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The role of endosarcomeric cytoskeleton proteins in the mechanisms of left ventricular diastolic dysfunction: focus on titin

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ABSTRACT

Recognizing the fact that isolated left ventricular (LV) diastolic dysfunction (DD) underlies approximately 50% of all heart failure cases requires a deep understanding of its principal mechanisms so that effective diagnostic and treatment strategies can be developed. Despite abundance of knowledge about the mechanisms underlying DD, many important questions regarding the pathophysiology of diastole remain unresolved. In particular, the role of endosarcomeric cytoskeleton pathology in the deterioration of the so-called active (relaxation of the LV myocardium and the atrioventricular pressure gradient at the beginning of diastole, closely related to it in a healthy heart) and passive (myocardial stiffness) characteristics of diastole needs to be clarified.

The lecture briefly discusses the complex hierarchy of DD mechanisms (from the sarcomere to the whole heart) and covers the role of the giant protein titin in the latter, which is the main determinant of intracellular stiffness. Impairment of myocardial relaxation and deterioration of its wall compliance under a wide range of pathological conditions (pressure overload, ischemia, inflammation, cardiotoxic effects, oxidative stress, etc.) underlying DD can be explained by a shift in titin expression toward its more rigid N2B isoform, hypophosphorylation by protein kinases A and G or dephosphorylation by serine / threonine phosphatase 5 of its molecule in the extensible protein segment containing a unique N2B sequence, hyperphosphorylation of PEVK regions of titin by protein kinase C, as well as inhibition of the Ca^{2}+-dependent titin – actin interaction.

The results of deciphering these mechanisms can become a tool for developing new approaches to targeted therapy for diastolic heart failure that currently does not have effective treatment, on the one hand, and the key to understanding the therapeutic effects of drugs already used to treat chronic heart failure with preserved LV ejection fraction, on the other hand.

Keywords: heart failure with preserved ejection fraction, diastolic heart failure, left ventricle, diastolic dysfunction, mechanisms, endosarcomeric cytoskeleton, titin, alternative splicing, post-translational modification

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Роль белков эндосаркомерного скелета в механизмах диастолической дисфункции левого желудочка: фокус на титин

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РЕЗЮМЕ

Признание того, что изолированная диастолическая дисфункция (ДД) левого желудочка (ЛЖ) лежит в основе примерно 50% всех случаев сердечной недостаточности, требует глубокого понимания ее основных механизмов, чтобы можно было разработать эффективные диагностические и терапевтические стратегии. Несмотря на то, что в настоящее время достаточно много известно о механизмах, лежащих в основе ДД, немало важных вопросов, касающихся патофизиологии диастолы, еще ожидают своего решения. В частности, нуждается в уточнении роль патологии эндосаркомерного скелета в ухудшении так называемых активных (релаксация миокарда ЛЖ и тесно связанный с ней в здоровом сердце атриовентрикулярный градиент давления в начале диастолы) и пассивных (миокардиальная жесткость) характеристик диастолы.

В лекции кратко рассматривается сложная иерархия механизмов ДД (от саркомера до целого сердца) и обсуждается участие в последних гигантского белка титина, который является основной детерминантой внутриклеточной жесткости. Лежащие в основе ДД нарушение активного расслабления миокарда и ухудшение податливости его стенки при широком спектре патологических состояний (перегрузка давлением, ишемия, воспаление, кардиотоксические воздействия, окислительный стресс и др.) могут объясняться смещением экспрессии титина в сторону его более жесткой N2B-изоформы, гипофосфорилированием протеинкиназами A и G или дефосфорилированием серин/треонин фосфатазой 5 ее молекулы в сегменте растяжимой части белка, содержащим уникальную N2B последовательность, гиперфосфорилированием PEVK элементов титина протеинкиназой C, а также нарушением Ca^{2+}-зависимого титин-актинового взаимодействия.

