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AGE FEATURES OF MORFOFUNCTIONAL CHANGES IN NORMAL CARDIAC MUSCLE AND UNDER THE INFLUENCE OF DAMAGING FACTORS (LITERATURE REVIEW)

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This article analyzes the recent literature on the age features of the structure and function of the intact heart muscle, as well as on the issue of heart remodeling in experimental animals of different ages under the influence of damaging factors. The myocardium undergoes morphological changes, with age, that occur as the restructuring of parenchymal and stromal components of the heart muscle. We point out the increase in mass of the heart and enlargement of its chambers with preferred hypertrophy and dilation of the left ventricular cavity during the aging process. The number of cardiomyocytes decreases throughout life. Quantitative changes of the cardiac cells are compensated by their hypertrophy. Reduction of the total volume of cardiomyocytes is accompanied by an increase of volume of connective tissue. The characteristic feature of aging is the accumulation of myocardial collagen in the interstitial space, exemia. The term "cardiac remodeling" includes the changes of both cellular and stromal components, volume of chambers of the heart cavities, which develop at pressure or volume overload, under the influence of various endogenous and exogenous factors. These lead to a structural reorganization of the heart muscle function. All chambers of the heart are remodeling. A significant number of clinical and experimental studies structural and functional reorganization of the heart under the influence of external and internal factors. However, the mechanisms of age-related changes in the myocardium at all levels of its organization structure are still questioned.

Key words: heart, age, remodeling.

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On the one hand, life expectancy of modern population has risen; it mostly associates with development of clinical and experimental medicine. On the other hand, cardiovascular disease has become a main course of mortality all over the world and it amounts to 30 % of all causes of death and 45 % of non-infectious reasons of death [11]. The cardiovascular death rate at people aged 85 to 89 is approximately 1 000 times higher than at people aged 25 to 29. By 2020, the number of people older 65 years will have reached 20 % of the general population [46]. As the elderly population is increasing, so scientists deeply study the morphological and functional changes in the heart

under the influence of various damaging factors and considering age. Despite a great number of papers that describe effects of aging on heart, biology and mechanisms of aging, the basis of these processes is still unclear.

Mikhailov S. S. [19] distinguishes 4 age periods of heart development. The period 1, which lasts for 2 years, is characterized by relatively intensive growth and differentiation of the components of the myocardium. Period 2 lasts from 2 to 10 years. During this period differentiation of cardiomyocytes slows down. In the period 3, so called puberty period (from 11 to 18 years), the heart growth accelerates. In period 4 (after 18

years) occurs stabilization and gradual involution of the heart muscle.

Borodina G. N. [4] assumes that the most significant changes in the macroscopic structure and organometric parameters occur on the verge of age periods. For example, a newborn's heart weight and size reduces by 1.1–1.3 times in comparison with an antenatal fetus aged 9–10 months during gestation. In early childhood, weight of the heart increases by 2.3 times and its size enlarges by 1.2–1.5 times. Weight of the heart of a teenager increases by 1.6 times and its size by 1.1 times. Only weight of the organ increases in the elderly.

Many experimental papers were devoted to study the morphological and functional remodeling/changes of the myocardium concerning age [2, 5, 6, 7, 14, 18, 20, 26, 27]. It occurs at all structural levels of the heart. In the organ level weight of the right and level ventricles with age increases unequally and disproportionately. During the experiments on the Vietnamese pigs, Hnatiuk M. S. and coauthors [20] concluded that 59.7 % of weight of the heart of mature pigs concentrated at the left ventricle; 16 % at the right ventricle; 7.5 % at the right atrium and 7.64 % at the left atrium respectively. Such gravimetric indices as the ventricular index of the mature animals decreased by 20.8 % in comparison with the young animals, but Fulton's index increase by 20.2 %. It proved the significant increase in the weight of the left ventricle [1; 20]. The similar results were presented in the papers by Misula I. P. [18] and Pogorielovoi O. S. [26]. This difference is caused by functions of the ventricles, the left ventricle acts as a pump, and the right ventricle acts as a displacement pump.

