

REMODELING OF THE HEART IN PATHOGENESIS OF INFLUENCY OF BLOOD CIRCULATION AND DILATED SYNDROME AT NON-CORONARY DISEASES OF MYOCARDIUM

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Bu makalede, myokard disfonksiyonu, tekrar düzenlenme (remodeling) ve kardiyak yetmezlik ile ilişkili problemlerin önceki literatürlerin tekrar gözden geçirilmesi güncellenmiştir. Remodeling gelişimindeki temel mekanizmalar, bunların çeşitleri ve tanısız çeşitli metotlar tanımlanmıştır.

Anahtar kelimeler: Kalp hastalıkları, Sistolik disfonksiyon, Diastolik disfonksiyon, Tekrar düzenlenme

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INTRODUCTION

Heart's remodeling now is the corner concept determining our representations about pathophysiology, clinical current, opportunities and ways of medicinal influence at chronic heart failure (CHF)¹.

This process arises in reply to various injuring influences on the myocardium. The ischemia and destruction of part of cardiac hystiocytes, mechanical overload, an inflammation and diffusive degenerate changes of heart result in development of numerous adaptive changes of microstructure and geometry of the organ, designated as "remodeling". These changes frequently proceed to clinical display of symptoms of CHF and render determining influence on function of heart, current of disease and the forecast of cardiologic patients².

That heart's remodeling precedes to clinic of CHF and decrease of contractive activity of left ventricle, determines doubtless importance of studying of this process and causes huge interest to it from the party of clinical physicians, as the forecast of disease at occurrence of symptoms of CHF adverse³.

By the majority of authors remodeling is considered as the compensatory and reparative process started by injuring factors. However after an initial "adaptive" phase another follows "maladaptive" when progressing changes of structure of heart independently aggravate current of CHF even in absence of

other damaging factors⁴.

All cells of a myocardium are involved in process of remodeling of cardiac hystiocyte, interstitial cells and vascular endothelium. Despite of distinction in etiology, it results in the general infringements for all diseases biochemical, tissular and biomechanical (diastolic and systolic functions) processes. As a whole, process of remodeling results in progressing increase of weight of a myocardium, expansion and deformation of its cavities - to change of geometry of LV from ellipsoid to more spheric. It is important to note, that the given changes proceed on a background of hyperactivity and at direct participation of circulating hormones, autocrine and paracrine factors⁵.

Since 60-th years of the last century increase of the sizes of heart began to consider as important, independent from systolic functions the factor determining the forecast of patients with CHF. However detailed studying of the basic laws and the factors determining development of remodeling, its hemodynamic and neurohumoral influences on occurrence and progressing of CHF began only in 90-th years after publication of works of M. Pfeffer and E. Braunwald (1990), devoted to studying of remodeling of LV after acute myocardial infarction⁶.

Traditionally CHF is connected to infringement of contractive functions of myocardium. However on modern representations about pathophysiology of CHF, systolic dysfunction is considered only as one of factors alongside with change of a pressure of walls and structure of diastolic fillings, i.e. with all that is included in concept of remodeling of LV⁷.

In opinion of Cohn J.N.⁸ remodeling, instead of

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contractive dysfunction of a myocardium underlies of CHF.

Last years even more often meet given to the big importance of diastolic dysfunction (DD) in occurrence, clinical current and forecast of CHF. It is shown, that at third of such patients with clinic of CHF is caused by infringements not systolic, and diastolic function of LV. Moreover, according to lines of authors in 30-40 % of cases of DD of LV not only accompany, but also precedes to systolic dysfunction and can result in occurrence of CHF even when parameters of central hemodynamics (ejection fraction, stroke volume, minute volume of blood, an cardiac index) have not changed yet⁹⁻¹¹.

Definition of DD means pathophysiological aspect incapacity of LV to be filled in volume of blood, sufficient for maintenance of adequate cardiac output at normal average pressure in pulmonary veins. According to this definition, DD is consequence of such damage of heart at which adequate filling cavity of LV needs the raised pressure in pulmonary veins and the left auricle^{12,13}.

In norm diastolic filling of heart is adjusted by complex interactions of set of cardiac and extracardiac factors. The principal causes influencing filling of LV at DD are: 1) change of atrioventricular gradient of pressure during diastole, 2) infringement of an active relaxation of myocardium of LV and 3) deterioration of a compliance of walls of LV¹⁴⁻¹⁶.

