Cardiomyocyte remodeling in ischemic heart disease

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***Key words**: ischemic heart disease; myocardial infarction; hypertrophy; cardiomyocyte remodeling.*

***Summary**. Objective. The aim of the study was to detect changes in left ventricular cardiomyocyte size and shape in response to chronic ischemia and loss of cardiac tissue (myocardial infarction) during the course of ischemic heart disease (IHD).*

Material and methods. Left ventricular cardiomyocyte dimensions (diameter and length) were estimated histomorphometrically, and their cross-sectional area and volume were assessed in 85 males who died suddenly out of hospital (within 6 hours of the onset of the terminal event) due to the acute first (preinfarction IHD group, n=53, aged 48.6±2.9 years) or repeated (postinfarction IHD group, n=32, aged 51.7±2.9 years) IHD attack, and had no other causes for the increased heart load. Twenty-nine males of similar age (mean age, 46.0±3.1 years) who succumbed to external causes served as controls.

Results. We have found cardiomyocyte hypertrophy in the preinfarction IHD group already. The cardiomyocyte volume was increased by 32.0% in comparison with the same index in the control group, and cross-sectional area and length – by 17.2 and 12.5%, respectively. In postinfarction IHD group, all studied cardiomyocyte parameters did not differ significantly from the analogous indices in the preinfarction IHD group (P>0.05). Cardiomyocyte hypertrophy was related to the increase in left ventricular cardiomyocyte parameters.

Conclusions. Left ventricular cardiomyocyte hypertrophy occurs before the first myocardial infarction. In postinfarction myocardium, cardiomyocyte dimensions do not differ significantly at least prior to the appearance of congestive heart failure syndrome.

Introduction

The essential function of the heart – to generate force to pump blood – depends upon the coordinated contraction of cardiomyocytes. Cardiomyocytes constitute approximately 76% of the structural volume of the myocardium, but make up only 20–25% of all myocardial cells.

Heart muscle cells are elongated, with step-like ends. In most cases (75%), they have one nucleus in the cell center; they are separated from each other by structures called intercalated disks and are connected into continuous network. The sarcoplasm is filled with longitudinally orientated myofibrils, interspaced by abundant mitochondria and sarcoplasmic reticulum.

The unit of contraction represents sarcomeres, longitudinally arranged within all muscle cells. This protein complex is organized into thick (myosin) and thin (actin, troponin, and tropomyosin) filaments, which in the presence of calcium and ATP, slide past each other and generate the force of contraction. The force of contraction is transmitted to cytoskeleton through a complex network of proteins linking the sarcomere to the sarcolemma and extracellular matrix. Structural and functional integrity between neighboring cardiomyocytes is supported by complex protein structures, called desmosomes. These complexes may transmit force between cells and participate in transduction of signals. They are important for the propagation of electric potential and ensure synchronized contraction of cardiomyocytes (1).

When various factors (ischemia, toxic substances, microorganisms, etc.) damage cardiomyocytes or they are lost (e.g. due to infarction) or when there is an increased load on the heart leading to in adequate contraction, the compensatory response of the heart is manifested by remodeling: they undergo hypertrophy, i.e. increase in size. During the hypertrophy, protein synthesis intensifies, new sarcomeres are pro-

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duced, cardiomyocytes become thicker and longer, the thickness of ventricular wall grows, and the cardiac contraction increases. This response temporarily eliminates, or at least reduces, the hemodynamic overload of the heart (2–5).

The article examines left ventricular cardiomyocyte remodeling, the relation of changes in cell parameters to left ventricular hypertrophy (increase in weight) and dilation (increase in endocardial surface area) indices in response to chronic ischemia and to loss of parenchymal cells, i.e. during progression of ischemic heart disease (IHD).

Material and methods

Heart specimens of 85 males who died suddenly out of hospital (within 6 hours of the onset of the terminal event) due IHD were investigated. Cases were divided into two groups: preinfarction IHD group consisted of 53 decedents with the first fatal acute attack (aged 48.6±2.9 years) and postinfarction IHD group – 32 decedents (aged 51.7±2.9 years) who had a postinfarction scar detected on autopsy. In both groups, the duration of acute ischemic lesions did not exceed 12 hours. Seeking to evaluate the impact of ischemia as isolated factor, examination was performed only on decedents who had no clinically or morphologically defined arterial hypertension, valvular pathology, primary cardiomyopathy, chronic bronchial or pulmonary disease, which could increase the heart load, and clinical symptoms of heart failure. Control group consisted of 29 males of similar age (mean age, 46.0±3.1 years), who succumbed to external causes.