Результаты расшифровки этих механизмов могут стать инструментом для разработки новых подходов к направленной коррекции не имеющей эффективного лечения диастолической сердечной недостаточности, с одной стороны, и ключем для понимания саногенных эффектов препаратов, уже применяемых для терапии хронической сердечной недостаточности с сохраненной фракцией выброса ЛЖ – с другой.

Ключевые слова: сердечная недостаточность с сохраненной фракцией выброса, диастолическая сердечная недостаточность, левый желудочек, диастолическая дисфункция, механизмы, эндосаркомерный скелет, титин, альтернативный сплайсинг, посттрансляционная модификация

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

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INTRODUCTION

Diastolic dysfunction (DD) of the left ventricle (LV) is often referred to as a key link in the cardiovascular continuum, developing into clinically significant chronic heart failure (CHF) not only in common cardiovascular diseases (ischemic heart disease, arterial hypertension) [1–6], but also in pathologies that are rare in many regions of the world, in particular, endemic parasitic diseases (for example, Chagas disease and opisthorchiasis) [7–11].

Intact ventricular diastolic function is crucial for maintaining a normal level of blood circulation, aimed at the fullest satisfaction of the metabolic needs of body tissues, by ensuring a balance between stroke volume and the amount of blood entering the ventricles in diastole, not only at macro-, but also at micro-time intervals, despite the fact that the conditions of both blood flow to the heart and its ejection constantly change. While DD naturally leads to an increase in the filling pressure of the heart, sooner or later it also adversely affects the efficiency of ventricular systole [12–14].

Recognizing that isolated LVDD underpins approximately 50% of all cases of heart failure, which has a poor evidence base for improving the prognosis, requires a deep understanding of its underlying mechanisms so that effective diagnostic and therapeutic strategies can be developed [13, 15–21].

Despite the fact that the mechanisms underlying DD are well studied, many important issues related to the pathophysiology of diastole are still to be resolved. In particular, the role of the endosarcomeric cytoskeleton pathology in the deterioration of the so-called active (relaxation of the LV myocardium and the atrioventricular pressure gradient at the start of diastole, closely related to the LV myocardial relaxation in a healthy heart) and passive (myocardial stiffness) components of diastole needs to be clarified [22–26].

The aim of this lecture was to discuss the role of pathology of endosarcomeric cytoskeleton proteins in the mechanisms of LVDD, which have a hierarchy that is difficult to understand.

HIERARCHY OF DIASTOLIC DYSFUNCTION MECHANISMS

Hierarchy of the main mechanisms of DD (from sarcomere to the whole heart) is presented in the most general form in the Table [27].

Table

Hierarchy of the main mechanisms of impaired ventricular filling [27]

Level of change	Note
Myofibrils (sarcomeres)	At the level of myofibrils, increased stiffness and impaired relaxation may be due to modification of proteins that make up thick and thin filaments, the endrosarcomeric cytoskeleton (in particular, titin, nebulin, αa-actinin-2, myomesin), as well as myosin binding protein-C [28–32].
Cardiomyocyte	At the cardiomyocyte level, the ionic (Ca2+) transport system and the interaction of myofibrils play an important role in the pathogenesis [33]. At the same time, the change in the state of the system of membrane intracellular channels (for example, ryanodine receptors type 2), calcium uptake proteins by the sarcoplasmic reticulum (phospholamban, Ca^{2+} ATPase of the sarcoplasmic reticulum), sarcolemmal ion exchanger (sodium-calcium exchanger) and ion pumps (Na + / K+ ATPase) is of great importance [34–37].
Extracellular matrix	The diastolic properties of the ventricle are directly related to the state of extracellular matrix proteins (collagens, proteoglycans / glycosaminoglycans, elastin, fibronectin, laminin, and some other glycoproteins). The predominant glycoprotein of the extracellular matrix is collagen, the fibers of which surround each myocyte and provide connections between muscle fibers (the endomysium surrounds and connects individual cardiomyocytes, perimysial fibers divide cardiomyocytes into groups, the epimysium surrounds and groups a large number of muscle fibers, for example, papillary muscles) [38]. Extracellular matrix rremodeling, which occurs in many cardiovascular diseases, naturally leads to depressed myocardial compliance and is characterized by an increase in the total content of collagen and a change in the ratio of its types (a decrease in type III collagen found most commonly in tissues exhibiting elastic properties and an increase in the content of type I collagen which confers strength to the tissue and the molecules of which are cross-linked) [39].
Heart	At the organ level, ventricular filling is affected by systemic and intracardiac hemodynamic parameters (e.g., changes in afterload, the presence and severity of septal defects, and valvular insufficiency), geometric factors (the type of ventricular remodeling largely determines chamber and myocardial stiffness), and external limitations (constrictive pericarditis, pericardial effusion).