The heart cavity enlarges in the same way/simultaneously. The endocardiac surface of the left ventricle of the mature animals increases by 2.9 times; the right ventricle – by 2.7 times; the left

atrium – by 2.68 times; the right atrium – by 2.52 times. The unequal increase and enlargement of the weight of the heart chambers in growing organisms are the natural processes that provide physiological adaptation during this age period [20].

Hypertrophy and enlargement of heart components with significant increase in the weight and dilatation of the left ventricle occur in old animals. These changes are caused by reduction of compensation abilities of the heart muscle with age [7, 18]. Other studies [57] present data that deny differences in left ventricular mass indices among the age groups. However, they emphasize significant increase in the weight of the interatrial septum of the elderly.

The valves, particularly the valve atrioventricularis dextra, also change with age. For example, tissue on the leaflets become denser; location and number of the papillary muscles and heart strings change [24]. In the mature period the papillary muscles contained at the left ventricular cavity have sharp tops, but in the old period they conjugate with the carneal trabecules and their borders become unclear [19; 29]. The heart strings of newborns have almost equal diameters; they consist of connective tissue and muscle components [24].

Hnatiuk M. S. and coauthors [6], who studied the rat's heart of different age periods at the cell level noticed that the diameter of left ventricular cardiomyocyte nucleus increased by 1.6 times (for mature rats) and by 1.8 times (for senile rats) compare with the newborn rats. It has influence on the nuclear-cytoplasmic ratio (NC ratio) of the studied cardiomyocytes. For instance, the NC ratio for the left ventricle of the newborns was higher than for other age groups by 38.4 %. The diameters of right ventricular cardiomyocytes of the newborn animals are higher than the diameters of left ventricular cardiomyocytes by 3.8 %. The

researches explain it by gestation hypertension progression in the small circulatory system. The diameters of right ventricular cardiomyocytes increase with age, but they are by 10.6 % smaller for mature rats and by 5.1 % smaller for senile rats. This index of the NC ratio for the right ventricle of newborns is higher by 22.8 % in comparison with mature rats; and by 23.9 % higher in comparison with senile rats.

After birth, cardiomyocytes undergo significant hypertrophy by increasing myofibrils, glycogen, mitochondria, and T-tubules. During birth nexuses are distributed equally across the membrane of cardiomyocytes. Their number increase progressively during the postnatal period. At the same time there is a loss of lateral intracellular contacts. In humans, this period lasts up to 6 years; in rats – up to 90 days. In adulthood ventricular myocardium gap junctions locate near the adhesive cells in the electromechanical drives across the terminal areas of cardiomyocytes [25]. In the aging myocardium due to necrosis or apoptosis the number of cardiomyocytes reduces [48]; polymorphism of the nuclei of cardiomyocytes occurs and the number of lysosomes increases [36].

During aging the hypertrophic changes occur in the myocardium; they stimulate the contractile function of the heart muscle in terms of age-related changes in blood vessels, including those that lead to increased peripheral resistance. An increase in the size of the ventricular cardiomyocytes and increased vascular resistance cause left ventricular hypertrophy, but myocardial contractile force significantly reduce [16].

Earlier scientists thought that cardiomyocytes were incapable to regenerate, and their life expectancy was the same as the heart. But studies on cardiac stem cells demonstrate that myocardium cells can regenerate. However, the issue of cardiomyocyte regeneration is still topical.

According to the literature, their regeneration is in the range of 0–20 % per year. Cardiomyocytes differentiate after birth and their number decreases significantly with age. Thus, the rate of regeneration of cardiomyocytes reduces and it cannot compensate for the loss of cells over time. Changes in the number of cardiomyocytes with age are compensated by cell hypertrophy [46]. Typical for aging is the occurrence of contractive changes in myofibrils due to increased transport of calcium ions and breach of their realizing [36]. S. Judge et al. [56] emphasize that the size of cardiomyocytes increase by sarcomers, and the amount of myofibrils decreases. The number of mitochondria reduces; their destruction and signs of acardiostrophia take place.

