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Review

Myocardial morphology in hypertrophic cardiomyopathy: the current state of the problem

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A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation; D – writing the article; E – critical revision of the article; F – final approval of the article

The objective. Based on the modern sources of scientific data to analyze the morphological features of the myocardium in hypertrophic cardiomyopathy.

The paper presents a literature review on current views on the features of structural remodeling of the left ventricular myocardium in patients with hypertrophic cardiomyopathy, as well as the most common classifications of this pathology. The emphasis is made on the problem of the interrelation of myocardial disarray and fibrosis.

The "small vessel disease" is an important pathogenetic link in the development of heart failure, which enhances the relation between disorder of myocardial histoarchitectonics and progressive cardiac ischemia in hypertrophic cardiomyopathy.

Conclusions. Notwithstanding the numerous research data on hypertrophic cardiomyopathy, no consensus among the authors regarding the etiology and pathogenesis of hypertrophic cardiomyopathy exists to date. Controversial data on the interrelation and sequence of disarray, myocardial hypertrophy, interstitial fibrosis, changes in the microvasculature and structural changes of the mitral valve in patients with hypertrophic cardiomyopathy hamper the search for adequate etiotropic treatment.

Polymorphism of clinical and morphological manifestations of hypertrophic cardiomyopathy requires collaborative efforts to study the disease by cardiologists and pathologists.

Key words: hypertrophic cardiomyopathy, endomyocardial fibrosis.

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Морфологія міокарда при гіпертрофічній кардіоміопатії: сучасний стан проблеми

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Мета роботи – на підставі даних сучасних джерел наукової літератури проаналізувати морфологічні особливості міокарда при гіпертрофічній кардіоміопатії.

Огляд показує сучасні погляди на особливості структурного ремоделювання міокарда лівого шлуночка серця у хворих на гіпертрофічну кардіоміопатію, наведені найпоширеніші класифікації цієї патології. Порушено проблему взаємозв'язку фігур дізарея кардіоміоцитів і фіброзу міокарда. Важлива патогенетична ланка розвитку серцевої недостатності, що підсилює зв'язок між порушеннями гістоархітектоніки міокарда та ішемією серця, яка прогресує, при гіпертрофічній кардіоміопатії – «хвороба дрібних судин».

Висновки. Незважаючи на велику кількість досліджень гіпертрофічної кардіоміопатії, у фаховій літературі немає єдиної думки щодо етіології та патогенезу гіпертрофічної кардіоміопатії. Суперечливі дані про наявність взаємозв'язку та послідовність розвитку фігур дізарея, гіпертрофії кардіоміоцитів, інтерстиціального фіброзу, змін мікроциркуляторного річища та мітрального клапана при гіпертрофічній кардіоміопатії ускладнюють пошук адекватного етіотропного лікування. Поліморфізм клінічних і морфологічних проявів гіпертрофічної кардіоміопатії зумовлює необхідність спільних зусиль кардіологів і патогістологів для вивчення цієї хвороби.

Ключові слова: гіпертрофічна кардіоміопатія, фіброз міокарда.

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Морфология миокарда при гипертрофической кардиомиопатии: современное состояние проблемы

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Цель работы – на основании данных современных источников научной литературы проанализировать морфологические особенности миокарда при гипертрофической кардиомиопатии.

Обзор освещает современные взгляды на особенности структурного ремоделирования миокарда левого желудочка сердца у больных гипертрофической кардиомиопатией, приведены наиболее распространенные классификации данной патологии. Уделено внимание проблеме взаимосвязи фигур дизарея кардиомиоцитов и фиброза миокарда. Важное патогенетическое звено развития сердечной недостаточности, усиливающее связь между нарушениями гистоархитектоники миокарда и прогрессирующей ишемией сердца при гипертрофической кардиомиопатии – «болезнь малых сосудов».

Выводы. Несмотря на большое количество исследований гипертрофической кардиомиопатии, в научной литературе нет единого мнения об этиологии и патогенезе гипертрофической кардиомиопатии. Противоречивые сведения о наличии взаимосвязи и последовательности развития фигур дизарея, гипертрофии кардиомиоцитов, интерстициального фиброза, изменений микроциркуляторного русла и митрального клапана при гипертрофической кардиомиопатии затрудняют поиски адекватного этиотропного лечения. Полиморфизм клинических и морфологических проявлений гипертрофической кардиомиопатии требует от кардиологов и патогистологов совместных усилий по изучению данной болезни.

