Adrenergic and Serotoninergic Regulation of Myocardial Contractility in Patients with Various Morphofunctional Changes in the Heart Resulting from Chronic Heart Failure

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A relationship between morphofunctional changes in the heart and predominance of adrenergic or serotoninergic influences on the strength of myocardial contraction in the right atrium was revealed in patients with chronic heart failure. During left ventricular hypertrophy, the strength of myocardial contraction in response to serotonin exceeded that induced by epinephrine and was realized via 5-HT2 receptors.

Key Words: *chronic heart failure; left ventricular hypertrophy; epinephrine; serotonin; 5-HT2 receptors*

Despite considerable advances in the therapy of patients with chronic heart failure, the pathogenesis of this disease is poorly understood. The pathogenesis of heart failure is explained on the neurohormonal model, which suggests activation of the sympathoadrenal system and increase in blood catecholamine level [3,4]. Coronary heart disease (CHD) and acute myocardial infarction cause the development of chronic heart failure. This state is accompanied by an increase in not only blood catecholamine level, but also serotonin (5-HT) concentration [7]. The role of 5-HT in this process remains unknown.

An essential stage of cardiovascular diseases is heart remodeling, which includes myocardial hypertrophy and dilation of heart cavities leading to changes in heart geometry and diastolic and systolic dysfunction. Left ventricular (LV) hypertrophy 15-fold increases the risk of chronic heart failure in patients under 65 [1]. Experiments on 5-HT2-knockout mice showed that these receptors are involved in the development of myocardial hypertrophy [5].

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Here we studied the effects of serotonin, epinephrine, and 5-HT2 receptor agonist m-CPP on the strength of right atrial contraction depending on the degree of morphofunctional changes in the myocardium.

MATERIALS AND METHODS

Segments of the left atrium auricle were obtained from CHD patients during coronary bypass surgery and from patients operated for mitral valve replacement (rheumatoid heart disease) at the Department of Cardiosurgery (Kazan Hospital No. 6). All patients received standard therapy.

The patients (46-61 years) were divided into 4 groups. Group 1 included 6 patients with diastolic dysfunction of LV, which had the following echocardiographic parameters: thickness of the interventricular septum and posterior wall of LV 1.0-1.1 cm (within normal), end-diastolic volume (EDV) of LV 123-156 ml (increased), end-diastolic size (EDS) of LV 4.9-5.6 cm (within normal range), and ejection fraction 50-75% (within normal range). Group 2 included 5 patients with LV hypertrophy, which had the following echocardiographic parameters: thickness of the interventricular septum and poste-

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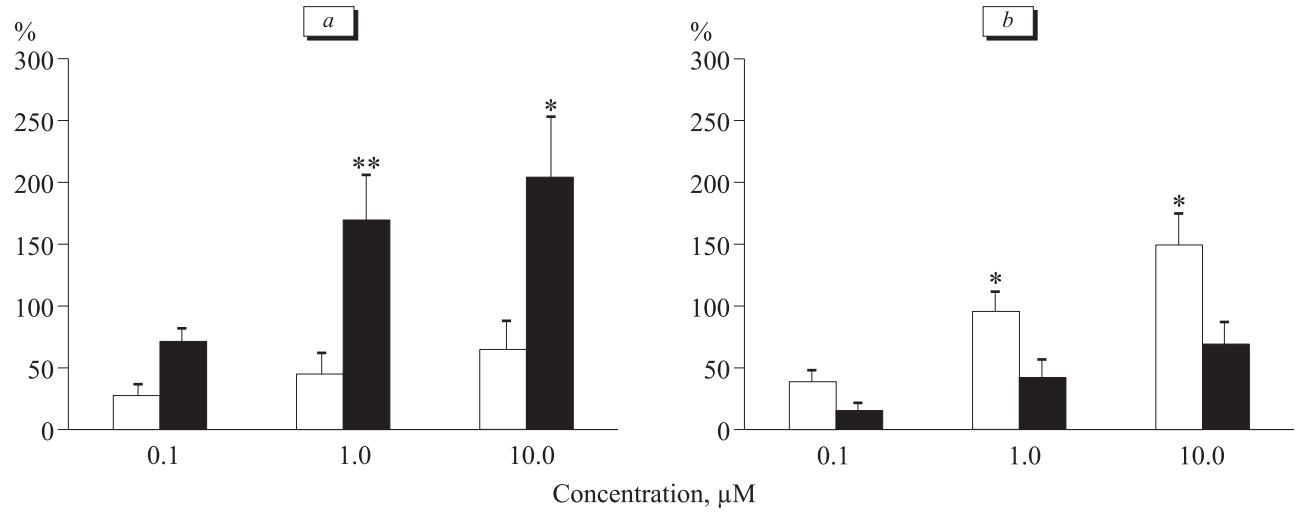