Receipt of blood in ventricle is carried out in two phases: fast filling in early diastole and slow filling in late diastole, coming to the end of systole of auricles. The role of auricles in conditions of normsystole and at absence of infringements of diastolic relaxation is rather insignificant does not exceed 25% that allows to count it only additional pump for filling of ventricles, however at progressing of CHF the systole of auricles gets essentially important compensatory role¹⁷.

Early diastole comes from the period of isovolumic relaxation of ventricle and results in alignment of pressure between an auricle and ventricle, which in turn depends on pressure in the auricle and speed of a relaxation of a myocardium of ventricle. It is shown that at gradual infringement of energy production the relaxation of heart changes earlier, than parameters of systolic functions are reduced. For this reason changes of parameters of diastolic fillings of LV are counted as one of the earliest infringements previous to developed clinical picture of CHF^{18,19}.

The phase of slow filling in late diastole consists

from diastasis and systole of auricles. Filling of ventricle in this period is defined by rigidity of the chamber of ventricle, pressure in an auricle and its contractive ability, preloading, postloading, heart rate and condition of pericardium. Rigidity of the chamber depends on mechanical properties of cardiac hystiocyte, conjunctive tissue, vascular channel and geometry of ventricle²⁰.

On the basis of research of a spectrum of trans-mitral diastolic streams (TMDS) allocate three basic such as infringements of diastolic functions of LV hypertrophic, pseudo-normal and restrictive^{21,22}.

First of them sometimes name type of the worsened or slowed down relaxation. Infringements of a relaxation are connected to delay of speed of pressure drop in LV, decrease of early diastolic transe-mitral gradient of pressure and speed of increase of peak E therefore the period of isovolumic relaxation is extended. Compensatory amplification of a systole of auricles increases speed of peak A.

Thus, the first pathological type is characterized by reduction of speed of formation of peak E, increase of speed of peak A and time of isovolumic relaxation, ratio E/A < 1.0. DD of LV comes to light at patients with hypertrophy of LV, an arterial hypertension, coronary artery disease and at older persons²³. The second pathological type comes to light at patients with heavier infringements of diastolic process. At progressing disease of heart extensibility of LV is reduced, resulting in increase of pressure in the left auricle. In this stage the mechanism of an "atrial swapping" any more in a condition to provide necessary filling of LV and cardiac output can be kept only by increase of pressure in the pulmonary veins. As a result, are increased: trans - mitral gradient of pressure in early diastole, speed of peak E, time of isovolumic relaxation is shortened and speed of peak A is reduced. Thus compensatory mechanisms (vasoconstriction and a delay of sodium), directed on increase of pressure in pulmonary veins, result in occurrence of attributes of stagnation in lungs which becomes even more expressed at physical loadings, that is accompanied by a short wind and decrease of tolerance to loadings²⁴.

The further increase of rigidity of the chamber of ventricle and pressure of filling of LV, completely "put out of action" auricles, thus speed of increase of peak E and parameter E/A are increased even more (E/A > 2) with appreciable reduction of isovolumic relaxation time (TIVR < 70ms) - restrictive type²⁵.

That fact is interesting, that in every FK of CHF

the typical features of spectrum of TMDS are inherent. It has allowed to Nishimura R.A., Tajik A. J.²⁶ to offer system of an estimation of severity of DD, allocating four degrees:

I- Patients with type of the slowed down relaxation without symptoms of CHF in rest. The short wind develops at strong or moderate physical loading (FK I- II by NYHA), and also at attacks of atrial fibrillation (size E/A is reduced up to $1,1\pm 0,12$ and is lower);

II- Patients with pseudo-normal type, symptoms of CHF develop at moderate or minimal physical loading (FK II-III by NYHA) (E/A $1,27\pm 0,15$);

III- Patients with restrictive type, symptoms of CHF develop at the minimal physical loading or in the rest (FK III-IV by NYHA) (size E/A grows up to $2,4\pm 0,27$) (convertible). Treatment of CHF and decrease of preloading it is possible to transfer parameters of the patient from III to II, and sometimes even in a I degree;

IV- Patients with heavy infringements of pliability of LV. The restrictive type is kept, despite of treatment (irreversible). Symptoms of CHF are observed in a condition of rest (IV FK by NYHA).