Table (continued)

Level of change	Note
	DD refers to such a pathological condition when the ventricle cannot receive blood at low pressure and fill without a compensatory increase in atrial pressure due to impaired active myocardial relaxation and / or deterioration of its wall compliance [39, 40]. It is necessary to distinguish between heart failure that has developed as a result of a primary impairment of active relaxation of the ventricular myocardium and / or deterioration of its wall compliance from that when the underlying impaired heart filling was not caused by ventricular DD [41]. The definition of LVDD does not include patients with mitral stenosis, in whom a mechanical obstruction of blood flow at the level of the left atrioventricular valve causes impaired ventricular filling and an increase in left atrial pressure [42]. A similar statement can be made in relation to constrictive pericarditis or pericardial effusion [16, 43]. Since in this pathology there is no impairment of myocardial relaxation and / or an increase in myocardial stiffness, after timely treatment (for example, valvotomy or effective removal of pericardial effusion), the LV regains the ability to receive blood at low pressure and fill without a compensatory increase in pressure in the left atrium [16].

Since the mechanisms of development and progression of diastolic heart failure have a complex hierarchy, it can be reasonably assumed that primary and secondary prevention will be effective only with a balanced (multifaceted) effect on various aspects of the pathogenesis [27]. At the same time, it is necessary to take into account the etiological heterogenic causes of heart failure which may include absolutely any cardiovascular disease, the features of the pathogenesis in which undoubtedly leave an imprint on the mechanisms and, very importantly, the sequence in which impairments of active myocardial relaxation develop and its stiffness increases [12, 44–48]. However, in most cases, the pathology of diastolic relaxation usually precedes an increase in ventricular stiffness [14, 42, 49]. As a rule, a decrease in cardiac output occurs later and is actually inevitable in patients with severe DD, since impaired filling eventually leads to a decrease in the cardiac index value [42, 50, 51].

The high diastolic stiffness of the damaged myocardium is stereotypically associated with the structural rearrangement of the extracellular matrix, characterized by changes in the qualitative and quantitative characteristics of interstitial proteins (primarily collagen), but with the development of DD modifications of proteins that make up the endrosarcomeric cytoskeleton are apparently no less important [52–54].

TITIN AND ITS ROLE IN THE MECHANISMS OF THE LEFT VENTRICULAR DIASTOLIC DYSFUNCTION

A significant difference between the myocardium and skeletal muscles, the contraction of which can normally be prolonged, is that the contraction in the muscle fiber of the heart always breaks naturally, and the relaxation cannot be prevented even with artificial extension of the cell excitation time. This feature of the myocardium is due to the need for mandatory relaxation to reduce pressure in the ventricles, without which it is impossible to fill them with blood from the venous bed during diastole. Complete recovery of length is typical even for isolated cardiomyocytes that do not experience any load.