Ключевые слова: гипертрофическая кардиомиопатия, фиброз миокарда.

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Hypertrophic cardiomyopathy (HCM) is characterized by the significant thickening of the left ventricle (LV) not associated with aortic valve stenosis, hypertension and other conditions, leading to left ventricular overload [1]. The prevalence of HCM was reported to be 1:200 in the general population [2]. This allowed the researchers to determine the HCM as the most common genetic cardiac pathology [3]. However, the etiology of hypertrophic cardiomyopathy remains unknown: several authors have reported a dysplasia of chordal apparatus and the papillary muscles of the mitral valve to play a leading role in the development of the disease [4–7]. Most researchers believe that the most common cause of primary myocardial hypertrophy is the inherited or spontaneous mutations in genes, encoding the synthesis of contractile sarcomere proteins of cardiomyocytes (CMs) [8], therefore, in the recent publications HCM is more commonly referred to as "the disease of the sarcomeres" [9].

The disease is characterized by the variety of clinical courses: from asymptomatic to the rapid progression of heart failure [5]. Currently, HCM is considered as the major cause of sudden cardiac death in young people, since it can be the first and the last manifestation of the disease [10]. Based on the data from autopsies of young people, conducted by various researchers in different years, N. T. Vatutin et al. in their work showed that the incidence of HCM as a cause of sudden death varied from 7 % to 25 % [11]. Clinical manifestation of HCM can be revealed at any age, but more frequently in the 3rd and 4th decades of life, and rarely first symptoms appear after 60 years of age [12].

The objective

The objective of this review is description of current views on the features of structural remodeling of the left ventricular myocardium in patients with hypertrophic cardiomyopathy, as well as the most common classifications of this pathology.

The complex of morphological changes of the myocardium in patients with HCM varies widely. First of all it concerns the location and extent of myocardial hypertrophy zone [13]. Macroscopically, symmetric and asymmetric HCM is distinguished [14]. The symmetric pattern with concentric LV hypertrophy is not common and is characterized by diffuse thickening of the left ventricular wall with a reduced cavity [15]. Asymmetric HCM manifests by local thickening of myocardium, which is not accompanied by LV dilatation, accounting for an estimated 70 % of the cases [3]. Hypertrophy of the interventricular septum (IVS) is more common. Asymmetric hypertrophy can be expressed over the entire length of the IVS from the basal part to the apex [16,17]; however, it is predominantly focal, when hypertrophy affects one or two segments of the IVS. Hypertrophy develops more frequently in the anterior part of the basal IVS: isolated or with the spread on the posterior part of the IVS and anterolateral free wall of the LV [18,19]. Clinically, the above hypertrophy is accompanied by obstruction of the LV outflow tract with the most pronounced changes in cardiac hemodynamics in most HCM patients [20].

Isolated focal hypertrophy of the LV apex is often diagnosed (25 %) in Asian patients [21]. In Europeans and Americans, the apical form of HCM is registered in 1–3 % of patients [22], and myocardial hypertrophy of apical segments extends usually to the anterior wall of the LV or the apical part of the right ventricle of the heart [3,21,23,24].

Cases when the process of hypertrophy extends only to papillary muscles of the LV with the preserved normal total mass of the LV myocardium have been reported [25,26]. Currently, some researchers consider the isolated papillary muscle hypertrophy as the possible initial stage of apical HCM [27]. Some authors believe that the hypertrophy of one or two papillary muscles up to 1.1 cm in either vertical or horizontal diameters can be a manifestation of independent HCM phenotype [18,28]. However, current literature data on the involvement of anterior cusp of the mitral valve in the pathogenesis of heart failure in HCM [4,29–33] presuppose that changes in papillary muscles may be secondary to the morpho-functional features of the cusps and chordae of the mitral valve in this pathology.

