Metabolic Alterations in Rat Myocardium in Experimental Acute Atrial Fibrillation

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Experimental atrial fibrillation in intact rats significantly decreased the content of catecholamines in atrial adrenergic fibers and phosphorylase activity, which attests to enhanced glycogen consumption in the heart. These changes were specific of the fibrillating myocardium and atria, but were absent in the ventricles. Induced atrial fibrillation did not modify activities of SDH and monoamine oxidase in cardiac subdivisions. It was hypothesized that increased energy requirements in the atria during myocardial fibrillation led to activation of anaerobic metabolism.

Key Words: *atrial fibrillation; catecholamines; monoamine oxidase; succinate dehydrogenase; phosphorylase*

Atrial fibrillation (AF) is the most widely spread type of persistent cardiac rhythm disturbances. AF frequently accompanies various cardiovascular abnormalities (CHD, essential hypertonia, rheumatic heart disease). Long-term disturbances of atrial contractility lead to morphological and electrophysiological myocardial remodeling [7,10,11]. In cardiomyocytes, the number of myofibrils decreases, glycogen accumulates, the shape and size of mitochondria change, fragmentation of the sarcoplasmic reticulum develops, and nuclear chromatin dispersion occurs [10]. These alterations are accompanied by enlargement of cardiomyocytes [7,10,11]. The mechanisms of these rhythm disturbances and the related metabolic changes remain poorly studied. The contractile apparatus consumes only 80% energy produced in cardiomyocytes, so changes in contractile activity reflect the state of energy metabolism [2]. In the early stage of AF, the nature of changes in energy metabolism is not evident. In contrast to clinical studies, experimental modeling of AF makes it possible to study the metabolic changes in the myocardium at the early stage of the disease.

Our aim was to study the changes in energy metabolism in the myocardium during acute experimental AF.

MATERIALS AND METHODS

The study was carried out on male Wistar rats (n=23) weighing 250-300 g. The thoracic cavity was opened under ether narcosis and artificial ventilation with room air. Under conditions of open access to the heart, electrical stimuli were delivered to the atria during the vulnerable period of the heart cycle at the rate of 1000-1200 Hz with the help of an Elcart (Elektropul's Ltd) firmware. Stimulation was stopped after the onset of AF. The induced fibrillation lasted for 5-10 min, thereafter cardiac rhythm recovered. Repeated stimulation was performed before the onset of fibrillation. AF was induced 8-10 times. Intact rats and sham-operated animals (surgery under ether narcosis and artificial ventilation without AF induction) served as controls. At the end of experiment, the left adrenal gland, the atria, and the ventricles were isolated and stored in liquid nitrogen for histochemical analysis.

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In cryostat sections of the heart and adrenals, catecholamines (CA) were assayed with 2% glyoxylic acid [6]. Activities of monoamine oxidase (MAO) [1], SDH, and phosphorylase [3] were also determined. The latter was used to assess the content of glycogen in the myocardium. The histochemical specimens were analyzed by cytophotometry under a LYuMAM-IZ microscope. Enzyme activities were evaluated by optical density of the reaction products in histological specimens.

In the adrenal gland, the level of CA fluorescence was determined. In the myocardial specimens, the volume density of the fluorescent adrenergic terminals and the activities of MAO, SDH, and phosphorylase were determined. The histochemical parameters of the left and right atria were similar, so the corresponding data were pooled.

The data were processed statistically using Student's *t* test and presented as $M \pm m$.

RESULTS

In the adrenal glands of sham-operated rats and in animals with simulated AF, fluorescence of CA significantly decreased ($p<0.05$; Table 1). Probably, intensive release of CA by the adrenal glands resulted from surgery manipulations performed before AF simulation, which is standard reaction of the organism to stress (e.g. surgery). However, surgical manipulations produced no effect on the level of CA in adrenergic fibers in the hearts of sham-operated rats, which probably attests to adequacy of the experimental protocol: severe stress, which is reflected by a drop of CA level in cardiac nervous terminals [4,5] did not develop in our experiments. Compared to intact rats, there were no changes in activity of MAO, SDH, and phosphorylase in the atria of sham-operated rats (Table 2). However, significant decrease in phosphorylase activity by 65% ($p<0.05$) was revealed in the right and left ventricles, which indicated enhanced glycogen consumption in the myocardium [3]. Probably, it was caused by pre-surgery stress resulting in additional load on the cardiovascular system, mostly on the ventricular myocardium.