Despite lacking of dilate of LV and presence of normal EF, at patients with DD is essentially reduced tolerance to physical loading, there are developments of stagnation in lungs and a short wind which can be counted conducting symptom of CHF. To the basic pathogenetic factors promoting to development of DD, carry fibrosis of myocardium, hypertrophy, an ischemia, and also increase of postloading at arterial hypertension²⁷.

In this connection it is necessary to specify, that by one of modern concepts of diastolic function of heart is provided by antistaging of contraction of various layers of a myocardium. According to this theory infringement of reduction of the subendocardial and subepicardial layers of myocardium providing change of the ventricle's form from ellipsoidal to spherical and decrease of intraventricular pressure, owing to influence of set forth above factors also is the reason of development of DD at various diseases of heart²⁸.

Proofs are received, that parameters of DD in the greater degree, than contractility of myocardium, correlate with clinical and instrumental markers of decompensation and even with quality of life of patients with CHF^{29,30}.

Process of remodeling mentions heart in the both way: on organic and histic levels, involving all types of cells of myocardium: cardiac hystiocytes, intersti-

tial cells, fibroblasts and vascular endothelium. At an overload in volume there is an increase of end-diastolic myocardial stress and it causes serial replication of sarcomeres, those results to dilatation of cavities, to decrease of radius of curvature of lateral walls of LV and normalization of diastolic pressure of the myocardium. Synthesis of contractive proteins is the adaptive reaction having multilevel value, and a condition of sarcomeres and ribosomes reflects a reserve of plastic adaptation of cardiac hystiocytes in process of heart's remodeling^{31,32}.

Strengthening of a collagenic infrastructure interferes with sliding cardiac hystiocytes from each other under the influence of increase of myocardial stress. However redundancy of fibrotic process is the integral attribute disadaptive remodeling of LV, conducting to restriction cardiac function at times irrespective of a condition of contractive capacity of cardiac hystiocytes. Thus accumulation of collagen occurs not only due to the increased of synthesis, but also due to decrease of rates their degradation owing to reduction of activity of metalloproteins of the myocardium³³⁻³⁵.

Other authors^{36,37} specify, that accumulation of interstitial collagen is negatively reflected not only on diastolic, but also on systolic function of heart. In general, on trope of Maisch B. "the loop of fibrosis oppresses heart all over again in a diastole, and then in a systole", thus expressiveness of fibrosis and development of collagen in a myocardium corresponds to the degree of severity of CHF³⁸.

To numerous works both in vivo, and in vitro it was proved, that effector hormones of the given process are angiotensin - II, aldosterone and sympathoadrenal system (SAS). Renin - angiotensin - aldosterone system (RAAS) is responsible for structural remodeling of myocardial collagenic matrix^{39,40}.

Last years were marked also by revision of a degree of participation of immune system of an organism in occurrence and progressing of CHF. In J.N. Belenkov's and et al opinion studying of a role of an immune inflammation, cytokine aggressions and apoptosis of cardiac hystiocytes at CHF will result in significant change of sights on pathogenesis of diseases and strategy of therapeutic influence⁴¹⁻⁴⁷.

Proceeding from above-stated, process of heart remodeling is the independent factor of pathogenesis of CHF, however it is necessary to specify: what structural infringements arise in connection with progressing the process of remodeling, i.e. with change of hemodynamic conditions and neuroendocrinal status.

The given problem is actively studied in branch CFH of the Scientific Cardiological centre at Russian Academy of Medical Sciences. According to the researchers, the most sensitive parameters describing remodeling of LV are an index of sphericity, myocardial stress, the attitude of thickness of walls of LV to its diameter and increase of weight of myocardium of LV⁴⁸⁻⁵⁰.

By the index of relative thickness of wall of LV distinguish its following models⁵¹⁻⁵³:

I- Normal geometry (normal weight and normal relative thickness of the wall);

II- Concentric remodeling (normal weight and the increased relative thickness of the wall);

III- A concentric hypertrophy (increase of weight and relative thickness of the wall);

IV- Eccentric hypertrophy (increase of weight at normal relative thickness of the wall);

V- Eccentric remodeling (increase of weight at decrease of relative thickness of the wall).