Fig. 1. Effects of 5-HT (light bars) and epinephrine (dark bars) on the strength of myocardial contraction in patients with diastolic dysfunction without (*a*) or with LV hypertrophy (*b*). **p*<0.05 and ***p*<0.001 compared to the effect of compounds in a concentration of 0.1 μM.

rior wall of LV 1.2-1.8 cm (increased), LV EDV 138-214 ml (increased), LV EDS 4.9-5.6 cm, and ejection fraction, 50-75%. Group 3 included 4 patients with systolic dysfunction and LV hypertrophy, which had the following echocardiographic parameters: thickness of the interventricular septum and posterior wall of LV 1.2-1.9 cm (increased), LV EDV 171-223 ml (increased), LV EDS 5.5-5.9 cm (increased), and ejection fraction 39-48% (decreased according to Teiholtz). Two patients of group 3 had one additional trabecula. Group 4 included 6 patients with systolic dysfunction of LV and thinning of the wall of LV, which had the following echocardiographic parameters: interventricular septum thickness 0.5-0.7 cm (decreased), LV EDV 194-286 ml (increased), LV EDS 6.2-7.3 cm (increased), and ejection fraction 35-48% (decreased according to Teiholtz).

The segment of the right atrium auricle was immediately placed in cold modified Krebs solution (4°C). The period from sampling to the start of the study did not exceed 50 min. The experiment was performed as described elsewhere [1]. Contraction strength of myocardial strips from the right atrium auricle was assessed after treatment with 5-HT (Sigma), epinephrine (Sigma), and 5-HT2 receptor agonist m-CPP (1-(3-chlorophenyl)piperazine hydrochloride, Tocris) in increasing concentrations of 0.1, 1.0, and 10.0 μM. The reaction to agonists was expressed in percent of the basal level.

For statistical processing of the experimental results M, m, and δ were calculated. The significance of differences was evaluated by Student's *t* test. The differences were significant at $p<0.05$.

The patients signed written informed consent form to enter the trial, which was approved by Ethical Committee of Kazan State Medical University.

RESULTS

In group 1 patients, the maximum strength of myocardial contraction to 5-HT and epinephrine was 65 and 204%, respectively (Fig. 1, *a*). Hence, in patients with diastolic dysfunction without LV hypertrophy, changes in the strength of myocardial contraction in response to epinephrine was 3-fold greater than to 5-HT.

LV hypertrophy in group 2 patients was accompanied by changes in myocardial reactivity to 5-HT and epinephrine. 5-HT induced a dose-dependent increase in the strength of myocardial con-

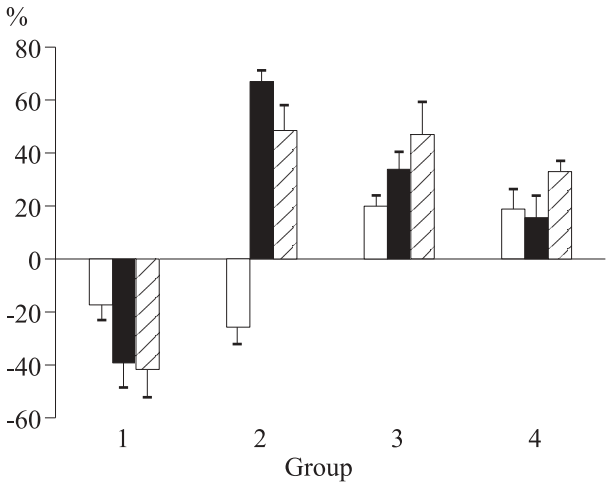

Fig. 2. Effect of 5-HT2 receptor agonist in concentrations of 0.1 (light bars), 1 (dark bars), and 10 μM (shaded bars) on contraction strength of the atrial myocardium in patients with chronic heart failure.