After AF modeling, the content of CA in adrenergic fibers of the left and right atria decreased to 7.0±0.3% compared to 8.2±0.6% in intact rats or 8.4±0.6% in sham-operated rats ($p<0.05$, Table 1). Later there was no additional drop of CA in the adrenal glands and adrenergic terminals. In both atria, AF 2-fold decreased activity of phosphorylase, but had no effect on this enzyme in ventricular myocardium (Table 2). These data attest to unfavorable physiological conditions for contraction in fibrillating myocardium. This is seen from disturbances in the cardiac adrenergic system and loss of glycogen. Thus, acute AF results in excessive

TABLE 1. Effect of Atrial Fibrillation on CA Content in Adrenal Glands and in Cardiac Adrenergic Fibers in Rats ($X \pm m$)

Index/tissue	Group		
	intact (n=5)	sham-operated (n=7)	AF (n=11)
CA fluorescence in rel. units adrenal gland	7.6±0.6	6.3±0.2*	6.5±0.2*
Density of adrenal fibers, %			
atria	8.2±0.6	8.4±0.6	7.0±0.3+
right ventricle	4.7±0.3	5.0±0.6	4.4±0.3
left ventricle	2.3±0.4	2.5±0.6	2.4±0.2

Note. Here and in Table 2: $p<0.05$ compared to *intact or +sham-operated groups.

TABLE 2. Effect of Atrial Fibrillation on Enzyme Activity in Rat Heart (rel. units, $X \pm m$)

Index/tissue		Group		
		intact (n=5)	sham-operated (n=7)	AF (n=11)
Atria	MAO	0.17±0.01	0.16±0.03	0.16±0.01
	SDH	0.22±0.01	0.23±0.01	0.22±0.01
	phosphorylase	0.36±0.04	0.34±0.04	017±0.03+
Ventricles	phosphorylase	0.37±0.06	0.13±0.05*	0.16±0.03

Note. MAO: monoamine oxidase.

consumption of myocardial glycogen for inefficient frequent contractions. This can be accompanied by disturbances in CA re-uptake by adrenergic terminals and CA release directly into the myocardium. Under these conditions, adequacy of myocardial contractility can vary due to sensitization of adrenoceptors by CA excess. In addition, the protective function of adrenergic fibers related to deposition of surplus of circulating CA can be deteriorated. Probably, both factors can aggravate the disturbances of myocardial contractile activity caused experimentally by frequent stimulation of the atria. It is noteworthy that sharp depletion of CA in myocardial adrenergic terminals was documented in some cases of sudden death, which are frequently preceded by fibrillation of the heart [5].

The absence of changes of SDH activity in our experiments can indicate that the processes related to AF had no effect on anaerobic energy metabolism of tricarboxylic acids, while changes in activity of this key enzyme in Krebs cycle could not manifest themselves during the short-term experiment. At the same time, increased energy demand in fibrillating atria is probably satisfied due to activation of anaerobic metabolism accompanied by significant increase of consumption of the glycogen stored by the myocardium.

Acute development of AF produced no effect on CA metabolism, because activity of MAO, the key enzyme of CA inactivation, did not change after several long-lasting episodes of AF.

The revealed decrease of glycogen store in the heart and the drop of CA level in cardiac adrenergic fibers are probably specific to acute AF, because these changes can be revealed only in the fibrillating myocardium (in the atria), but not in the ventricles contracting normally in this case.

Thus, it is established that the development of acute AF is characterized by stimulation of CA release from adrenergic terminals of fibrillating myocardium. CA are capable to stimulate some energy systems [4]. In our experiments, AF dramatically activated the glycogen-phosphorylase system; thereafter local glycogen depot was mobilized in the myocardium. Probably, these changes could partially compensate for markedly enhanced energy demand in fibrillating myocardium. The acute period of AF development is characterized by CA release from adrenergic fibers and up-regulation of glycogen-phosphorylase system in the fibrillating myocardium. These changes could be considered as the adaptive processes maintaining atrial function during more energy-consuming mode of contraction mode. Probably, the development of acute AF does not directly relate to the level of oxidative metabolism in the cardiomyocytes.

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