Apart from the muscular component of the myocardium, which is presented as cardiomyocytes, the scientists distinguish another component, so called "non-muscle" or connective tissue (stromal) component, which also undergoes age-related changes [9, 10, 45, 48]. Modern studies have established its role in the regulation of cardiomyocyte function by aligning potential between the intracellular and intercellular spaces [47, 49, 61, 64]. Due to different data, the volume ratio of cardiomyocytes (parenchyma) and connective tissue component (stroma) varies from 3:1 to 4:1 in the myocardium. Gorbunov A. A. [9], who studied a series of consecutive sections, notes that the ratio of the specific area of the muscle component is 54.7 %, extravascular stroma – 29.9 % and the vascular bed – 15.4 %. Myocardial stromal component is formed by cells and intercellular substance (matrix), which is composed of fibers and ground substance. According to other researchers, about 70 % of the ventricular myocardial cells are not cardiomyocytes [32]. K. K. Parker et al. [61] report that at birth the

relative number of cardiomyocytes is 75 %, whereas in the adult heart – only 1/3.

Stromal cells are presented as fibroblasts (90–95 %) and mast cells. Fibroblasts separate groups of cardiomyocytes from surrounding capillaries and adjacent bundles of cardiomyocytes together. It is believed that every cardiomyocytes is in contact with at least one fibroblast. One of the types of fibroblasts is myofibroblasts, which inherent features of fibroblasts (collagen) and smooth muscle cells (presence of miofilament, ability to contract). Researchers believe in the ability of myofibroblasts to change the intercellular substance volume and influence the orientation of its fibers. The increase in their number is observed during fibrotic and sclerotic processes in the heart [10]. In the aging myocardium naturally decreases the total volume of cardiomyocytes and increases the amount of connective tissue [5; 15]. Horn M. A. et al. [41] indicate that a characteristic feature of aging is the accumulation of myocardial collagen in the interstitial space. Restructuring infarction heart failure is characterized by the accumulation of collagen in the heart muscle of young animals and its loss in individuals of old age. Experiments on animals showed a linear increase with age in collagen content of the left ventricle, but during the later years of life, its content can increase twice. Increasing in the number of collagen deposition and increased stiffness lead to significant ventricular dysfunction, which is also a major feature of aging heart [46]. Tarasov K. V. et al. [32] indicate that aging of fibroblasts, blood vessels, and extracellular matrix have influence on the aging process of cardiomyocytes.

In the early period of the myocardium development there is a special vascular network. From 2 to 10 years, the number of blood vessels decreases, although the diameter of each vessel is increased [19]. In reviews Akhtemiichuk Y. T. et al.

[3] focus on reducing the number of reserve and plasma capillaries in the myocardium of the left ventricle of mature people due to the intensity of functional state of the capillary bed ventricular myocardium. If the ratio of newborn muscle fibers to capillaries is 5–6:1, the ratio for adult is reduced to 1.24:1. A part of the myocardial vessels are empty in the old. The walls of some blood vessels get microstrains and protrusion; reserve and plasma capillary vessels are replaced with empty vessels as winding strands. With age, atrial and ventricular myocardium reduces the diameter of capillaries, capillary net is diluted by increasing the size of capillary loops, especially in the atria; the shape of the capillary loops from changes from narrow to wide-loop; vascularization valve area reduces and the distance from the vessel enters its base to the free edge.

One of the hypotheses of aging is the oxidative stress hypothesis. It suggests that the accumulation of oxidative damage is a key factor in changes in physiological functions during aging [38, 39]. Babusíková et al. [39] studied the age-sensitivity to oxidative modification of proteins and lipids of cardiac sarcoplasmic reticulum isolated from 6, 15 and 26-month-old rats. Structural changes in the membranes of the sarcoplasmic reticulum accompanied with tryptophan degradation and significant accumulation of dytyrozyne protein, protein conjugates of lipid peroxidation products related dienes and reactive compounds of thiobarbituric acid. Sensitivity to oxidative damage is most evident in the sarcoplasmic reticulum of 26-month-old rats. These results indicate that aging and oxidative stress are associated with the accumulation of oxidation-damaged proteins and lipids, and these changes may cause cardiovascular shock.