This elastic straightening of myofibrils (elastic recoil) can be explained by some elastic formations in them that contract when shortened and straighten when relaxed [51, 54]. Similarly, the elastic structures of the myocardium make it more elastic than skeletal muscles, protecting sarcomeres from overstretching, which is theoretically possible during an overload of blood volume. Even when the muscle fiber of the heart is stretched with great force that is not encountered under physiological conditions, the length of the sarcomere increases very moderately, which prevents the complete extension of actin filaments from the interaction with myosin [54]. Elastin and collagen fibers of the extracellular matrix can poorly fulfill this function, since elastin is stretched only under the action of a sufficiently large force, and collagen proteins are practically inextensible (the extracellular matrix takes on the load only when stretched to large degrees) [54].

The significantly lower extensibility of the isolated cardiac muscle compared to the skeletal one is largely due to the presence of a well-developed endosarcomeric cytoskeleton in the cardiomyocyte. The state of several proteins of the endosarcomeric cytoskeleton is known to determine the elasticity of the cardiac muscle

fiber: titin (also known as connectin), nebulin, α-actinin, myomesin, etc. [32, 55–57]. But titin is the main determinant of intracellular stiffness, in the physiological range of the sarcomere length (1.9–2.2 μm) it causes 90% of passive tension in the cardiomyocyte (the elasticity of titin in the myocardium is 20 times higher than in the skeletal muscle) [27, 53, 58–60].

Titin is the largest of the known single peptides, consisting of a sequence of about 30,000 amino acids, the listing of which would take a third of this issue of the journal. Taking into account the molecular weight approximately equal to 3 MDa (up to 18% of all myocardial proteins), it is no coincidence that titin is called giant [54, 61, 62].

Titin with its N-terminus is anchored in the Z-line and is located in the I-band (the light band of the sarcomere, which like an elastic spring undergoes elongation when the muscle is stretched). In the A-band, titin with its C-terminus is attached to myosin (each myosin thread binds 6 titin molecules) (Figure), actually covering half of the sarcomere [51, 63]. When the sarcomere contracts to a length that is less than the unloaded or "passive" one, the elastic spring in the I-band compresses (Figure, *a*). When the sarcomere is stretched, titin exerts resistance, which is expressed in the creation of a resting tension (Figure, *b*).

During systole, when titin is compressed, potential energy is accumulated. During diastole, titin acting like a spring (elastic recoil force) applies this energy and develops the so-called restoring force to restore the initial sarcomere length, as a result of which the myocardium rapidly "straightens out" and the blood is sucked into the LV cavity, since at the beginning of diastole, the LV volume changes faster than the blood flow that should flow into it. At the beginning of systole, which is another part of the compression / stretch cycle, a stretched giant protein that accumulated elastic potential energy by the end of diastole transforms it into kinetic energy. This energy transformation and the optimal sarcomere length provided by the elastic titin components in diastole, when in accordance with the Frank – Starling law, the maximum contraction force is achieved, are extremely important factors for maintaining the systolic function of the cardiomyocyte, which, however, is not the subject of this lecture [51, 54, 64–66].