Studying of interrelation of infringements of diastolic filling of LV, clinical displays of decompensation and parameters of heart remodeling will give the clinical physician enough idle time, the reliable and exact tool of an estimation as weight and the forecast of disease, and results of treatment; will allow to lead early diagnostics of CHF to estimate a condition of the patient and dynamics of disease^{54,55}.

The researches devoted to studying of heart remodeling process at patients with NM (non-rheumatic myocarditis) in the scientific literature are individual⁵⁶⁻⁵⁹, described groups are small and non-uniform. Besides interpretation of the received results, as a rule, will be carried out in comparative aspect with parameters of remodeling of myocardium ischemic and rheumatic genesis, and on-phasic studying of NM on the enough big of contingent of patients practically is absent.

At the same time by Uskova O.V. with authors^{30,32} was established, that process of remodeling of ventricles of heart and a degree of infringement of intracardiac hemodynamics do not depend from etiology of CH and age of patients.

In work⁶⁰ it is shown, that relapsing current of NM is connected to recurrence of stages of an inflammation on a background autoimmune changes and steady increase of fibrosis. For the first time it is revealed, that at chronic myocarditis a dystrophy, an inflammation and fibrosis not consecutive, but the parallel processes resulting to remodeling of a cardiac muscle.

Special attention deserves Florja's V.G. and

Mareev's V.J. researches⁶¹. By the method of ventriculography it was surveyed 121 patients with DCMP, 45 - chronic myocarditis and 46 - by alcoholic defeat of heart. It is shown, that progressing CHF as gain FK by NYHA is accompanied by authentic change of geometry of LV, prevalence of dilatation above a hypertrophy of its wall and progressing linear growth of size myocardial stress. The given changes are determined in all investigated groups. Thus it is revealed, that size of FK NYHA in the greater degree depended on parameters of volume and geometry of LV, than from speed circular shortening of myocardium fibres and cardiac output.

Pronina V. P. et al⁶² by method of Doppler echocardiography allocates set of hemodynamic parameters (minute volume, pressure in pulmonary arteries, E/A, coefficient of contractility - CC, general peripheric vascular resistance, mitral regurgitation, dp/dt), allowed to construct model of interrelation of the parameters determining with a high degree of reliability belonging of patients with NM to FK of CHF. It is established, that initial attributes of defeat of the myocardium are shown by lengthening of the power-intensive period of isovolumic contraction and increase of Doppler index of contraction (CC).

"Kuznetsov's G.E. et al are one of the basic researches in this area^{63,64} in which it is convincingly shown, that remodeling of LV in development of CHF of any etiology is accompanied by steady decrease of myocardium contraction, shown in the increasing discrepancy of global contractive abilities of LV to tested loading on a myocardium. Appeared, that the interrelation of structure of diastolic filling and geometrical parameters of LV has by nonlinear character. Thus irrespective of initial type of a hypertrophy, on a measure of heart remodeling and progressing of CHF, there is natural dynamics of development of DD from "hypertrophic" up to "restrictive" types.

The data of authors are coordinated with the results received by Orlova J.A.⁶⁵, which showed that the various stages of LV remodeling are most precisely characterized by sizes of myocardial stress, an index of relative walls thickness and an index of LV sphericity and can be marked at identical clinical expressiveness of CHF, i.e. process of remodeling does not fully comply with changes of FK CHF. Thus it can be divided in to adaptive and disadaptive phases. Preservation of the ellipsoid form and conformity of walls thickness to dilatation of their cavity is typical to the first form. Disadaptive remodeling accompanies by approximation of LV form to sphere and the prevalence of dilatation LV cavities above its

hypertrophy.

Among the domestic works which were devoted to studying of NM V.V. problems Benberin's research is market out⁶⁶. The author established, that patients with NM with kept contractive function of myocardium come to light diastolic infringements - reduction of high-speed parameters ratio in a phase of early and late filling (E/A). With progressing of disease there is the further aggravation of DD developing by infringement process of relaxation in early and decrease of extensibility in late diastole. Close positive correlative communication was established between the maximal speed in a phase of early and late LV filling and final diastolic volume that testifies initial infringement of diastolic LV filling at NM.

