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SHORT COMMUNICATIONS

Contribution of α-Adrenoceptors to the Contractility of the Human Myocardium in Chronic Coronary Heart Disease

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Abstract—The inotropic response of isolated myocardial strips to α_1-adrenoceptor stimulation was compared for patients with chronic coronary heart disease (CHD) and patients with WPW syndrome. The α_1-adrenoceptors were stimulated with 1×10^{-5} M phenylephrine after blocking of the β-adrenoceptors with 3×10^{-1} M propranolol. The inotropic activity was recorded in the isometric mode. In the myocardium without signs of ischemic damage, stimulation of the α_1-receptors caused a slowly developing single-phase positive inotropic response. The myocardium of the CHD patients was characterized by a three-phase response. The specific features of the inotropic response to α_1-adrenoceptor stimulation in the CHD patients were assumed to be determined by changes in intracellular homeostasis of Ca^{2+}. Electromechanical coupling in cardiac myocytes of CHD patients depends on Ca^{2+} deposited in the sarcoplasmic reticulum to a greater extent than coupling in the intact myocardium. An additional positive inotropic effect is possible upon exogenous calcium influx into cardiac myocytes.

Sympathetic regulation of the myocardium is mediated by a population of β- and α-adrenoceptors. Even the myocardium isolated from patients with chronic coronary insufficiency retains some basal adrenoceptor activity. A blockade of these receptors causes a negative inotropic effect [1]. Under the conditions of an α-adrenoceptor blockade, the effect of norepinephrine on the isolated myocardium of patients with chronic coronary heart disease (CHD) is augmented by a factor of 1.5 [1]. This finding is in good agreement with the fact that simultaneous stimulation of adrenoceptors is accompanied by mutual attenuation of their inotropic effects [2]. Conversely, a blockade of receptors of one type is equilibrated by an increased activity of receptors of the other type.

Inotropic effects of the α-adrenoceptors are related to phosphoinositide metabolism, the products of which play the role of intracellular messengers. Therefore, α-adrenoceptor stimulation is one of the possible mechanisms of endogenous cardioprotection [3]. It is in this connection that Academician E.I. Chazov remarked, "Disturbance in the adrenergic regulation of the myocardium in chronic cardiac insufficiency is a topical problem" [4].

The present study aims to investigate the capability of the α_1-adrenoceptors for maintaining the contractile function of the myocardium in chronic coronary insufficiency.

The study was performed on perfused myocardial strips isolated from biopsy material of the right atrial auricle. The excision of the right atrial auricle is obligatory during surgery conducted under the conditions of extracorporeal circulation. We investigated the myocardium in two groups of male patients. The test group included six patients with chronic CHD and angina of effort (functional classes III–IV according to the NYHA). These patients (mean age 50 ± 3 years) underwent aortocoronary bypass grafting. The control group included four patients with WPW syndrome (mean age 43 ± 2.4 years).

Muscle strips were no less than 5 mm in length and no more than 1 mm^2 in section, had parallel fibers, and lacked a connective tissue membrane. The strips were perfused with Krebs–Henseleit solution saturated with carbogen (95% O_2 and 5% CO_2) in a thermally stabilized chamber (1 ml) at 36°C [1, 5].

The frequency of muscle contractions was determined by rectangular-shaped electrical pulses with a 5-ms duration and an amplitude exceeding the excitation threshold by 20–30%. The pulses were transmitted through two massive silver electrodes located in the chamber. By means of a micromanipulator, the muscles were stretched out to achieve the maximum possible inotropic effect. The muscle tension was monitored throughout the adaptation period (60 min). After the end of adaptation, the final muscle tension was produced and contractive activity was recorded.

The muscle contractive activity was assessed in the isometric mode by changes in the curves of tension and its first derivative [1, 5]. A 6MKh1S mechanotron converter was used as an isometric sensor. The following parameters were recorded: the maximum tension (T_{max}) and the maximum rates of its increase ($+dT/dt$) and decline ($-dT/dt$). The maximum tension in all muscle samples was no less than 400 mV at the end of the adaptation period.

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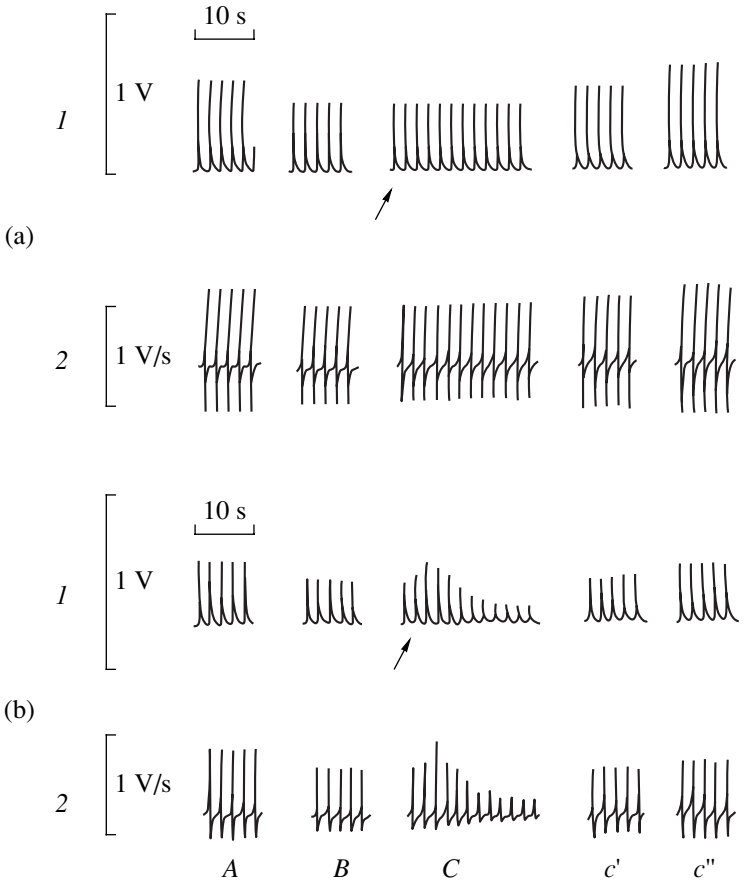

