On Some Pathogenetic and Adaptation Mechanisms of Acute Coronary Disease

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Acute coronary failure was modeled in rabbits by ligation of the descending left coronary artery at the interface of its middle and lower thirds. The function and morphology of left-ventricular and right-ventricular myocardium were studied on days 1, 3, and 5 of the pathological process. It was found that left-ventricular contractility decreased, while right-ventricular contractility increased. Deep morphological changes were observed in both ventricles: pronounced extracellular edema, increased content of collagen, decreased percentage of myofibrils. Hence, acute coronary failure involves both compartments of the heart, but the adaptive mechanisms more actively develop in the right ventricle.

Key Words: *acute coronary failure; cardiomyocyte apoptosis; collagen; contractile activity*

According to WHO data, more than 16.5 million people die from cardiovascular diseases every year, more than 7 million of these from coronary disease, which constitutes 29.3 and 12.6% of total mortality, respectively [10]. No doubt, manifestations of acute disorders in coronary circulation (acute coronary disease) deserve special attention.

The terms "acute coronary syndrome" and "acute coronary failure" are often used in recent Russian and foreign publications; they are not synonyms. Acute coronary syndrome unites such diseases as unstable angina, myocardial infarction with elevation of *ST* segment, and myocardial infarction without elevation of *ST* segment [5]. Hence, this diagnosis is tentative and requires more precise definition after thorough instrumental and laboratory studies. Acute coronary failure with foci of degeneration is a focal ischemic myocardial injury without necrosis; it can be reversible ("hibernated myocardium") [2,8,9]. Coronary bloodflow deficit in hibernated myocardium is insufficient for necrosis development, but it can cause pH changes, which, in turn, impairs contractile function of cardiomyocytes [7]. Clinically this form of coronary disease differs little from small focal myocardial infarction. However, subsequent course and outcome of the disease depend on what, specifically, developed in the myocardium — a necrotic focus or reversible dystrophy. Importantly, that in obvious myocardial infarction the area of macroscopically intact myocardium bordering the necrotic area is also subjected to morphological and ultrastructural changes to this or that measure [4]. Therefore, it is important to study the pathogenetic, defense, and adaptive mechanisms, developing in the course of acute disorders of coronary circulation in ischemic, but still viable myocardium. We think it is essential to compare the type and severity of destruction of the cardiac left- (LV) and right-ventricular (RV) myocardium in the course of acute coronary disease.

Here we studied the pathogenesis of acute coronary failure and possible mechanisms of adaptation to this condition.

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MATERIALS AND METHODS

The study was carried out on 28 male Chinchilla rabbits (2.5-3.5 kg). Acute coronary failure was induced in narcotized animals by ligation of the left descending coronary artery between its middle and lower thirds. Verification of the resultant disease was carried out by ECG: changed terminal part of the ventricular complex presented as elevation or depression of *ST* segment, indicated the presence of an ischemic zone [2]. Animals without these changes on the ECG were excluded from the study. Myocardial ischemia was also confirmed by significant reduction in the number of functioning capillaries, detected by morphological analysis of semithin sections of LV myocardium. Acute experiment was carried out after 24, 72, and 120 h of ischemic process. The choice of these periods was explained by the need to study not only pathogenetic, but also adaptation mechanisms over the course of acute coronary failure. The earliest changes in the myocardium develop after simulation of any typical pathological process in the heart (including ischemia) by the end of the first 24 h; defense and adaptive reactions start stable functioning after 3 days, and by day 5, deep injuries develop in the myocardium [3]. Control group consisted of intact rabbits.

Cardiac status during these periods was studied by functional and morphological methods. The functional methods included measurements of the basic parameters of systemic and intracardiac hemodynamics on a Micard programmed device (analog digital transformer with electromagnetic pickups and PC for recording, mathematical processing, and analysis of curves). Myocardial contractility (LV and RV) was evaluated by parameters of intracardiac hemodynamics, measured in narcotized rabbits by catheterization of cardiac cavities. The real (IPr) and maximum intraventricular pressure (IPm) were evaluated separately in the LV and RV (LVIPr, LVIPm, RVIPr, and RVIPm).