Mesoventricular (midventricular) obstructive hypertrophy is a rare variant of asymmetric cardiomyopathy and is characterized by the maximally marked hypertrophy in the middle third of the LV at the level of papillary muscles, resulting in separation of the LV into two parts by hourglass-type [34].

If examination of the patient has not revealed reasons that could cause LV overload with secondary development of myocardial hypertrophy (aortic valve stenosis, etc.), then the LV wall thickness ≥ 15 mm gives reason to suspect HCM [35]. Many experts consider that HCM can be suspected in adult individuals at any value of the IVS thickness exceeding 12 mm, since patients may have normal LV myocardial thickness with genetically confirmed HCM [36,37]. Based on the degree of thickening of the myocardium, A. G. Osiev et al. distinguish a moderate (15–20 mm), medium (21–25 mm) and severe (over 25 mm) hypertrophy [10]. If myocardial thickening reaches a value greater than 30 mm, such hypertrophy, according to K. P. Varma and other researchers, has a high risk of arrhythmias and sudden cardiac death development [38,39]. The second generally accepted diagnostic criterion of HCM is the ratio of IVS thickness to the lower LV wall thickness in diastole greater than 1.5 [40].

The structural changes of the myocardium in HCM, as well as its clinical manifestations, are variable and nonspecific, consequently, it is almost impossible to differentiate HCM from secondary myocardial hypertrophy, cardiac amyloidosis, glycogenosis or other infiltrative processes without histological study [41]. Numerous studies report that histopathological basis for HCM diagnosis is a triad of the signs of structural remodeling of myocardium: hypertrophy of CMs, disorientation of muscle fibers (also known as muscle fiber disarray) and fibrosis of different degrees [42,43]. However, it is noted that in addition to the modified CMs in hypertrophied myocardium, normal-sized cell area without disarray may be determined. Varnava A. M. et al. and Almaas V. M. et al. convincingly demonstrated that patterns of disarray were most pronounced in younger patients, whereas myocardial fibrosis was predominant in the elderly patients [44,45]. This can be seen as an illustration of the dynamics of morphological changes in the myocardium in HCM from CMs alteration to sclerosis.

Disarray patterns consist of hypertrophied CMs of bizarre shape, arranged in a random order at different angles to each other and to the direction of the main muscle bundle. A characteristic microscopic feature of the HCM, according to H. Masuda et al., is end-to-side coupling of CMs, which is particularly pronounced in areas of maximal hypertrophy [46]. Cunningham et al. compared such unordered CMs couplings in muscle fibers with a "wicker basket", where the myocytes form the branches that come into contact with the connective tissue [47].

Disarray is not considered as a pathognomonic morphological feature of HCM: it is also found in myocardial hypertrophy of other genesis (aortic valve stenosis, hypertension) [48]. However, researchers are unanimous in the opinion that severity of disarray in IVS patients with HCM is significantly higher than in patients with indicated diseases. In the earlier studies, the authors reported that in patients with HCM disarray area was equal to 5–10 % [49]. According to the most recent research data, the areas of disarray in HCM occupies on the average of 30 % [12,50] of investigated myocardium, though this index can significantly vary on the proliferation and severity degree in the different fields of view of histology samples of the same patient. Ordinarily, myocardial disarray is most pronounced in the areas of maximal thickening of the cardiac muscle, so-called hypertrophic nodes, but is also detected in macroscopically normal areas. Thus, no consensus about the quantitative indicator of disarray expression exists among the histopathologists, which is essential to establish the morphological diagnostic criterion for HCM. There is also no clear understanding of the mechanisms of disarray patterns development.

