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The pathogenesis of heart failure due to dilated cardiomyopathy

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Introduction. Dilated cardiomyopathy is considered as the most common cause of chronic heart failure syndrome.

The place of dilated cardiomyopathy in the classification of cardiomyopathies. The complexity of dilated cardiomyopathy, as well as that of other cardiomyopathies, is well reflected in the two proposed classifications of cardiomyopathies. Interestingly, these two classifications, one of them being prepared by the American Heart Association and the other by the European Heart Society, have some differences which are discussed in the article.

Etiology and pathogenesis of dilated cardiomyopathy. Recently, a lot of data have appeared concerning the complicated pathogenesis of this condition. It is clear now that not only the sympathetic nervous system and the renin–angiotensin–aldosterone system are important for the progression of dilated cardiomyopathy to heart failure. Autoimmunity, genetic defects, metallomatrixproteinases, increased collagen depostition and degradation, beta2-adrenoreceptors and many other factors also seem to play a crucial role here. They become the new targets of novel treatment methods and drugs that are under development.

Conclusions. In this article, we briefly outline the place of dilated cardiomyopathy in the new proposed classifications of cardiomyopathies and summarize the novelties of investigations in the field of this condition.

Key words: dilated cardiomyopathy, heart failure

The World Health Organization (WHO) defines dilated cardiomyopathy (DCM) as a condition in which the ventricular chambers exhibit increased diastolic and systolic volume and a low (<40%) ejection fraction (1, 2). The prevalence of DCM in the adult population in Western countries is 1–1.5% and as already mentioned, it is considered as the most common cause of chronic heart failure (HF) syndrome. The natural history of the condition is progressive. Despite improved treatment, the mortality rate for dilated cardiomyopathy remains high, with a median period of survival of 1.7 years for men and 3.2 years for women (1). A minority of patients with recent-onset DCM improve spontaneously, even some sick enough initially to be considered for cardiac transplantation.

In this article, the place of DCM in the newly proposed classifications of cardiomyopathies, its etiology and novelties of HF pathogenesis due to DCM are reviewed.

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THE PLACE OF DCM IN THE CLASSIFICATION OF CARDIOMYOPATHIES

The 1995 WHO / ISFC (International Society and Federation of Cardiology) classification of cardiomyopathies was based mainly on the anatomic descriptions of cardiac chambers in systole and diastole, but the pathopysiologic background, natural history and response to treatment of these conditions were not considered. Therefore, recently the American Heart Association scientific group has prepared a new classification (3) in which DCM and restrictive cardiomyopathy are defined as mixed cardiomyopathies (predominately non-genetic). Hypertrophic cardiomyopathy, caused by mutations in contractile proteins, Ion channelopathies, arrythmogenic right ventricular dysplasia (cardiomyopathy) and left ventricular noncompaction, which also have genetic reasons, were defined as genetic cardiomyopathies. As acquired cardiomyopathies the following were classified: peripartum, tachycardia-induced, stress-provoked (Tako–Tsubo

syndrome) cardiomyopathies and myocarditis (Fig. 1). Cardiomyopathies in which myocardial involvement is part of a large number and variety of generalized systemic disorders were considered as secondary.

However, recently the European Society of Cardiology working group has proposed another classification of cardiomyopathies (4). In their opinion, distinguishing primary and secondary cardiomyopathies is challenging, as many of the diseases classified as primary cardiomyopathies can be associated with major extra-cardiac manifestations and conversely, pathology in many of the diseases classified as secondary cardiomyopathies can predominantly or even exclusively involve the heart. They define cardiomyopathy as a myocardial disorder in which the heart muscle is structurally and functionally abnormal, in the absence of coronary artery disease, hypertension, valvular disease and congenital heart disease sufficient to cause the observed myocardial abnormality. In their classification, cardiomyopathies are grouped into hypertrophic, dilated, restrictive, arrhythmogenic right ventricular and unclassified phenotypes. Each of these phenotypes is then sublclassified into familial and non-familial forms (Fig. 2). Familial cardiomyopathies refer to the occurrence in more than one family member of either the same disorder or a phenotype that is caused by the same genetic mutation. Monogenic cardiomyopathies occurring for the first time in the family are then also classified as familial, as they can be subsequently transmitted to the offspring. Non-familial cardiomyopathies are clinically defined by the presence of a cardiomyopathy in the patient and the absence of it in other family members. They are further subdivided into idiopathic and acquired cardiomyopathies.

It should be mentioned that in both of these classifications pathological myocardial processes and dysfunction that are a direct consequence of other cardiovascular abnormalities such as that which occur with valvular heart disease, systemic hypertension, congenital heart disease or atherosclerotic coronary artery disease, are not considered as cardiomyopathies.