Special morphological (macroscopic and microscopic) study of the heart and coronary arteries was performed using methods suggested by WHO experts and modified at the Laboratory of Cardiac Pathology, which enables to obtain information about the changes in the whole coronary artery tree and the entire left myocardium (6). Every third perpendicular by sliced tissue block of the left ventricle wall myocardium was embedded in paraffin and sectioned at 4-μm thickness, stained by modified azan, and taken for histomorphometric investigation. Longitudinally cut cardiomyocytes were measured only when both intercalated disks and a nucleus in the center were observed, and when there were no changes in the contractile structure. Cardiomyocyte diameter at nucleus region and distance between intercalated disks were determined using automated system of biological image analysis "Quantimet 520" (Cambridge Instruments), connected to "Reichert Jung" light microscope. Cardiomyocyte cross-sectional area and volume were assessed from $\pi \times r^2$ and $\pi \times r^2 \times l$, respectively, where r is ½ of the diameter, l – the length of cardiomyocyte, considering it to have a shape of a cylinder. In each case, 65 cardiomyocytes were measured. The measurements, performed by different observers, and repeated measurements of the same observer differed less than by 3%.

Analysis of variance (ANOVA) was applied to compare histomorphometric parameters between two groups (IHD and the controls) and more groups, evaluating statistical significance of differences between dispersions of morphometric parameters of each group and every case separately (nested design). One-factor method was used to test for significant differences between means of cardiomyocyte parameters. Regression analysis was applied to determine relationships of investigated parameters. Values of $P<0.05$ were considered to be significant. Data are presented as mean ± standard error.

Results

A significant increase in the size of cardiomyocytes was found already in the preinfarction IHD group: the diameter was by 8.2% and length by 12.5% greater than in the control group. After assessment of spatial parameters, it was determined that cross-sectional area of cardiomyocyte was by 17.2% and volume by 32.0% greater than corresponding parameters in the control group. Although the parameters of the postinfarction IHD group were somewhat greater, they did not differ significantly from the preinfarction IHD group ($P>0.05$) (Figs. 1 and 2).

The relationship between the cardiomyocyte diameter and length was positive and significant, but weak: in the control group, $r=0.26$, $P<0.05$; in the presence of chronic myocardial ischemia, $r=0.32$, $P<0.05$; and in the presence of myocardial postinfarction scars, $r=0.42$, $P<0.05$.

Changes in cardiomyocyte size were related to the increase of left ventricular weight and endocardial surface area. The left ventricular weight in the preinfarction IHD group was greater by 23.2% (128.4±1.9 g) as compared with the same index in the control group (104.2±2.6 g, $P<0.05$); in the postinfarction IHD group – greater by 43.8% (149.8±3.8 g, $P<0.05$) than in the control group, and greater by 16.7% as compared with the same index in the preinfarction IHD group ($P<0.05$). Left ventricular endocardial surface area in the preinfarction group was by 34.4% (50.4±1.5 cm^2, $P<0.05$) and in the postinfarction IHD group by 60.8%