Mitochondria play an important role to regulate life and death of cells [53, 66], they provide cells

with energy via oxidative phosphorylation but can quickly turn into an organelle that stimulate apoptosis in response to stress [54, 57, 60]. Mitochondrial property of "fusion" and "fission" was found in cardiomyocytes of young animals, but adults almost never had it [51]. This suggests that differences in mitochondrial dynamics and young adult cardiomyocytes are associated with specific structural features of the organization and interaction of mitochondria with the cytoskeleton in these cells [32]. During long time violation of mitochondrial function regarded as the main cause of cardiomyocytes loss during aging. Damaged mitochondria produce increased amounts of reactive oxygen species, causing adverse structural and functional effects on the cardiovascular system. Mitochondrial theory of aging cells is based on the fact that mitochondrial DNA has a high rate of mutation and limited capacity for repair. Over time, the accumulation of mutated mtDNA violates the integrity of the mitochondrial genome. Dysfunctional mitochondrial population in the cell increases with age, especially in highly differentiated nonproliferative organs (the brain and heart). It causes a lack of energy and increase oxidative burden. This results in damage or cell death. In other words, this theory examines mitochondrial DNA and the frequency of mutations as "aging clock" that triggers the aging process, affecting the overall lifespan of the organism [46]. E. Marzetti et al. [63] suggest that the age-related accumulation of dysfunctional mitochondria is the result of a combination of a violation of the clearance of damaged organelles by autophagy and inadequate mitochondrial genesis.

Research results by Huynh M. B. et al. [40] indicate the age increase in myocardial levels of glucosamine glycans and heparin. But glucosamine glycans of the aging heart muscle gradually lose the ability to bind heparin sulphates. It is known that

glucosamine glycans are important components of the extracellular matrix, the natural environment, which is implemented through the regulation of the cell. Thus, structural and functional changes in these polysaccharides affect the integrity of the tissue at critical physiological and pathological processes.

Comprehensive information on the age characteristics of myocardial morphofunctional reorganization is required for the comparative evaluation of changes in the heart muscle during exposure to its pathological factors. Structural and spatial changes that occur in the heart under the influence of damaging factors and lead to organ pathology, called cardiac remodeling [13, 15, 22]. The term "remodeling" is literally translated as reconstruction or restructuring. In the scientific literature, the term was introduced in the late 70's of the twentieth century. And the reason for its appearance was a detailed study of the structural transformation of the heart after myocardial infarction. Features of postinfarction myocardial remodeling and hypertension are discussed in details in national and foreign scientific works [13, 17, 22, 31, 42, 43, 44, 52, 55, 58, 59]. Quite a long time, the term "cardiac remodeling" associated exclusively with restructuring myocardium of the left ventricle. In the modern sense cardiac remodeling sees change as a cell and stromal components infarction, cardiac chamber volumes of cavities developing pressure overload or volume, with a variety of endogenous and exogenous intoxications, infections, etc. and lead to structural and functional reorganization of cardiac muscle [13]. The problem of cardiac remodeling has been the focus of research for several decades. Even today cellular and molecular mechanisms leading to the development of contractile dysfunction are still unclear. Swift F. et al. [65] determined the term "ultrastructural remodeling." Their study showed

significant changes in some parts of CMC during heart disease, including the sarcoplasmic reticulum and transverse tubules; and in location of ion channels and pumps that are critical in the regulation of myocardial contraction and relaxation. Thus, it is likely that ultrastructural remodeling may explain some important aspects of systolic and diastolic heart failure of different etiologies. Doenst T. et al. [50; 67] separated the term "metabolic remodeling of the heart", and Feihl F. et al. [40] – "microvascular remodeling."

Nowadays there are many experimental papers are devoted to the study of cardiac remodeling under the influence of a variety of simulated pathological conditions.

