'_{max}	from 0.5 to 1 Hz	183±6	151±6	63±8	60±4
Rate of decrease of tension, T'_{min}		167±3	140±6	60±3	
Maximal developed tension, T_{max}		48±3	75±6	121±4	136±5
Rate of increase of tension, T'_{max}	from 0.5 to 0.1 Hz	33±5	67±6	113±4	130±3
Rate of decrease of tension, T'_{min}		33±4	65±7	116±3	140±3

Note. All values are reliable ($p<0.05$) in comparison with 0.5 Hz.

rameters to the initial values. On the other hand, a subsequent decrease of the stimulation rate to 0.1 Hz led to an enhancement of contractile activity of the muscle preparations. Analogous experiments performed on muscle preparations from rat heart revealed the same changes in contractile parameters in response to an increase and decrease of the stimulation frequency (Table 1).

When comparing the increment of the developed tension of the muscle preparations isolated from the heart of UPW and IHD patients in response to an increase and a decrease of the stimulation frequency, respectively (28 and 21%), it can be seen that in our observations coronary ischemia in the IHD patients did not cause disturbances in the contractile function of cardiomyocytes. The reported data on a reduced contractile activity of the ischemized myocardium [7] appear to be true just for major aberrations.

The alteration in the rhythmoinotropic response observed by us, when the pattern of functioning of the human myocardium approaches that of the rat myocardium, is presumably related to changes in the Ca^{2+}-transporting systems of the cardiomyocytes. A similar inversion of the inotropic response of human myocardium was also noted for patients with rheumatic heart disease of differing severity [3], and was attributed to disturbances in electromechanical coupling. In our experiments the reverse chronotropic dependence was obtained on muscles from operated patients with a minimum one-year history of IHD. In this case we should probably speak of a rearrangement rather than of disturbances of the Ca^{2+}-transporting systems in cardiomyocytes. In fact, adaptation measures have been shown to reduce the sensitivity of cardiomyocytes to an altered content of Ca^{2+} [8]. Moreover, adaptation leads to changes in the membranes of the sarcolemma and sarcoplasmic reticulum, thus preventing damage and improving the mechanisms of storage and transport of Ca^{2+} [1,5,10].

Thus, the results obtained by us suggest that chronic coronary ischemia virtually does not affect the contractile function of the myocardium, but radically changes the nature of its rhythmoinotropic reactions. Elucidating the mechanisms of the discovered phenomenon calls for additional studies of the Ca^{2+}-transporting systems.

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