Fig. 1. Typical mechanograms reflecting the development of the inotropic response of myocardium strips of (a) subjects without ischemic lesion of the heart and (b) patients with chronic CHD on exposure to propranolol and phenylephrine. Curves *1* and *2* show the muscle tension and its first derivative, respectively, for (*A*) background contractions, (*B*) the effect of propranolol (20 min), and (*C*) the effect of phenylephrine at the beginning of exposure (arrows) and (c') 1 and (c") 2 min later.

The functional activity of the α_1-adrenoceptors in the myocardium strips was studied after blocking the β-adrenoceptors with 3×10^{-1} M propranolol (Sigma, United States). This concentration was selected in preliminary experiments and allowed us to block the β-adrenoceptors reliably regardless of individual features of a patient. The α_1-adrenoceptors were stimulated with 1×10^{-5} M phenylephrine (Sigma) [6]. The pharmacological agents were delivered to the muscle strips with the perfusion medium. Student's *t*-test was used for statistical analysis of the results.

Figure 1 shows some typical mechanograms of the muscle strips in the groups studied. Perfusion of muscles with propranolol inhibited their inotropic response. In the test group, the greatest decrease ($42 \pm 9\%$) was observed for the tension decline rate, while the tension amplitude decreased by $35 \pm 5\%$ and the tension increase rate, by $26 \pm 5\%$. Similar changes were detected in the control group. Supplementing the perfusate with the α_1-adrenoceptor agonist phenylephrine additionally changed the inotropic response of the muscle strips (Fig. 1). However, the features of these changes were different in the groups studied. A monotonic increase of the inotropic response was typical of the control group.

In the test group, stimulation of the muscle strips with phenylephrine caused a more complicated three-phase inotropic response. During the first phase, an evident increase was observed for the tension amplitude ($40 \pm 8\%$) and the tension increase rate ($60 \pm 5\%$). The first phase developed in the first few seconds of contact of muscle strips with phenylephrine (Fig. 1). Subsequently, the inotropic response decreased (the second phase) to no more than 50% of the values recorded with propranolol. The duration of this phase did not exceed 40 s. Then, the contractive activity increased (the third phase), and, 1 min later, the inotropic response of muscles exceeded the values recorded with propranolol (Fig. 1). Two minutes later, we observed a plateau of a delayed positive inotropic response.

It should be noted that the reactions of the rates $+dT/dt$ and $-dT/dt$ differed fundamentally between the first and third phases of the inotropic response. Thus, in the first phase, we did not observe any changes in $-dT/dt$, whereas, in the third phase $-dT/dt$ increased to

150 ± 11%, while +*dT*/*dt* did not exceed 117 ± 5% of the values recorded with propranolol.

Several studies have described a three-phase inotropic response of the myocardium to stimulation of the α_1-adrenoceptors in intact rats [6–8]. The first phase of the inotropic response is related to the cleavage of phosphatidylinositol 4,5-diphosphate by phosphodiesterase and the consequent formation of inositol triphosphate. This mediator activates Ca^{2+} release from the sarcoplasmic reticulum (SPR).

We observed the three-phase inotropic response to α_1-adrenoceptor stimulation of the myocardium only for the CHD patients (Fig. 1). The duration of the first, inositol triphosphate–dependent phase of the inotropic response did not exceed 10 s; T_{max} increased by approximately 40%. In the myocardium of intact rats, the increase in the inotropic response during the first phase did not exceed 20%, but this phase was three times longer [8]. The greater increase in contractility and the transience of the first phase in the myocardium of the patients with CHD may be caused by an initially high level of Ca^{2+} in the SPR of their cardiac myocytes. Quick mobilization of Ca^{2+} from the SPR provokes a temporary Ca^{2+} overload of cardiac myocytes, which becomes functionally apparent as a decrease in the contraction amplitude (the second phase of the inotropic response). The third (stable) phase of the inotropic response may be related to the effect of diacylglycerol. This messenger potentiates slow calcium channels by activating protein kinase C [6, 9].

The absence of the first two phases in the inotropic response of muscles in the control group may be due to poor development of the SPR, which is specific for intact cardiac myocytes of some animal species, including humans [10, 11]. On the contrary, in rats, it is Ca^{2+} deposited in the SPR that determines the electromechanical coupling [11]. The specific organization of the electromechanical coupling affects the chrono- and inotropic responses of the myocardium in different animal species.

We have shown previously that the chrono- and inotropic responses of the human myocardium in CHD resemble the responses of the rat myocardium [5]. Most probably, this phenomenon is caused by adaptive and/or pathological changes in cell metabolism. This assumption agrees well with the fact that stimulation of the α_1-adrenoceptors in the myocardium changes predominantly the third phase of the inotropic response in patients with CHD (this study) and in rats subjected previously to prolonged hypoxia [7, 8].

CONCLUSIONS

We assume that the three-phase inotropic response to stimulation of the α_1-adrenoceptors in CHD reflects an increasing role of the SPR in maintaining the contractility of human cardiac myocytes. The main mechanism underlying the stable phase of the positive inotropic response is diacylglycerol-dependent activation of protein kinase C. On the contrary, inositol triphosphate has a low capability for inducing a positive inotropic response in a compromised myocardium [9].

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