It was found that the changes can be observed not only in the left ventricle, but also in all parts of the heart. Thus, Blagonravov M. L. [3, 31], describing the morphological changes of the right ventricle in ischemic damage to the left, said that the right ventricle is a subject to deep morphofunctional remodeling. This process included: evident extracellular edema developing and the increased areas of the damaged and destroyed myofibrils. The intensity of apoptosis of cardiomyocytes increased only during the first day of the process, and then returned to the normal level, indicating a high sensitivity of right ventricular damage to the left, and proving the early inclusion of compensatory mechanisms.

Tverskaya M. S. et al. [23] studied pathomorphology of myocardial circulation by increasing afterload on the left or right ventricle and he pointed out generally similar changes. In both cases, there were a plethora of all coronary departments; stasis of blood in the capillaries and perivascular edema, even more evident in the arteries. These changes are about equally observed in both ventricles and the interventricular septum. Significant differences are regional increasing in

density of functioning capillaries. The maximum increase occurs in hemodynamically congested ventricle and interventricular septum. According to the authors, it is caused by strengthening of contractile activity. In intact (regarding pressure overload) ventricle functioning capillaries density increases, but to a lesser degree this may be associated with systemic neurohumoral regulation.

According to Souders C. A. et al. [62], a change of heart tissue in rats with transverse narrowing of the aorta develops very fast. It shows as an increase in the number of collagen and fibroblasts on the 7th day of the experiment, a decrease in the density of capillaries on the 2nd day after the surgery and recovery on day 7.

Simulating hyperglycemia, Trach-Rosolovska S. [34] studied the features of the components of the heart in rats of before- and reproductive age. The researcher points out that the nature of cardiac remodeling depends on the duration of experimental hyperglycemia and age of animals. Hyperglycemia during 1 month leads to a restructuring of the heart by hypertrophic type and has the adaptative-compensatory manner. Prolonged hyperglycemia leads to remodeling of dilated ventricular chambers, reducing the relative amount of CMC and blood vessels. Besides, the fibrosis area enlarges and stromal-cardiomyocyte indices increase. The above changes were most evident in animals of before-reproductive age.

Nepomnyashchikh L. M. et al. observed ultrastructural features of the remodeling of cardiomyocytes of rats at anthracycline damage in age aspect. They found that the development of regenerative and plastic insufficiency of cardiomyocytes in different groups accompanied by ultrastructural stereotype reorganization. Dramatic changes affected the nuclear apparatus, myofibrillar component and agranular sarcoplasmic reticulum. Intra-cellular reorganization of cardiomyocytes in

young animals is characterized by a significant decrease in the volume density of myofibrils in the same periods of observation compared with elderly animals. Restoration of cardiomyocyte ultrastructure in young rats happens earlier. In cardiac myocytes of old rats are found more significant structural modifications of mitochondria and more evident lytic changes of myofibrillar beams. An important feature of the cardiotoxicity of doxorubicin in young animals is a significant destruction of the endothelium of the capillaries in the early stages after exposure [20, 35].

Recent papers are devoted to the study of problems of cardiac remodeling under conditions of pulmonary hypertension. Hnatiuk M. S. [8] et al. modeled *cor pulmonale* on rats. We performed right pneumonectomy on them. According to the research, spatial characteristics of the heart chambers changed significantly. These changes were irregular and disproportionate. So, 3 months after the start of the experiment endocardial area of the left ventricle increased by 4.2 %, and the endocardial area of the right ventricle – by 20.2 %. As the planimetric index declined, expansion of both ventricular chambers was disproportionately.

Pryshlyak A. [28] studies mechanisms of cardiac remodeling under conditions of cadmium chloride and carbon (IV) oxide. He notes that poisoning of animals by these compounds leads to unequal increase in the mass of the heart with the overwhelming left ventricular hypertrophy and dilatation disproportionate heart chambers (greatest degree of expansion occurs in the right ventricle). Also there is a severe restructuring of the arteries of the heart mainly of small caliber. Cadmium chloride resulted in predominant vascular lesions of the left ventricle, and carbon (IV) oxide – the right ventricle. Effects on the body of these toxic substances cause changes of secretory activity of cardiomyocytes fibrillation. Thus, in terms of

compensation the number of secretory granules of myoendocrine cells increased and their number significantly decreased during decompensation.