ETIOLOGY OF DILATED CARDIOMYOPATHY

The phenotype of dilated cardiomyopathy is very heterogeneous and not always consistent with DCM, and according to the novel classifications not even with cardiomyopthies. Heart chamber dilation can be caused or accelerated by the following processes and agents (5):

- genetic reasons (autosomal dominant, autosomal recessive, X-linked inheritance)
- specific heart muscle diseases (myocardial ischemia, valvular heart disease, chronic systemic hypertension)
- metabolic diseases (nutritional deficiencies, endocrine disorders (e. g. diabetes mellitus, hypothyroidism, thyrotoxicosis, Cushing disease, pheochromocytoma), electrolyte disturbances (e. g. hypocalcemia, hypophosphatemia)
- infections (viral, bacterial, rickettsial, mycobacterial, fungal, spirochetal, parasitic)
- toxins (e. g. alcohol, anthracyclines, antiretroviral agents, cocaine, lithium, phenothiazines)

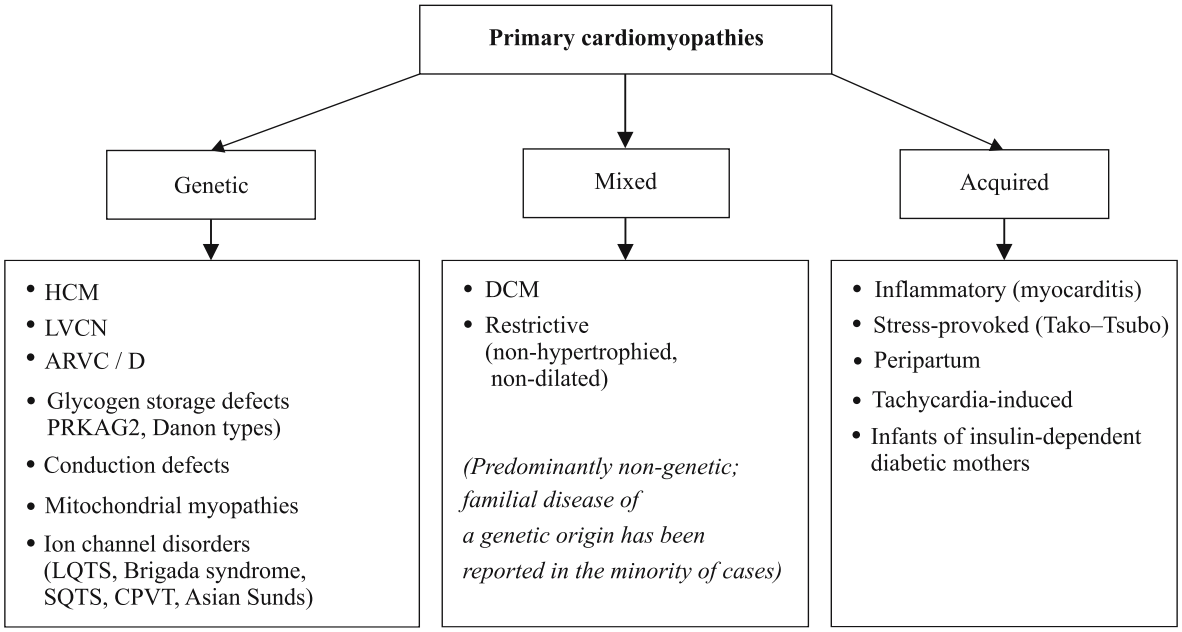

Fig. 1. Classification of cardiomyopathies proposed by the American Heart Association: primary cardiomyopathies (adapted from Richardson P, McKenna W, Bristow M et al. Circulation Mar 1 1996; 93(5): 841–2). HCM – hypertrophic cardiomyopathy; LVCN – left ventricular non-compaction; ARVC / D – arrhythmogenic right ventricular cardiomyopathy / dyspalsia; LQTS – long-QT syndrome; SQTS – short-QT syndrome; CPVT – catecholaminergic polymorphic ventricular tachycardia; DCM – dilated cardiomyopathy