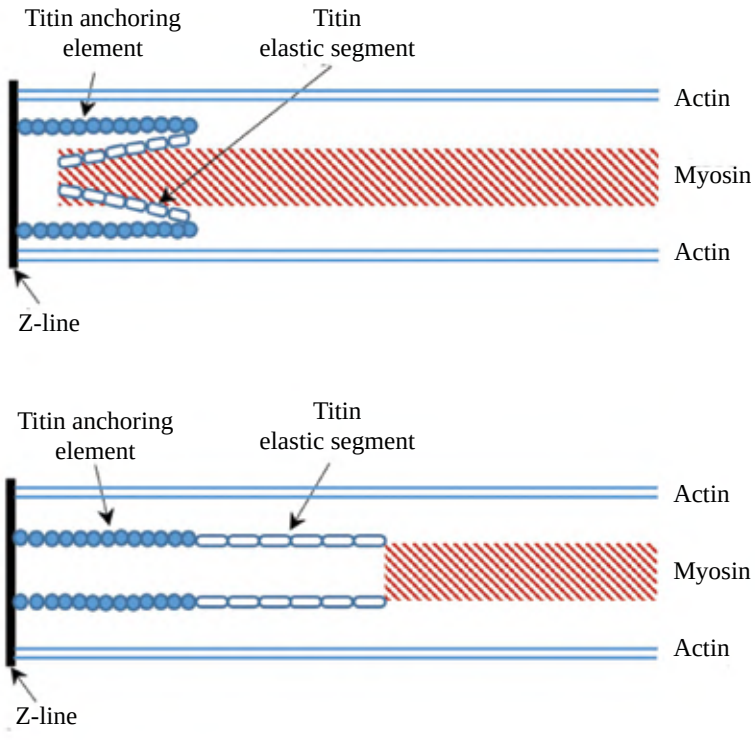

Figure. Titin in the sarcomere I-band (simplified scheme) (adapted from [63]): *a* – systole; *b* – diastole. Not adjusted to scale. To keep it simple, only two thin filaments (actin) and two titin molecules per thick filament (myosin) are shown, with titin A-bands and myosin heads omitted. A short inelastic titin I-band segment located at the A/I junction and regulatory proteins of thin filament are also omitted

In the structure of titin, there are: 1) sequentially connected immunoglobulin-like domains (Ig-segments), which are identified in the proximal (close to the Z-line), intermediate (alternatively spliced only in the N2BA-isoform), and distal part of the protein (close to the A-band); 2) a segment consisting of proline, glutamic acid, valine, and lysine residues (PEVK); 3) the unique N2B sequence (found in the myocardium, but not in skeletal muscles), to which the N2A element is added in the N2BA isoform, similar to that found in the skeletal muscle [54, 63, 67].

The elasticity of titin molecules, which determines both active (relaxation) and passive (stiffness) characteristics of the ventricular myocardium in diastole, is determined by the length and composition of the segments of the so-called extensible part of the protein in the I-band. Two main isoforms of titin have been described. The first one is a short (up to 26,926 amino acids in the human myocardium) and rigid N2B-isoform, which has a short extensible segment in the I-band. Due to its shorter length, higher resistance is created when the sarcomere is stretched. The second isoform is a more compliant N2BA-isoform with up to 34,350 amino acids, with a long elastic segment, characterized by a high content of immunoglobulin (the most extensible) and PEVK (more elastic) elements, as well as the presence of the N2A sequence [20, 25, 54, 63].

There is species-specific expression of the isoform profile: the N2B isoform dominates in rodents (the N2BA/N2B ratio is 20:80), while N2BA is dominant in most large mammals and in humans (the N2BA/N2B ratio ranges from 60: 40 to 80:20). In this case, two isoforms can coexist in one sarcomere, and each isoform functions independently. The co-expression of isoforms in different ratios leads to the modulation of the passive mechanical properties of the sarcomere and makes it possible to regulate diastolic parameters [54, 68].

A shift in expression toward the N2B isoform may determine an increase in diastolic ventricular stiffness. Moreover, the expression of various forms of titin (N2BA and N2B) largely determines the variant of myocardial remodeling that develops in various forms of myocardial damage and overload by the type of eccentric and concentric hypertrophy (concentric remodeling), which is characterized by the formation of classical systolic and diastolic CHF, respectively [53, 69–72].

In the experiments that focused on heart failure in dogs caused by accelerated pacing and spontaneous systemic arterial hypertension in rats, an increase in diastolic myocardial stiffness is associated with an increase in expression of the N2B-isoform of titin (more rigid), while in experimental infarction in rats and in patients with end-stage ischemic cardiomyopathy, the expression of the N2BA isoform that is sometimes called fetal is more pronounced [73–76]. Although the results of studies aimed at identifying the relationship between titin isoforms and myocardial stiffness generally correspond with each other well, the mechanisms that lead to isoform shift in heart failure remain unclear [27, 30, 77, 78].