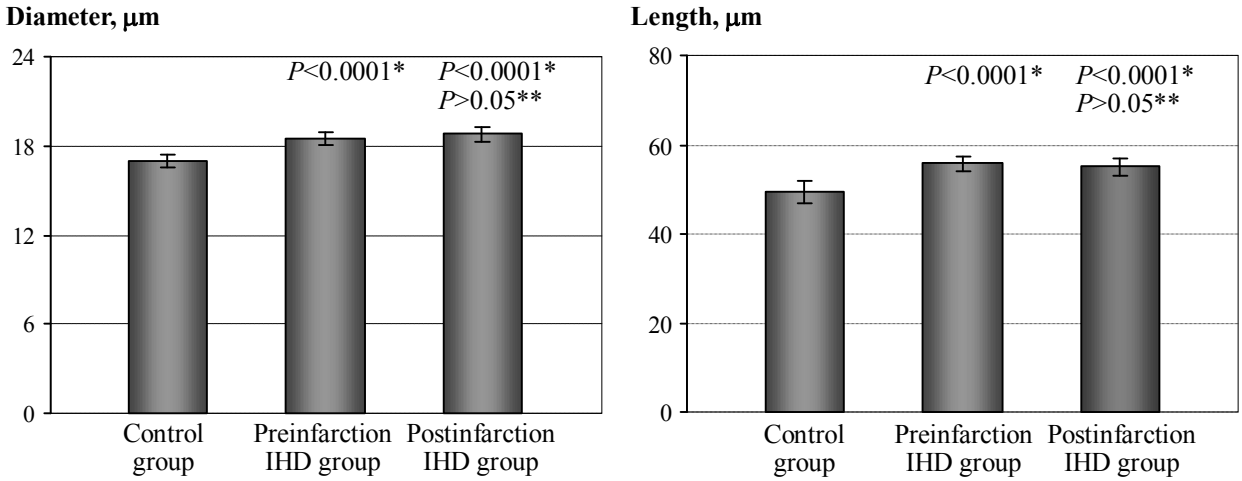

Fig. 1. **Diameter and length of cardiomyocytes (mean and standard error)**
*Difference between research group and control group.
**Difference between postinfarction IHD group and preinfarction IHD group.

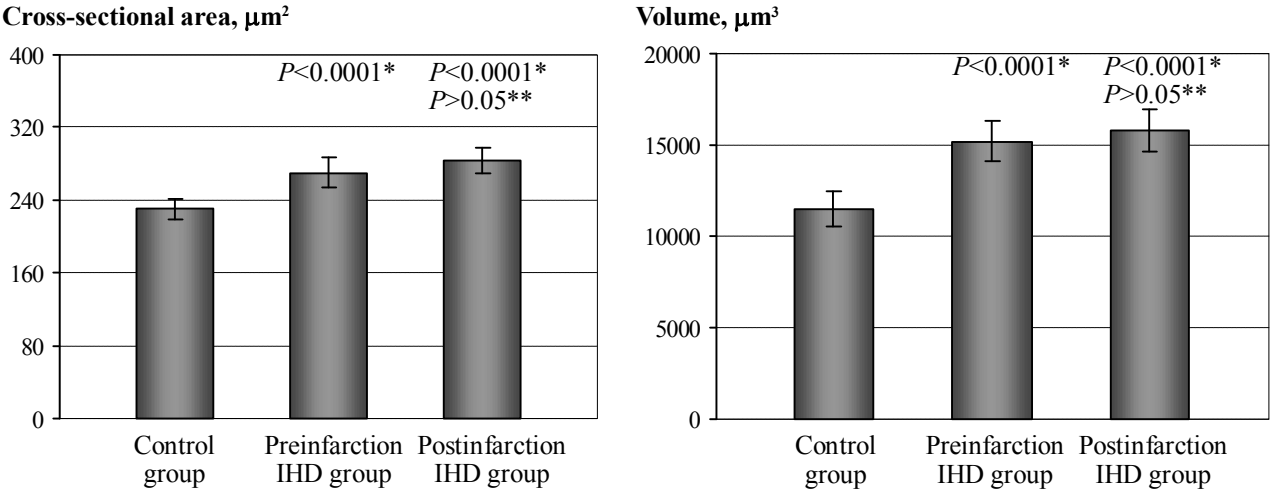

Fig. 2. **Cross-sectional area and volume of cardiomyocytes (mean and standard error)**
*Difference between research group and control group.
**Difference between postinfarction IHD group and preinfarction IHD group.

(60.3±2.2 cm^2, P<0.05) greater as compared with the same index in the control group (37.5±1.4 cm^2). The latter was also by 19.6% greater than the same index in the preinfarction IHD group. The relative weight index (the ratio of left ventricular myocardium weight to endocardial surface area) did not differ among all three groups (the index in the control group, 2.87± 0.11; preinfarction IHD group, 2.73±0.09; postinfarction IHD group, 2.60±0.08, P>0.05), indicating a proportionate increase in left ventricular weight and endocardial surface area, i.e. eccentric heart hypertrophy.

