# CHANGES IN THE INTENSITY OF PROTEIN SYNTHESIS IN THE MYOCARDIUM DURING COMPENSATORY HYPERFUNCTION OF THE HEART

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Compensatory hyperfunction of the heart is one of the chief symptoms of circulatory pathology. In heart defects, hypertonic disease and hypertonia of the pulmonary circulation, the maintenance of normal hemodynamic indices, clinical compensation and, therefore, the patient's life largely depends on stable compensatory hyperfunction of the heart. Under these conditions, the heart works continuously under an increased load for many years without reaching a state of exhaustion. The mechanism which prevents cardiac exhaustion, despite the continuous nature of its hyperfunction, has not yet been explained; the existing theory of the "reserve forces of the heart" needs rather than offers explanation. Also unexplained is the mechanism of the cardiac exhaustion which often sets in after many years of compensatory hyperfunction and marks the beginning of decompensation.

The myocardial hypertrophy which develops in all cases of compensatory hyperfunction of the heart is very important in these processes.

In this work, we studied the intensity of protein synthesis in the myocardium of animals with compensatory hyperfunction and hypertrophy of the heart, induced by an experimental defect.

## EXPERIMENTAL METHODS

The intensity of protein synthesis in the heart muscle was estimated according to the inclusion in the proteins in vivo of the amino acid methionine, labeled with $S^{35}$. Radiomethionine was injected subcutaneously into rabbits in a dose of 600 impulses per minute per 1 g of animal weight. In order to standardize the conditions, all the rabbits were starved for 18 hours before the administration of the methionine. The rabbits were killed four hours after the injection, i.e., during the period of approximately maximal inclusion of the amino acid in the proteins, and the radioactivity of the heart and blood plasma was determined. The heart was washed free of blood, ground into a homogeneous state and treated three times with 20 and 5% trichloroacetic acid, then with alcohol, a mixture of alcohol and ether, and, finally, with ether to obtain preparative precipitation of the dry protein. An end-window counter was used to determine the radioactivity of each batch of this protein (10 mg).

Experimental aortic stenosis was induced in the experimental animals by an earlier described method [2, 3]. The hearts of these animals were examined for radioactivity 2, 7, 30 and 155 days after the creation of the heart defect. Four experimental and four control animals were examined at each of these intervals.

## EXPERIMENTAL RESULTS

The results obtained in all the experiments are given in the table.

The data in the table show that, during the emergency stage, when the heart is rapidly increasing in weight, there is also an increase of about 100% in the intensity of methionine inclusion in the proteins of the myocardium. The intensity of this inclusion then gradually diminished, reaching the normal level after a month, when the stage of relatively stable myocardial hyperfunction is observed, and the weight of the heart has become stabilized. Five months after the creation of the defect, methionine inclusion had decreased to approximately half the normal level.

There was some increase in the intensity of methionine inclusion in the plasma proteins during the first seven days following the creation of the defect. On the whole, however, the data in the table indicate a lack of proportionality between the intensity of methionine inclusion in the myocardial proteins and that in the plasma proteins. For example, five months after the creation of the defect, the intensity of methionine inclusion in the proteins of the heart was sharply reduced, but, in the plasma proteins, it was normal or even increased. In our experiments, therefore, the intensity of methionine inclusion in the myocardial proteins was not by any means determined by the content of methionine in the plasma proteins, but depended on

the dynamics of the metabolic processes in the heart muscle.

According to contemporary opinion, the intensity of radiomethionine inclusion reflects the protein synthesis rate, or to be more exact, the rate at which the protein structures of the myocardium are renewed. Therefore, the data obtained give reason to suppose that the vigorous development of hypertrophy which takes place during the emergency stage is attended by a corresponding increase in the protein synthesis rate in the myocardium; during the stage of relatively stable hyperfunction, normalization of the synthesis rate is observed, while during the stage of gradual exhaustion and cardiosclerosis, the rate of synthesis decreases, sharply inhibiting the normal restoration process of the myocardial protein structures.

Intensity of $S^{35}$ Methionine Inclusion in the Proteins of the Heart and Blood Plasma of Rabbits with Experimental Heart Defect

| Rabbit No. | Time after operation (in days) | Number of impulses per min per 10 mg of protein: heart, absolute values | heart, average | plasma, absolute values | plasma, average |
|---|---|---|---|---|---|
| 6 | Control | 102 | | 182 | |
| 7 | " | 121 | 126 | 148 | 169 |
| 8 | " | 132 | | 189 | |
| 9 | " | 148 | | 156 | |
| 3 | 2 | 223 | | 185 | |
| 4 | 2 | 228 | 252 | 122 | 158 |
| 5 | 2 | 288 | | 148 | |
| 2 | 2 | 270 | | 178 | |
| 17 | 7 | 309 | | 348 | |
| 18 | 7 | 175 | 239 | 260 | 298 |
| 19 | 7 | 220 | | 285 | |
| 1 | 7 | 250 | | 340 | |
| 10 | 30 | 140 | | — | |
| 11 | 30 | 132 | 150 | — | — |
| 12 | 30 | 190 | | | |
| 13 | 30 | 140 | | | |
| 14 | 155 | 54 | | 195 | |
| 15 | 155 | 70 | | 179 | |
| 16 | 155 | 84 | 71 | 212 | 199 |
| 20 | 155 | 77 | | 210 | |

The data obtained regarding the intensity of protein synthesis in the myocardium during experimental heart defect, combined with the results published earlier of research conducted by one of us on the same model [2-8], permit the conclusion that the heart passes through three main stages in the process of compensatory hyperfunction.