Obviously, the structural rearrangement of the sarcomere, which underlies long-term adaptation, depends on the type of overload (volume or pressure) or damage to the myocardium (ischemic, metabolic, or cardiotoxic) and requires reconfiguration of alternative splicing [54, 76]. When there is a need for increased stroke volume (for example, aortic insufficiency or a loss of a significant proportion of viable cardiomyocytes due to myocardial infarction), the N2BA / N2B ratio shifts toward the long (N2BA) titin isoform. On the contrary, if the load is predominantly forceful (in particular, with systemic arterial hypertension, LV outflow tract obstruction, or aortic stenosis), the ratio shifts toward a shorter, more rigid N2B titin isoform [54]. The last scenario, in which the RNA-binding motif protein 20 (RBM20) is the repressor, is a classic one for the development of DD and heart failure with preserved LVEF [31, 39].

However, it is possible to exactly reproduce some scenario in the experiment, but, in clinical practice, a patient with comorbid pathology often has a combined type of damage and overload of the myocardium. For example, a patient with metabolic syndrome developed myocardial infarction which then led to papillary muscle dysfunction and relative mitral valve insufficiency. This all makes it difficult to understand the mechanisms of alternative splicing restructuring. However, it is clear that the final reorganization of alternative splicing will be determined by the characteristics of the dominant mechanical stress of the myocardium, an important sensor of which is titin together with other proteins of the endosarcomeric cytoskeleton. Titin interacts with these proteins with its N-terminus in the Z-line (α-actinin, telethonin and others) and its C-terminus in the A-band (for example, myomesin), as well as in the I-band and M-line (for example, obscurin), which are important points of mechanotransduction [32, 53, 54, 76, 79]. Altering the expression of numerous

titin-based mechanotransduction-associated proteins (for example, CRYAB, ANKRD1, muscle LIM protein, p42, CAMK2D, p62, NBR1, FHLs) makes it possible to regulate myocardial stiffness [54, 80, 81].

The functional state of the thyroid and pancreas also affects the sarcomere stiffness. A change in the isoform pattern toward a more rigid N2B-titin may be caused by hyperthyroidism and hyperinsulinemia, in which the phosphatidylinositol 3-kinase/Protein kinase B/mTOR axis is activated with an increase in RBM20 transcription. Conversely, low levels of triiodothyronine and insulin contribute to a shift in the isoform pattern toward a compliant N2BA titin [79, 82–85]. Another hormone angiotensin II whose maladaptive chronic activity surplus is observed in diastolic heart failure [19, 86, 87] increases myocardial stiffness by affecting the titin isoform profile, activating the mitogen-activated protein kinase/ELK1 signaling pathway, and increasing RBM20 transcription [88].

Changes in the expression of titin isoforms may take days or weeks, but the adjustment of the titin contribution to passive myocardial tension can also occur quickly (even within one cardiac cycle) [80]. As for the short-term modulation of cardiomyocyte elasticity, post-translational modification of titin is closely related to the mechanisms of rapid adaptation of the myocardium to varying hemodynamic requirements to the heart (for example, during exercise), when it is necessary to rapidly change the parameters of blood expulsion and its inflow to meet the metabolic needs of body tissues [67].

Catecholamines, nitric oxide, and natriuretic peptides can reduce the stiffness of titin springs, rapidly modulating diastolic function. Thus, β1-adrenergic agonists activate the signaling pathway through protein kinase A (cAMP-dependent), which phosphorylates the titin molecule in the segment of the I-band protein extensible part containing the unique N2B sequence (influence on PEVK elements can lead to the opposite effect), mainly in the N2B isoform (the elasticity of the N2BA isoform increases), which leads to a decline in its elasticity and an increase in myocardial extensibility, contributing to better ventricular filling [54, 79]. Nitric oxide and natriuretic peptides modulate titin elasticity in the same direction with the participation of another second messenger, cGMP-dependent protein kinase G, which along with proteinase A phosphorylates the same site in the N2B structure [54, 67, 89, 90]. In addition to the above protein kinases, protein kinase CaMKII and protein kinase D, which also phosphorylates the titin molecule in the segment containing the unique N2B sequence, have a similar effect on the extensibility of titin [54, 91].