Relationship between the parameters of cardiomyocytes and the left ventricular weight, as well as endocardial surface area, was determined. Cardiomyocyte diameter and length in the control group was related to the left ventricular weight (R=0.35, P<0.05 and R=0.43, P<0.05, respectively), but no significant relationship was determined in the other groups (Figs. 3 and 4). Different relationship was found between the cardiomyocyte diameter and endocardial surface area: in the pre- and the postinfarction IHD groups, it was negative (R=–0.47, P<0.05 and R=–0.33, P<0.05, respectively), but there was no such significant relationship in the control group. In separate groups, there was no relationship between the cardiomyocyte length and left ventricular endocardial surface area.

No relationship was found between the cardiomyocyte parameters and the postinfarct scar size.

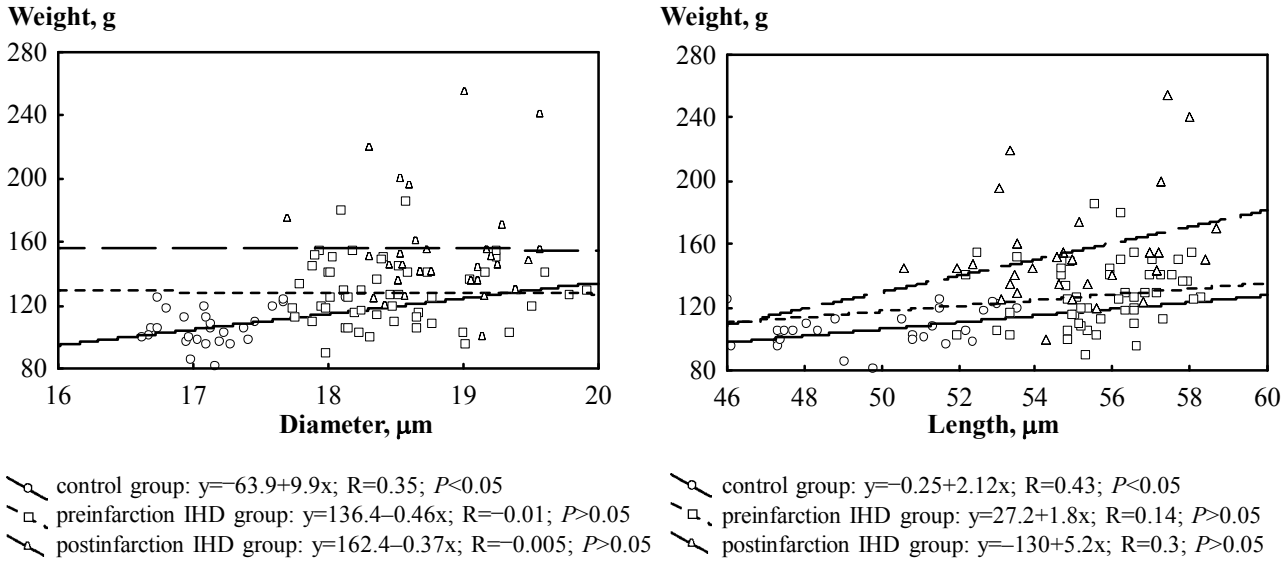

Fig. 3. **Relationship between diameter and length of cardiomyocytes and left ventricular weight**