The First Stage. The emergency stage of acute overstress is characterized by the development of tonogenic cardiac dilatation, which approximately doubles the diameter of the heart. There is a 10-12% daily increase in the weight of the heart. Protein synthesis in the myocardium accelerates to about twice the original rate; the muscle fibers appear swollen, and the myofibrils pull apart from each other; the glycogen content of the myocardium decreases to 1/2-1/3 its former value, the lactic acid content increases 18-20%, the phosphocreatine content is reduced to 1/10 its original value and the ATP content remains normal. Changes in the T wave and the S-T segment are observed on the electrocardiogram.

The Second Stage. During the stage of prolonged and relatively stable hyperfunction, the heart is characterized by stable dimensions. The weight of the heart is also stabilized at about 100% more than the normal weight. The rate of protein synthesis in the myocardium is normal, and there are no signs of protein or fatty dystrophy; hypertrophied muscle fibers with compactly arranged myofibrils are observed. The myocardial content of phosphocreatine, ATP and glycogen is normal, but the lactic acid content is 200% the normal. No changes in the T wave and the S-T segment are apparent on the electrocardiogram, but there is a shift of the electrical axis of the heart to the left.

The Third Stage. This stage of progressive exhaustion is characterized by stable heart weight, some increase in the dimensions of the heart due to additional dilatation and pronounced and progressive cardiosclerosis. Foci of fatty dystrophy appear in the muscle fibers; the protein synthesis rate in the myocardium is 2-2½ times less than the normal rate; the glycogen content of the myocardium is normal, and the lactic acid content is 250-300% of the normal value. The electrocardiograph shows an increasing shift to the left of the electrical axis of the heart.

The transitions between these three stages are gradual. One very important factor in the transition of the heart from the first, or emergency, stage to the second stage of relatively stable hyperfunction [8, 9] is the rapidly developing hypertrophy based on the increase we established in the rate of protein synthesis in the myocardium. The hypertrophy increases the mass of the myocardium, especially the mass of sarcosomes within which are localized the enzyme systems of oxidizing phosphorylation which provide for the aerobic resynthesis of ATP. After the development of hypertrophy, therefore, the disappearance of the signs peculiar to the emergency stage, indicating mobilization of anaerobic sources of ATP resynthesis, is evident from the decrease in the myocardial supply of glycogen and phosphocreatine. Hypertrophy increases the ability of the heart as a whole to resynthesize high-energy compounds, but at the same time causes the concentration of capillaries in the myocardium to decrease to almost half the original [13]. Due to the acute prolongation of the path of oxygen diffusion from the capillary wall to the center of the muscle fiber, a certain degree of myocardial hypoxia develops, which in turn causes an accumulation

of lactic acid in the myocardium. During the first stage of the process, therefore, hypertrophy is a very important factor in the heart's adaptation to a long increased load, but it subsequently becomes the prelude to cardiosclerosis and other pathologic changes in the myocardium.

The inhibition of protein synthesis in the myocardium established in our experiments may be very important to the development of cardiosclerosis and cardiac exhaustion in the final stage of the process.

It has recently been shown that change in the properties of actomyosin, the principal protein contractile complex of the myocardium, becomes of essential importance in the development of insufficiency of a hypertrophied heart under conditions of flaws and hypertonia. In this case, the myosin content of the myocardium is reduced, the viscosity of the actomyosin precipitated in pure form decreases, and the ability of glycerinated muscle fibers to contract upon the addition of the ATP is diminished [10, 12]. One can assume that the disturbance of the ability of the myocardial contractile proteins to convert the potential energy contained in the high-energy phosphoric acid compounds into the kinetic energy of cardiac contractions is connected with the inhibition of the normal restoration process of the myocardial protein structures.

There are two reasons which can be given at this time for the inhibition of protein synthesis in the myocardium under conditions of cardiac hypertrophy.

1. Accumulation of lactic acid in the myocardium regularly accompanies cardiac compensatory hyperfunction of long duration; this indicates oxygen deficiency and a decrease in the level of the oxidation-reduction processes and is attended by some decrease in the ATP content of the myocardium. Disturbances of this type in the energy sources utilized in protein synthesis naturally can result in a reduced rate of protein synthesis and in the inhibition we observed in the exhaustion stage of the normal restoration process of the myocardial protein structures.

2. It is generally acknowledged that myocardial hypertrophy is not attended by hyperplasia of the muscle fibers, but consists only of an increase in their size; consequently, there is a much greater increase in the mass of sarcoplasm in a hypertrophied myocardium than in the mass of nuclei. A relative deficiency of desoxyribonucleic acid DNA, which is chiefly concentrated in the cell nuclei and is of great importance to the process of protein synthesis, can develop in such a situation [11]. Such a relative deficiency of DNA can, in turn, disturb the synthesis of protein in the myocardium.

## SUMMARY

Compensatory hyperfunction of the heart in vitium cordis, hypertension and other diseases of the circulatory system connected with the cardiac overstrain of long duration represents the main factor in preservation of normal hemodynamic indices and clinical compensation. The rate of protein synthesis in the myocardium was studied under conditions of compensatory cardiac hyperfunction provoked by experimentally induced vitium cordis. As established, rapid development of hypertrophy during the first emergency stage of compensatory hyperfunction is accompanied by an intensified rate of protein synthesis (it about doubles). In the second stage of relatively stable hyperfunction the rate of protein synthesis is normal, while at the third stage—characterized by cardiosclerosis and progressive exhaustion—it is reduced 2–2.5 times. This depression of the normal renovation process of the protein myocardial structures may bring about a change in the contractile proteins of the heart, thus playing an important role in the development of cardiosclerosis and cardiac insufficiency.

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