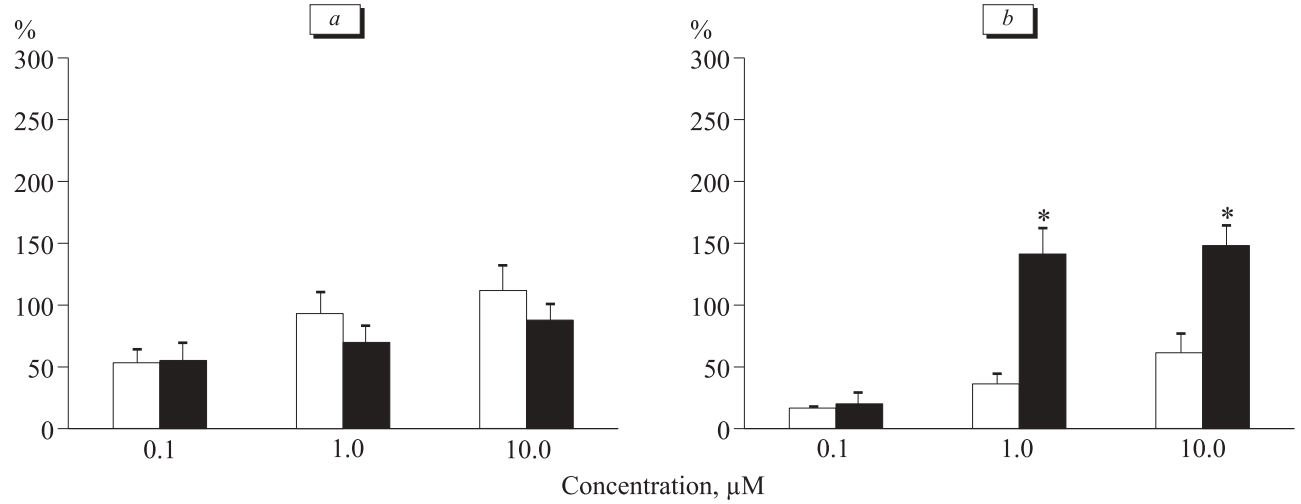

Fig. 3. Effects of 5-HT (light bars) and epinephrine (dark bars) on the strength of myocardial contraction in patients with systolic dysfunction with LV hypertrophy (*a*) and thinning of the LV wall (*b*). **p*<0.001 compared to the effect of compounds in a concentration of 0.1 μM.

traction (Fig. 1, *b*). The maximum change in contraction strength in response to 10 μM 5-HT was 149%, which 2-fold exceeded the myocardial reaction in group 1 patients. Epinephrine in a concentration of 10 μM increased the strength of myocardial contraction in these patients by 69%, which was 3-fold lower compared to the myocardial reaction in group 1 patients. Hence, patients with LV hypertrophy have higher myocardial reactivity to 5-HT and lower myocardial reactivity to epinephrine compared to patients without hypertrophy. In patients with LV hypertrophy, changes in the strength of myocardial contraction in response to 5-HT were 2-fold higher than to epinephrine.

5-HT2 receptor agonist had a positive inotropic effect on the myocardium in group 2 and 3 patients with LV hypertrophy. 5-HT2 receptor agonist induced a negative inotropic effect in the myocardium in group 1 and 4 patients without LV hypertrophy (Fig. 2). Activation of 5-HT-mediated cardiac regulation probably serves as a compensatory mechanism maintaining contractility, which is realized via myocardial hypertrophy under conditions of reduced myocardial reactivity to epinephrine due to desensitization of adrenoceptors [6].

In group 3 patients with systolic dysfunction and LV hypertrophy, changes in the strength of myocardial contraction to 5-HT and epinephrine were 146 and 70%, respectively. Hence, 5-HT and epinephrine had similar positive inotropic effect (Fig. 3, *a*).

In group 4 patients with thinning of the LV wall, changes in the strength of myocardial contraction to 5-HT and epinephrine were 61 and 148%, respectively (Fig. 2, *b*). Hence, systolic dysfunction and thinning of the LV wall are accompanied by a 2-fold greater increase in the strength of myocardial contraction in response to epinephrine compared to that induced by 5-HT.

These data illustrate the relationship between morphofunctional changes in the myocardium of patients with chronic heart failure and predominance of adrenergic or 5-HT-ergic influences on the strength of myocardial contraction in the right atrium. During LV hypertrophy, changes in the strength of myocardial contraction in response to 5-HT are more pronounced compared to those induced by epinephrine. This reaction is realized via 5-HT2 receptors.

Our results demonstrate the existence of compensatory interrelations between adrenergic and 5-HT-ergic influences regulating inotropic function of the myocardium in patients with chronic heart failure. This fact should be taken into account in the study of the pathogenesis and therapy for cardiovascular diseases.

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