These results prove other researches in which the important role is devoted to structural - geometrical changes of LV in progressing remodeling and CHF at inflammatory affect of the myocardium. At the same time, it is necessary to note, that the specified scientific researches were limited to an estimation only of cardio-functional infringements of LV and influence of the found out changes on the clinical status of patients, pathogenetic aspects of dilated syndrome at early stages of development of NM and an opportunity of pharmacological correction of heart remodeling were not mentioned.

Now to role of atrial natriuretic peptide (NUP) in pathogenesis of CHF is given a great value. Importance of its is difficult for overestimating, as it is the basic peptide, "resisting" to effects of RAAS, SAS and vasopressin, in norm it is in balance with them^{67,68}.

NUP is synthesized in endocrine cardiomyocytes. At the present time three isoforms of NUP are known: type A (atrial - ANUP, ANP), type B (brain - BNUP, BNP) and type C (endothelial). The Source of ANUP are atriums (in rather smaller degree - ventricles of heart), BNUP - ventricles and a brain tissue, CNUP - a brain tissue and endothelium of vessels⁶⁹⁻⁷².

The main stimuli to mark out NUP are a stretching of atrium and/or ventricles, increase of transmural atrial pressure. In blood NUP with the help of cGMF cooperates with specific receptors which are on cells membranes of renal epithelium, smooth myocytes of arteries, of adrenal glands cells, hypophysis, lungs, liver and small intestines⁷³⁻⁷⁵. Basic physiological effects of NUP: increase of glomerular filtration, level, reduction of sodium reabsorption and water in kidneys, increase of blood flow into the brain matter of kidneys, reduction of renin

development, vasodilation of renal and coronary vessels, decrease of systolic pressure, oppression of renin's secretion, AT II, aldosterone and vasopressin^{76,77}.

NUP is unique contr-regulative system resisting to effects practically of all known pressing systems. Definition of concentration at least one of NUP IN blood plasmas at patients with CHF has important diagnostic and prognostic value^{78,79}.

Now BNUP it is recognized as the most important in class of NUP, and is the predictor of survival probability at patients with CHF. It is considered, that in this case NUP improves contractive function of myocardium and increases cardiac output not only in connection with reduction of resistance of peripheral vessels, but also by means of reduction of preloading at preservation of adequate venous return to heart. Besides it is not excluded the direct inotropic effect of NUP on diastolic function of ventricle^{80,81}.

Taking into account above-stated, it is possible to assume that key value of that peptide in preservation of the compensated condition of patients with initial attributes of CHF at which with increase of pressure in auricles and their stretching owing to adaptive increase of venous return to the heart, it is observed compensatory increase of NUP production in 4-6 times in comparison with norm that counteracts the delay of Na + in organism by RAAS^{82,83}.

On account of hyperproduction of NUP begins already at the earliest stage of CHF development, its content in blood is considered in the recommendations for diagnostics of CHF of European cardiologists' society as the important diagnostic criterion of myocardium asymptomatic dysfunction and severing of marker CHF^{84,85}.

Lopatin A.S. et al⁸⁶ have shown that the growth of concentration ANUP begins with I FK of CHF and progresses in the process of decrease of myocardium contraction and increase of CHF severity. For all that feebly marked correlation connections of ANUP concentration in blood plasma with parameters of central and peripheral haemodynamics, myocardium metabolism testify to about the independent contribution of this neurohormone in pathogenesis of CHF.

According the data Rykova M.S. and her coauthors⁸⁷ decrease of BNUP plasma is accompanied by increase of FK of CHF, improvement of bearableness of physical loading and restoration of global systolic LV function.

On account of the big interest to NUP, works about its mutual relation with immune system began to appear. It is established, that NUP itself has

immunomodulatory action at animals and the person⁸⁸. It is convincingly shown, in the work⁸⁹ that this peptide induces the apoptosis of cardiomyocytes, suppresses development of nitric oxide and a number of proinflammatory cytokines, such as TNF and IL - 1. For all that it does not render essential influence on synthesis of anti-inflammatory cytokines by macrophages. Poskrebysheva A.S. and her co-authors⁹⁰ examining the patients with CHF genesis marked authentic in comparison with the control increase of TNF-alfa, IL - 6, BNUP level and catecholamines.