Investigating the influence of heavy metals on the heart of rats of different ages, Pogorieleva O. S. [27] concluded that compensatory hypertrophy of the myocardium developed under the first stage of heavy metal salts influence. If the experiment continues, the structural changes in the hearts of all animals of age groups will occur. The changes are shown as: the decrease in heart weight and left ventricular mass reduction is minimal in mature animals, but the maximum – in old animals. There are development of irregular dilatation of the ventricular cavities; decrease in the diameter of cardiomyocytes and their nuclei for both ventricles; decrease in relative volume of cardiomyocytes and vascular infarction. Moreover, the areas of connective tissue increase by 8.54 and 18.91 % in young and senile animals.

Tvorko V. M. [33], describing the morpho-functional features of infarction in the general dehydration, marks stages of morphological, structural and ultrastructural changes in cardiac muscle: prevalence of degenerative processes and dyscirculatory with mild dehydration, further deepening their degrees with an average and exhaustion of compensatory mechanisms in sublethal degree of dehydration. The researchers also point on violations of water-electrolyte metabolism in the myocardium, namely an increase in the content of the sodium, magnesium and potassium cations and a decrease in calcium concentration; activation of lipid peroxidation; significant violations of submicroscopic membrane integrity of cardiomyocytes; destabilization of endocrine regulation of water and electrolyte balance of the heart, which shows substantial hyperplasia of secretory granules and an increase in

their volume density of endocrine cardiomyocytes in the auricular dextra.

Kvitnytska-Ryzhova T. Yu. et al. [14] describe the age-structural features of secretory and contractile responses of rat cardiomyocytes to enter vasopressin. Thus, secretory activity of atrial cardiomyocytes and activation of protein synthetic processes in cardiomyocytes of the left ventricle increase in young animals under the influence of vasopressin. In old rats along with the abovementioned changes we observe growth of destructive processes in cardiomyocytes as well as in the vascular wall.

Shcherbinina A. Yu. [37] presents in her studies the correlation between the relative changes in heart weight of rats of all ages under the influence of gravitational accelerations. The dramatical changes are found in 2-month-old rats. In the group of 12-month-old rats relative heart weight changes are absent. The insignificant change in this parameter is observed in case of combination of physical protective methods and administration of glutargin.

Abel E. D. et al. [38], despite the generally accepted statement that mitochondrial dysfunction develops during heart failure, suggest some evidence that it cannot be observed in early (compensatory) phase of left ventricular hypertrophy and it evident during progression of the pathological process. These changes present as mitochondrial swelling and destruction of cristae. Swelling of mitochondria is correlated with mitochondrial dysfunction and injury.

Conclusion

The myocardium undergoes morphological changes, which are presented as the restructuring of parenchymatous and stromal component of the heart muscle. During aging occurs an increase in heart weight and expansion of its chambers with overwhelming hypertrophy and dilatation of the left ventricle. However, the number of cardiomyocytes

decreases; polymorphism of nuclei is observed; dysfunctional mitochondria accumulate, and the number of lysosomes increases. Quantitative changes of cardiac cells may compensate hypertrophy and reduce the NC ratio. Reducing in the total number of cardiomyocytes is accompanied by the growth of connective tissue. The distinguishing features of aging are the accumulation of myocardial collagen in the interstitial space and vascular emptying. Numerous clinical and experimental works are devoted to study cardiac remodeling under the influence of external and internal factors. Each department of the heart is proved to be remodeled. However, a few works reflect the changes of the myocardium considering age and at all levels of its structural organization. Besides, they do not fully describe the mechanisms of morphological changes in the myocardium. In-depth study of the processes occurring in the heart in various pathological conditions may give clinicians the ability to predict the course of disease and prescribe adequate treatment.

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