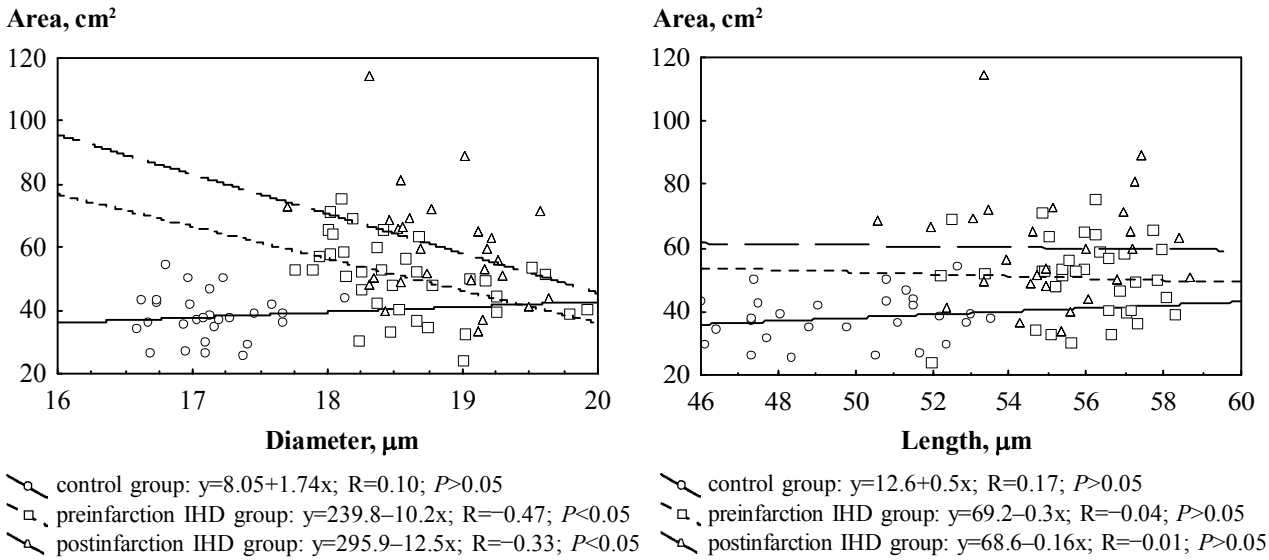

Fig. 4. **Relationship between diameter and length of cardiomyocytes and left ventricular endocardial surface area**

Discussion

Our data indicate that myocardial hypertrophy, characterized by increased diameter as well as the length of cardiomyocytes, develops during chronic ischemia before the first acute attack of IHD. According to the data of experimental studies, the change in cardiomyocyte parameters is determined by the nature of cardiac muscle overload: when the overload is due to increased pressure, increase in cardiac myocyte diameter predominates, while the overload due to augmented volume leads to the increase in length. Anversa et al. (7) have found that after 8 days of pressure overload caused by experimental constriction of abdominal aorta, an increase in weight of papillary muscle by 51% in rats was in direct relation to increased diameter of cardiomyocytes with no change in their length. The number of parallel myofibrils was increased by 84%. After experimental volume overload induced by moderate physical strain, the length of cardiomyocytes increased by 22%, with an increase in the number of sarcomeres along the myofibrils. When the overload lasts for months, the increase in both cross-sectional area and the length is observed, but depending on the nature of the overload, one of the two parameters may predominate. Apparently, isolated increase in cross-sectional area or length, depending upon the type of overload, may be present in the initial period of the overload, which was studied

by the above authors.

We have failed to find data of similar studies on human myocardium in the literature. It is worthy of attention that Ischijima (8) in his studies on autopsied material also detected an increased diameter of left ventricular cardiomyocytes, with the existing severe (≥75%) stenosis of all three coronary arteries (without postinfarction scar). Okada et al. studying human left ventricular myocardium, obtained during coronary bypass operation, found a 49% increase in the diameter of cardiomyocytes in patients with moderate (50–75%) and 61% increase in case of severe (≥75%) atherosclerotic stenosis of coronary arteries (confirmed by coronarography) (9). These authors did not estimate the length of cardiomyocytes.

Literature abounds in data on cardiomyocyte hypertrophy following myocardial infarction in humans as well as in animal models. After loss of myocardial tissue, thicker and longer cardiomyocytes may be observed in the intact myocardial zone. On the third day of experimental rat myocardial infarction, occupying more than 50% of the left ventricle, cardiomyocyte volume in the intact zone was found to be increased by 28%, cross-sectional area – by 12%, length – by 14% (10). In our studied postinfarction IHD group, cardiomyocyte parameters were increased in the intact zone as compared with the control group: cross-sectional area by 22.5%, length – by 11.2%, volume – by 36.9%, but surprisingly did not differ significantly from the data of the preinfarction IHD group. Our findings on the absence of significant increase in cardiomyocyte hypertrophy after infarction could not be compared with those of other studies because we have failed to find data on comparative changes in cardiomyocyte parameters before and after infarction. One could attribute it to the presence of not particularly large scar (in most cases not exceeding 20% of left ventricular and septal volume) or make an assumption of the cardiomyocyte ability to replicate. The weight of the left ventricle in the preinfarction IHD group was greater by 23.2%, postinfarction IHD group – by 43.8% than the same index of the control group.