Preparations for morphological studies were made after heart perfusion with 2.5% glutaraldehyde solution through the ascending aorta. The papillary muscles of LV and (separately) RV were resected, postfixed in OsO_4 at pH 7.2-7.4, and embedded in epon-araldite. Semithin sections of the myocardium were prepared on a Reichert-Jung-Ultracut ultramicrotome and stained as described previously [6]. The preparations were then studied under a Nikon Eclipse E400 optic microscope at immersion magnification (×1000). Morphometry by Avtandilov's method was carried out in 30 visual fields in each series of experiment: the percentage of myofibrils, collagen, vessels, sites of myofibril destruction, and volume of extracellular spaces were evaluated in volume percent. Quantitative evaluation of the intensity of cardiomyocyte apoptosis was carried out by the method developed at Department of Pathology and Pathophysiology of Russian University of Peoples' Friendship. The method consists in morphometrical evaluation of the total number of nuclei and of the nuclei located in the cell-cell spaces or in completely destroyed cells (the so-called free nuclei), after which the apoptosis index (percent ratio of free nuclei to total number of nuclei) is calculated. The intensity of cardiomyocyte apoptosis was evaluated by this estimated index.

The data were processed using software developed at Department of Pathology and Pathophysiology of Russian University of Peoples' Friendship and Biostat statistical software. The results were analyzed using Student's *t* test (the differences were considered significant at $p<0.05$). Relationship between the processes was detected by analysis of correlations.

RESULTS

The study of cardiac function over the course of acute coronary failure showed a significant reduction of LV IP on day 1 under conditions of real hemodynamics, while the RV IP increased significantly during this period (Fig. 1, *a*).

These changes in intracardiac hemodynamics are quite justified, because LV is in a state of ischemia and its contractile function is reduced, which leads to reduction of LVIPr. However, impairment of the pumping function of LV is paralleled by the development of congestion in the lesser circulation and hence, the RV load increases, which manifests by an increase in RVIPr. Later, a slight trend to return of these parameters to the previous level is observed, indicating triggering of certain adaptation mechanisms.

The time course of maximum developing IP is presented in Fig. 1 (*b*). Reduction of LVIPm was observed, more intense in comparison with LVIPr, which means that the potential working capacity of the LV ischemic myocardium suffered even greater than the real one. The RVIPm was significantly higher than normally at all terms of the study, this indicating mobilization of the energy resources of RV myocardium, caused by hemodynamic overload.

Morphometry on semithin sections showed some specific features. The percentage of myofibrils in LV myocardium was reduced significantly in comparison with the normal during all periods of the study. The dynamics of changes was more intricate

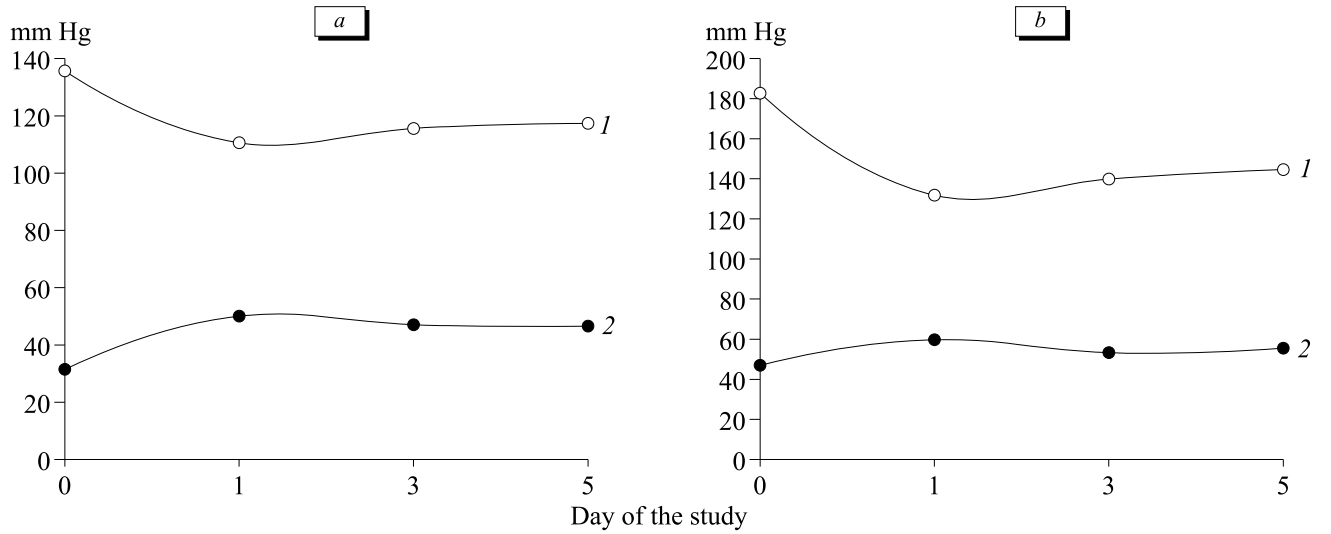

Fig. 1. Myocardial contractility over the course of acute coronary failure. *a*) real intraventricular pressure; *b*) maximum intraventricular pressure. *1*) LV; *2*) RV.