Muscle fiber disarray in patients with HCM is associated with the variable ultrastructural changes. First of all, hypertrophied CMs show significant increase in the diameter with the appearance of giant cells, which can be 10–20 times higher than its normal volume [6]. Nuclei demonstrate polymorphism: enlarged stellate, horseshoe, ugly, rod-shaped nuclei have been described. Shlyakhto E. V. et al. emphasized the presence of "chains" of nuclei in the myocardium of patients with HCM that can indicate their proliferation without cytokinesis [51]. The author linked this discovery with asynchronous synthetic processes in hypertrophied CMs. Gudkova et al. in their work highlighted the CMs with perinuclear vacuoles [52]. The authors explain the phenomenon of perinuclear vacuolization by the processes of myocytolysis, leading to dissection of intracellular myofibrillar structures and thinning of the CMs. This is accompanied by an increase of myocardial stromal component [52]. Fidzianska A. et al. consider that CMs vacuolization may represent autophagic vacuoles that contain mitochondria, glycogen, degraded residues of sarcoplasmic reticulum and myelin structures [53]. Myofibers of CMs show disarray at the ultrastructural level: intermittence, shortening of Z-lines, expansion of interfibrillar spaces and increase in the number of intra- and intermyofibrillar couplings. H. Kimura et al. report that hypertrophy and destruction of myosin filaments is characteristic ultrastructural feature of HCM [54] and may play a key role in heart failure progression [55]. The pathology of intercellular junctions in myocardial disarray is of special attention. According to C. Pinali et al., disorganization of intercalated discs and mutations of gap junction proteins may be a substrate of arrhythmia development, due to the fact that the structural elements of intercellular contacts are not concentrated in the intercalated discs, but are fragmented and are located across the surface of the CMs [56].

Myocardial fibrosis is the third key feature of the heart muscle remodeling in patients with HCM. It is most pronounced in the areas of CMs hypertrophy and disarray [57]. Many researchers extensively studied the connective tissue distribution in myocardium in various pathologies, including HCM. It can determine the degree of diastolic dysfunction of LV in patients with HCM. However, the quantitative assessment of fibrosis is very difficult, as the process of myocardial sclerosis develops simultaneously with growing CMs hypertrophy, and also dependent on the patient's age [45]. Ho C. Y. et al. believe that an increase of the stromal component in genetically determined myocardial hypertrophy is associated with an early increase in collagen synthesis due to mutations in the genes of sarcomeric proteins [58]. Shirani J. et al discovered that interstitial and perivascular collagen fibers in the myocardium of young adults with sudden cardiac death from HCM were considerably enlarged and partially responsible for the thickening of myocardium. The authors suggested that these changes were the primary, and the development of HCM was determined not only by sarcomeric mutations, but also by changes in the connective tissue elements, without discussion the problem of local spread of the pathological process [59]. The publications also discuss the possible role of apoptosis in the development of the CMs in myocardial fibrosis with HCM: accumulation of fibroblasts occurs in response to death of CMs, thereby contributing to development of substitutive fibrosis [60,61].

In addition to the described triad of signs, many authors consider that the structural changes in the intramural arteries ("small vessel disease") is the classical morphological manifestation of HCM in the form of its reduced density per unit area of the myocardium and hypertrophy of the walls of small arteries and arterioles. Publications report that such changes of the coronary vessels are observed in 80 % of patients with HCM and are especially pronounced in the IVS [59]. Some authors presume the possibility of genetic determination of vasculopathies in HCM. However, reduced density of the microcirculatory bed can be a consequence of a cumulative increase in the area of hypertrophic CMs and an increase in the volume of the myocardial stroma. This is accompanied by an increase of the distance between the capillaries and CMs (especially in the perinuclear regions), which reduces the efficiency of oxygen diffusion and leads to myocytes hypoxia. Ischemic coronary death of CMs exacerbates interstitial and perivascular fibrosis with blockade of many capillaries [62,63]. The total reduction in microvasculature causes an increase in peripheral resistance to blood flow in coronary arteries and their response in the form of remodeling and intimal thickening due to media proliferation of smooth muscle cells and collagen with a significant narrowing of the lumen [9,47,64]. Varnava et al. in their study have not found the dependence of fibrosis formation and small vessel disease on propagation of myocardial disarray. The authors suggested that the development of myocardial fibrosis in patients with HCM was dependent on LV mass, gender of the patient and local autocrine factors [42].

Conclusions

Notwithstanding the numerous research data on HCM, no consensus among the authors regarding the etiology and pathogenesis of HCM exists to date. Controversial data on the interrelation and sequence of disarray, hypertrophy of the CMs, interstitial fibrosis, changes in the microvasculature and structural changes of the mitral valve in patients with HCM hamper the search for adequate etiotropic treatment, and encourages to the prospective studies of HCM.

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