Protein kinase C also phosphorylates the titin molecule in the segment of the I-band protein extensible part. Unlike the above-mentioned protein kinases A and G, phosphorylation of titin PEVK elements by protein kinase C (for example, during stimulation of α1-adrenergic receptors), the expression of which is increased in a wide range of pathological conditions (myocardial hypertrophy, heart failure with preserved LVEF) and cardiovascular diseases (coronary heart disease, essential hypertension), is accompanied by an increase in myocardial elasticity [54, 92–94].

Impaired phosphorylation of certain parts of the titin molecule or activation under the influence of certain factors of its dephosphorylation by serine / threonine phosphatase 5 (for example, HSP90 chaperone, oxidative stress inducers and products or proinflammatory cytokines) are considered titin-dependent mechanisms of developing increased myocardial stiffness and diastolic heart failure [12, 49, 53, 54, 95–98]. Since differentiated segments of individual titin isoforms in the I-band extensible part can be phosphorylated by different protein kinases, which leads to different effects, it is important to clarify the status of titin phosphorylation when a comprehensive understanding of the mechanisms of changes in myocardial stiffness during the development of heart failure with preserved LVEF is required [80, 99].

The diastolic stiffness of a cardiomyocyte does not only depend on the titin length (compliance), but is also determined by the titin – actin interaction, which is Ca^{2+}-dependent. Thus, the dependence of passive myocardial stress on Ca^{2+} concentration was described, which is associated with the ability of PEVK domains of titin I-band to bind to actin at an increased macroelement concentration, leading to a slowdown in sliding of titin and actin [54]. It is well known that the alteration of proteins regulating Ca^{2+} metabolism, such as the Ca^{2+} ATPase of the sarcoplasmic reticulum, its modulator phospholamban, other channels of the sarcoplasmic reticulum and their modulators (for example, FK506-binding protein 12.6) and the Na^{+}/Ca^{2+} exchanger is accompanied by impaired removal of Ca^{2+} from the cytosol and, as a result, a slowdown in relaxation [27, 100, 101]. Finally, titin-dependent diastolic elasticity may be determined by the work of stretch-activated potassium channels, the dysfunction (including a genetically determined one) of which can

increase the risk of developing CHF with preserved LVEF [102–104].

An acute and chronic increase in the passive stiffness of titin leads to an increase in its mechanical deformation and potentially nears the time of its degradation (half-life can vary from several hours to two or three days), the multi-stage process of which is very difficult to understand. The role of ubiquitin-proteasome and autophagosomal – lysosomal (autophagy) systems, proteases (such as calpains and matrix metalloproteinase-2, and heat shock proteins are discussed. However, to date, the exact mechanisms of degradation / protection of the titin molecule, given its impressive mass and length (about 1 μm), have not been fully studied [23, 78].

The impaired active myocardial relaxation and deterioration of its wall compliance in a wide range of pathological conditions (pressure overload, ischemia, inflammation, cardiotoxic effects, oxidative stress, etc.) underlying DD can be explained by a shift in titin expression toward its more rigid N2B isoform, hypophosphorylation by protein kinases A and G or dephosphorylation by serine / threonine phosphatase 5 in the segment of the extensible part of the protein containing the unique N2B sequence, hyperphosphorylation of titin PEVK elements by protein kinase C, as well as impaired Ca2+-dependent titin – actin interaction.

CONCLUSION

Maladaptive shifts in alternative splicing of titin and the pathology of its post-translational modification associated with impaired active relaxation of the myocardium and / or worsening compliance of its wall are the key mechanisms of the development of LVDD and diastolic heart failure. On the one hand, the results of deciphering these mechanisms can become a tool for developing new approaches to targeted therapy for patients with diastolic heart failure that does not have effective treatment. On the other hand, they can become the key to understanding the therapeutic effects of drugs already used to treat chronic heart failure with preserved LV ejection fraction.

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