Thus, it can be stated that the cardiomyocyte hypertrophy is the process, appearing during the chronic IHD, i.e. in persistent or chronic ischemia before the first myocardial infarction, and helping to adapt and maintain adequate heart function. Heart muscle undergoes hypertrophy by increasing cardiomyocyte diameter and length. Hypertrophy is associated with hemodynamic changes brought about by disordered contractility. Persistent myocardial ischemia (a major factor for chronic IHD) usually occurs when the blood flow through coronary arteries with atherosclerotic stenosis does not meet oxygen demand of cardiomyocytes. One of the most important changes of myocardial function is the decreased contractility, worsening the blood ejection from the left ventricle, and causing signs of systolic dysfunction. The most important and mutually closely related compensatory mechanisms for left ventricular dysfunction induced by myocardial ischemia, which help to maintain arterial pressure and perfusion of vitally important organs, are Franck-Starling mechanism, myocardial hypertrophy with or without cavity dilation and activation of neuroendocrine systems, i.e. autonomous sympathetic nervous system and renin-angiotensin-aldosterone system, and increased production of natriuretic peptide. The first two of them directly increase contraction, the latter – increases the heart rate and decreases the hemodynamic load (11).

Central hemodynamics at normal level is maintained by adapting the heart to the diastolic blood volume. It is related to the extension of myocardial cells before the contraction: the force of contraction in systole is directly related to their length in diastole. This is the Frank-Starling mechanism – the most important mechanism in myocardial self-regulation of the contraction function. In physiological conditions, it is an adaptation of the ventricle to the increasing load and in injured myocardium – the most important compensation factor. The left ventricular wall tension is in direct ratio to blood pressure in its cavity and the radius of the cavity, and in inverse ratio to wall thickness. It is postulated that cardiomyocyte length and cross-sectional area are analogous to the diameter of ventricular cavity and wall thickness. Thus, the changes in the relation between the cardiac myocyte length and cross-sectional area are directly related to the changes in the wall tension. Cardiac myocytes hypertrophy decreases the wall tension and normalizes the heart function (11, 14–16).

Morphological manifestation of adaptive and compensatory changes in myocardium is different in comparison with other organs, because of its functional and structural characteristics. Up to now, it is universally accepted that cardiac myocytes are able to divide only for a short time (around 7 months) after birth; thus, their hypertrophy, i.e. intracellular hyperplasia of contractile and energetic elements, is the only possible way to compensate for the lost function and to maintain a sufficient functional activity. Hypertrophy occurs on the existing "basis" and is a more "rapid" way of structural realization. The rate of contractile protein synthesis and the amount of proteins and mRNAs per cell increase. Due to overload, new sarcomeres are developed to meet increased mechanical demands, to reduce the energy consumption of

single myofibrils, and to decrease the tension of every failing cell. As energy consumption during every systole is in inverse ratio to wall tension, hypertrophy increases the effectiveness of contraction and has an energy-sparing effect. But prolonged (months-to-years) exposure to hypertrophy stimulus uncovers negative side features, especially such as the damage in heart architecture and cell structure, accentuating the energy deficit of the cell (3, 12).

When there are reversible changes in cardiomyocytes, and the cell does not die, intracellular reparative regeneration occurs – injured ultrastructures undergo normalization or increase in number. When there is myocardial necrosis, compensatory hyperplasia of intracellular ultrastructures takes place, and the function of the organ normalizes by renewing former ultrastructural level, but it occurs in unaffected cells (13).

The mode of intracellular hyperplasia depends upon the stimulus. During pressure overload, thickening of myofibrils predominates, the contractile proteins (new sarcomeres) appear in parallel fashion to the others, making the diameter of cardiomyocytes larger without obvious increase in length. The thickness of the ventricular wall increases in comparison with the radius of the ventricular cavity – a sign of concentric hypertrophy, while during volume overload, the ventricle undergoes hypertrophy and dilation, i.e. eccentric hypertrophy. Both ventricular wall thickness and ventricular cavity radius are increased, with the predomination of increase in cardiomyocyte length. Myofibrils become longer due to additional contractile proteins attached to the already present ones along the myofibril axis. After the reduction in contractile myocardium mass, both longer and thicker cardiac myocytes are found (14, 15).