In researches^{91,92} it is shown that at patients with CHF levels of BNUP (Nt-proBNP) and ANUP (Nt-proANP) are directly proportional to FK of CHF and expressivenesses of infringements of haemodynamics. At patients with higher levels of NUP than the received average values was severe degree of CHF, infringements of haemodynamics, proinflammatory status and immunity infringements. Levels of BNP and ANP are positively correlatea with concentration of inflammation markers such as C-reactive protein and plasma's NP that reflects interrelation neurohumoral of infringements mechanisms haemodynamics and processes of inflammation at CHF.

Thus, compensatory action of NUP includes immune and anti-inflammatory components.

Other not less important biologically active factor influencing on the process of remodeling of myocardium is fibronectin, including extracellular matrix (EM).

Fibronectin (FN) is a class of structurally and immunologically connected high-molecular glycoproteids, determined in plasma, on the surface of some cells (fibroblasts, monocytes), in epithelium, in an extracellular liquid, in a connecting tissue and basal membranes, including the wall of capillaries⁹³⁻⁹⁶.

FN functions of are rather varions: 1) cellular adhesion; 2) formation of cellular morphology; 3) the organization of cells skeleton; 4) oncogenic transformation; 5) cellular migration; 6) phagocytosis; 7) cellular differentiation of immunocompetent cells; 8) hemostasis; 9) activity inhibition of natural killers⁹⁷⁻¹⁰².

In biological environments of FN organism exists in 2 kinds: soluble, circulating in blood and found out in basal membranes and insoluble, belonging to matrix. FN takes part in pathogenesis of many diseases, development of autoimmune process, reactions of blood curtailion, inflammation and regeneration of tissues^{93,103-107}.

Any change in structure of EM means as a fact infringement of balance stability between

synthesis speeds pateins and their coming apart tires I, II¹⁰⁸⁻¹¹⁰.

To fibrosis development, IM proteins growth of, mainly collagen and FN, partial destruction to a collagenic network precedes. The structure of collagenic molecule makes it very steady against the action of proteinases, except intercellular collagenase or matrix metalloproteinase - I (MMP - I). This enzyme breaks up a collagenic molecule into 2 fragments which are exposed to the further break down within the action of gelatinases MMP - 2 and MMP - 9¹¹¹⁻¹¹³.

In myocardium MMP and their tissue inhibitors are located in and express together. Taking it into consideration, the inflammation itself can be considered as the as the reason of inflammatory DCMP with accompanying disorganization and breaking down of EM thin tissue. During the experiment in 2 weeks after vaccination of Coxsackie virus there were focal centers of an inflammation with necrosis of cardiomyocytes. The big changes of collagenic matrix and intercellular fibrosis were observed at long, more than 2 months at an intercellular inflammation with the infringement of immune regulation. High collagenic activity in LV endocardium in comparison with right is also found out. It has allowed to think, that activity of collagenases in myocardium - an element of remodeling, resulting the LV expansion and reduction of the thickness of their wall¹¹⁴⁻¹¹⁷.

Thus, the given data testify, that EM remodeling and activation of MMP are responsible for structural deformation and development of CHF.

Results of researches by definition of volumetric collagen fraction and FN at patients with DCMP have established the important role of structure change connective tissue frame in the pathogenesis of myocardium remodeling, at early stages of disease¹¹⁸⁻¹²⁰. As a criterion of collagen formation activation is the increase of FN the level blood in plasma. Regression one-factorial analysis has revealed linear interrelation between increased level of FN, volumetric fraction of collagen and a degree of LV dilatation. Pathognomic for remodeling at DCMP is the increase of the ratio percentage of collagen volumetric fraction and fibrosis to the mass of LV myocardium.

Now questions of remodeling of myocardium in early and late postinfarction periods at coronary artery diseases (CAD) are rather well investigated. Little-studying of dilated syndrome at NM is due to some objective reasons: often asymptomatic course at early stages of already have been developed changes of heart geometry; often the absence of etiological factor and difficulties in differential diag-

nostics.

Practically problems of early and late remodeling at various variants of current of NM are not investigated, when structurally functional shifts carry other pathophysiological character, rather than at CAD.

Thus, the carried out analysis about the important value of an immune inflammation, local neurohumoral regulative factors influencing on processes of hypertrophy, dilatation and activation of fibroplastic reactions at NM allows to consider from qualitatively new positions mechanisms of development of dilated syndrome and to determine pharmacotherapeutic approaches in inhibition of the pathological remodeling.

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