in RV. On day 1 the content of myofibrils reduced significantly, by the end of day 3 it approached the normal, and on day 5 again reduced significantly (Fig. 2, *a*). The area of extracellular spaces in both ventricles was inversely proportionally to the muscle volume (Fig. 2, *b*). This morphological picture suggests that the absolute content of myofibrils in the myocardium does not drop so abruptly, while the decrease in their percentage can be caused by the development of pronounced extracellular edema. It is noteworthy that edema was observed in both cardiac compartments despite ischemic damage to LV alone. However, the pathogenetic mechanism underlying the development of edema can be different for LV and RV. In LV it is most likely a result of ischemia, while in RV it seems to develop as a result of its hemodynamic overload.

The severity of extracellular edema decreases in both cardiac ventricles by day 3 of the process, which can indicate triggering of certain adaptive mechanisms during this period and hence, certain compensation for the injury. However, edema progressed again on day 5.

TABLE 1. Correlations between Myofibril Content and Area of Cell-Cell Spaces for Cardiac LV and RV in the Course of Acute Coronary Failure

Ventricle	Control	Ischemia, day		
		1	3	5
LV	-0.56*	-0.52*	-0.73*	-0.5*
RV	-0.57*	-0.42*	-0.28*	-0.5*

Note. *Significant correlations.

The content of collagen in the myocardium increased significantly, starting from day 1 in LV and from day 5 in RV (Fig. 3). It seems that the increase in collagen synthesis is one of the early defense reactions of the myocardium to injury aimed at fortification of the myocardial tissue. Presumably, the myocardium is more sensitive to ischemia than to overload, because of which LV is subjected to fibrosis earlier than RV. Another mechanism is probable, with the development of fibroplastic process in LV as a result of myofibril destruction and gradual involvement of RV in this process. This hypothesis is supported by the results of correlation analysis, which detected a significant negative correlation of medium intensity for the myofibril-collagen pair, observed during the entire study in LV and on day 5 in RV (Table 1).

The study of cardiomyocyte "nuclear system" showed the following picture. The process in general is characterized by a trend to a reduction of the total number of nuclei in the myocardium of both ventricles. This parameter was reduced significantly in comparison with the normal level in RV on day 3 and in LV on day 5. Hypothetically these changes could result from reduction of the total cardiomyocyte count (and hence, count of nuclei). However, on day 3 the RV muscle weight returned to the initial level, while the number of the nuclei was the minimum. In addition, the absence of correlation between these two parameters was characteristic of both ventricles for all periods of the study. Presumably, nuclear regeneration is somewhat inhibited in the course of acute coronary insufficiency. This hypothesis is indirectly supported by a decrease in the number of dividing nuclei,