The increase in myocardial weight is usually employed in the grading of myocardial hypertrophy related to cardiac pathology, thought to be a reliable index of reactive increase of cardiomyocytes. However, Beltrami et al. (12) are of the opinion that it is reliable only in circumstances when the proportion among different ventricular structural components is maintained, and the number of ventricular cells is constant. But the hypertrophy of ischemic myocardium consists of the hypertrophy of cardiac myocytes and diffuse interstitial fibrosis (17).

It is noteworthy that at the present time, there are doubts about human cardiac myocyte loss of their ability to divide after birth. A new concept of cardiac myocyte regeneration is based on assumption that myocyte death and regeneration are characteristics of normal and diseased heart (18–20). Study on histological and biochemical markers of cell division (Ki67 and mitotic index) shows that division occurs in normal myocardium and increases in the impaired one, primarily in the zone between the infarct and the intact viable myocardium. Investigators indicate that most adult cardiomyocytes are terminally differentiated, and only a small part of them divide, especially when the myocardium is impaired and its cells are irreversibly injured. These mechanisms of cellular replacement are not capable to regenerate the whole infarcted myocardium and limit themselves merely with the intact zone cardiomyocytes (21). Evidence about a limited population of myocardial stem cell-like cells, which may regenerate instead of lost cardiomyocytes, increases. The most important proof of this is the phenomenon of chimerism, when in female hearts transplanted to men, cardiomyocytes with Y chromosome were found. This might support a possibility that cardiac stem/precursor cells, able to divide, may exist (in the remaining atria) (21, 22).

It is supposed that left ventricular dysfunction and failure are associated with cardiomyocyte renewal, and hypertrophy is more evident when the ventricular function is still compensated. Debates are still ongoing.

Conclusions

Left ventricular cardiomyocyte hypertrophy, when their volume exceeds the same parameters in the control group by 32%, was found before the first myocardial infarction. In postinfarction cases, cardiomyocyte parameters do not differ significantly from those in preinfarction ischemic heart disease group, on condition that the congestive heart failure syndrome is absent.

Sergančiųjų išemine širdies liga kardiomiocitų remodeliavimasis

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Raktažodžiai: išeminė širdies liga, miokardo hipertrofija, kardiomiocitų remodeliavimasis.

Santrauka. *Darbo tikslas.* Nustatyti kairiojo skilvelio kardiomiocitų remodeliavimosi – dydžio ir formos parametrų pokyčius atsakant į lėtinę išemiją ir kontrakcinių elementų netektį (miokardo infarktą), t. y. plėtojantis išeminei širdies ligai (IŠL).

Tirtųjų kontingentas ir tyrimo metodai. Histomorfometriškai įvertinta 85 vyrų, mirusių staiga ikihospitaliniu laikotarpiu nuo pirmosios (n=53, amžiaus vidurkis – 48,6±2,9 metų) ir pakartotinės ūminės IŠL atakos (n=32, amžiaus vidurkis – 51,7±2,9 metų) ir neturėjusių kitos padidėjusį krūvį širdžiai sukeliančios patologijos, apskaičiuotas kairiojo skilvelio kardiomiocitų skersmuo, ilgis, skerspjūvio plotas ir tūris. 29 analogiško amžiaus vyrai, mirę nuo išorinių priežasčių, sudarė kontrolinę grupę (amžiaus vidurkis – 46,0±3,1 metų).

Rezultatai. Sergantiesiems IŠL dar ikiinfarktiniu laikotarpiu nustatyta kairiojo skilvelio kardiomiocitų hipertrofija: kardiomiocitų tūris padidėjęs 32,0 proc., lyginant su kontrolinės grupės tiriamųjų analogišku rodikliu, skerspjūvio plotas – 17,2 proc., ilgis – 12,5 proc. Poinfarktinės IŠL grupės visi tirtieji kardiomiocitų parametrai reikšmingai nesiskyrė nuo analogiškų ikiinfarktinės grupės tiriamųjų rodiklių ($p>0,05$).

Išvados. Sergantiesiems IŠL, dar iki įvykstant pirmajam miokardo infarktui, nustatyta kairiojo skilvelio kardiomiocitų hipertrofija, persirgus miokardo infarktu, kai nėra didelio laipsnio širdies nepakankamumo, kardiomiocitų dydis iš esmės nekinta.

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