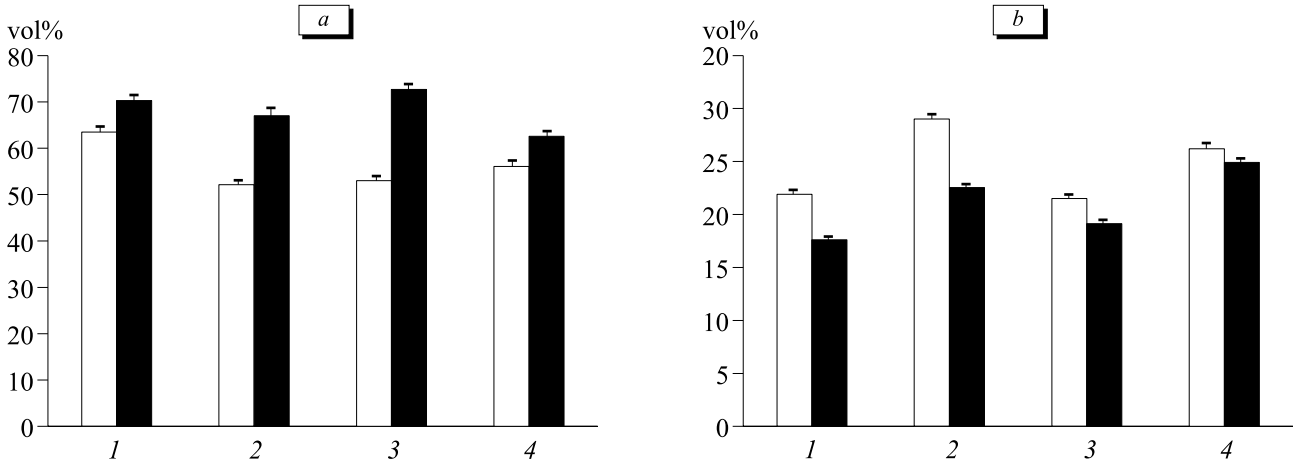

Fig. 2. Time course of muscle weight and extracellular myocardial edema in acute coronary failure. *a*) myofibrils; *b*) cell-cell spaces. Light bars: LV; dark bars: RV

detected by visual analysis of semithin sections at all terms of the study.

Index of cardiomyocyte apoptosis in the control was the same for LV and RV. For LV it a trended to decrease during the first 3 days of the study and slightly increased by day 5; no statistically significant differences in comparison with the norm were observed at any of the terms. The RV apoptosis index sharply increased by the end of day 1, but by day 3 the value virtually normalized and stabilized at this level by day 5. Hence, myocardial ischemia, developing in our experiment in LV, was not associated with appreciable changes in cardiomyocyte apoptosis intensity. However, the immediate reaction of RV myocardium to its hemodynamic overload presented by intensification of cardiomyocyte apoptosis, while later (days 3 and 5) some mechanisms seemed to be triggered, aimed at inhibition of myocardial cell apoptotic death.

Deterioration of LV contractility, observed during acute coronary failure, is justified, because the myocardium is in a state of deep energy deficiency. Our study revealed pronounced morphological changes, pathogenetically significant for the process development: extracellular edema, increase in the number of sites of myofibril destruction, and reduced percentage of myofibrils. On the other hand, some characteristics of LV morphology suggest their defense and adaptive significance. Activation of collagen formation can fortify the myocardial site damaged by ischemia. The trend to a reduction of cardiomyocyte apoptosis intensity observed in LV during the first 3 days after coronary artery occlusion can somewhat alleviate the negative effect of cell loss resultant from their necrotic death.

Pressure increase in cardiac RV can be explained by excessive hemodynamic load resulting from blood congestion in the lesser circulation because of reduced pumping function of ischemic LV. However, the potential working capacity of RV increases under these conditions, even despite obvious morphological abnormalities. All these facts suggest urgent mobilization of RV energy resources under conditions of acute cardiovascular disease, which indicates the leading role of this compartment in heart work in general [1]. In addition, it seems that ischemia is more destructive for LV in acute coronary failure than the reactive overload of RV, though by day 5 the structural changes in the myocardium of both cardiac compartments are virtually similarly deep.

Hence, acute coronary failure leads to the development of pronounced changes in the morphology of both cardiac ventricles, some of these changes being pathogenetically significant, while others

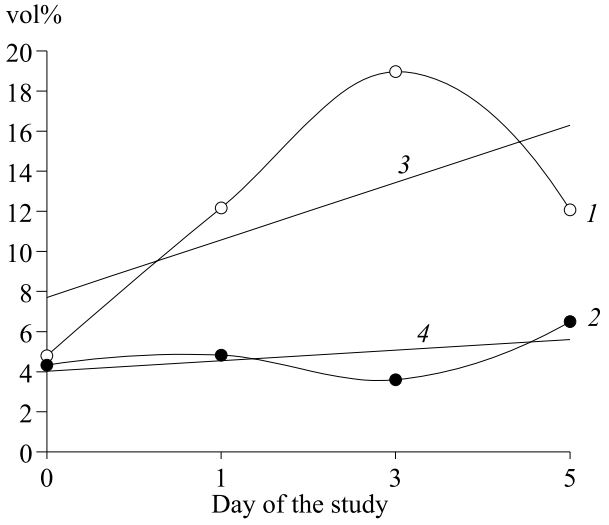

Fig. 3. Myocardial collagen in the course of ischemic process. *1*) LV; *2*) RV; *3*) trend for LV; *4*) trend for RV.

can be interpreted as defense and adaptive. During the period of our study the contractile potential of LV reduced, while that of RV increased.

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