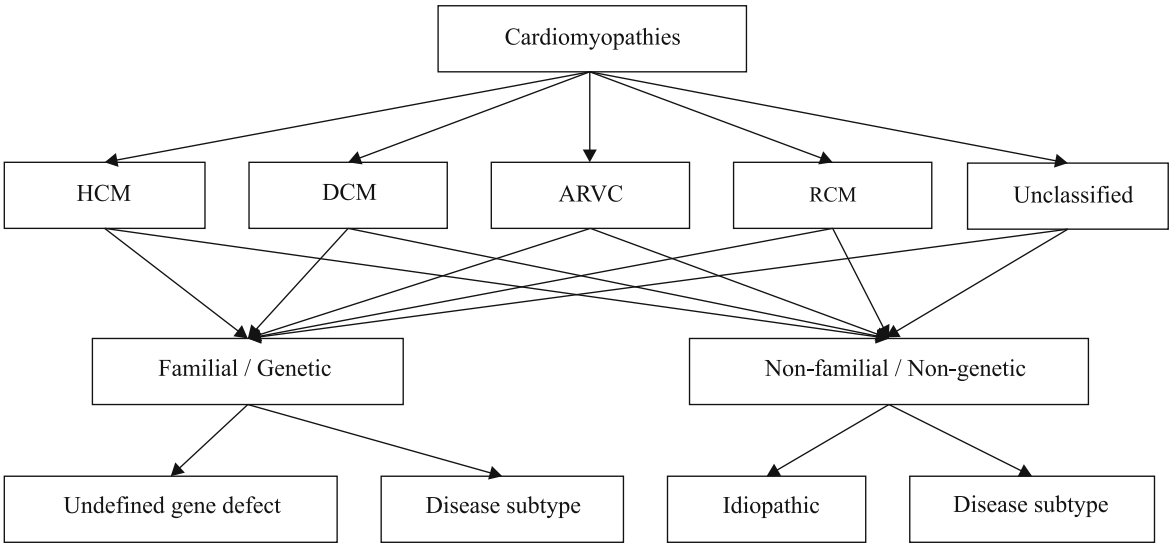

Fig. 2. Classification of cardiomyopathies proposed by the European Society of Cardiology (adapted from Elliott P, Andersson B, Arbustini E et al. Eur Heart J 2008; 29: 270–6). HCM – hypertrophic cardiomyopathy; DCM – dilated cardiomyopathy; ARVC – arrhythmogenic right ventricular cardiomyopathy; RCM – restrictive cardiomyopathy

- systemic, autoimmune diseases (e. g. systemic lupus erythematosus, amyloidosis, sarcoidosis)
- peripartum state
- tachyarrythmias (supraventricular, ventricular, atrial fluter)
- arrhythmogenic right ventricular dysplasia or cardiomyopathy
- neuromuscular dystrophies (e. g. X-linked cardioskeletal myopathy)
- hematologic disorders (e. g. chronic anemia, as in sickle cell disease or thalassemia)
- idiopathic DCM.

The variety of possible etiologic factors shows how complicated the differential diagnosis of DCM might be. Idiopathic DCM can be considered only when after rigorous evaluation all other possible etiologic factors are excluded; and even then idiopathic DCM makes up more than a half of patients with DCM.

A lot of scientists work to elucidate the possible reasons for idiopathic DCM, most of them concentrating on genetic and autoimmune mechanisms. Transmitted genetic alterations responsible for familial DCM have already been identified. However, none of the other revealed genetic or autoimmune system alterations can independently cause idiopathic DCM.

Genetics

Three main categories of genetic mechanisms are involved in the development of DCM: single gene defects, altered expression of normal genes, and polymorphic variations in modifier genes. Familial dilated cardiomyopathies are associated with multiple single gene mutations, usually encoding cytoskeletal, nuclear membrane, or contractile proteins, including desmin, titin, and troponin T. The transmission is usually autosomal dominant, although autosomal recessive and X-linked inheritance are also known (6).

In all types of cardiomyopathies, when heart failure progresses, an altered expression of normal, so-called wild-type genes can be found. The examples are as follows: downregulation of beta1-adrenoreceptors, ATPase genes, upregulation of atrial natriuretic peptide (ANP), angiotensin converting enzyme (ACE), tumour necrosis factor alfa (TNFα), endothelin, etc. (7).

The last genetic mechanism, which could probably contribute to the genesis of idiopathic DCM, is based on polymorphic variations (slightly different size or number) of modifier genes. These are not so rare in population, and usually they do not cause any differences in function and are considered normal. Yet some of these polymorphisms can cause differences in the function of encoded proteins, which might be considered as a biological variation, but also might account for a higher susceptibility for disease or different response to treatment. Polymorphic variants of genes encoding ACE, angiotensin AT1 receptors, beta1-adrenoreceptors, beta2-adrenoreceptors, alfa1-adrenoreceptors and endothelin receptor type A are known to influence the natural history of cardiomyopathies, as well as their different response to medications (6, 7).

Autoimmunity

Autoimmune features in DCM include a weak association with HLA-DR4 (XIII, 2) abnormal expression of HLA class II on cardiac endothelium (8, 9) and increased levels of circulating cytokines and cardiac autoantibodies (8, 1–14). Recently, a lot of studies have been performed concerning cardiac autoantibodies in DCM. These autoantibodies are not

necessarily pathogenic, but represent markers of immune-mediated injury; they are found in patients and relatives at risk, but not in normal and disease control subjects, and react with autoantigens unique to heart (8, 15). Antibodies to sarcolemmal and myofibrillar antigens, to mitochondrial antigens, such as M7, adenosine nucleotide translocator and other respiratory chain enzymes have been found in DCM patients, but some of these were cross-reactive with skeletal muscles, or their specificity to DCM has not been properly tested (8, 12–14). Particular interest has been recently shown to autoantibodies against beta1-adrenoreceptors, especially the ones that target the functionally important second extracellular loop. They have been found to activate beta1-adrenoreceptor signalling cascade *in vitro* (16–18), and *in vivo* they are associated with a poorer LV function (19), a higher prevalence of serious ventricular arrhythmias (20) and a higher incidence of sudden cardiac death (21). It is still unclear whether DCM develops because of these antibodies, or whether the antibodies develop as a result of cardiac tissue injury (17).

However, neutralization of these circulating autoantibodies is the principle of a novel treatment method called immunoadsorption it is usually targeted to autoantibodies against beta1-adrenoreceptors. Studies have been published showing acute hemodinamic improvement persisting for three months after immunoadsorption in patients with DCM (22, 23). Its benefit on long-term outcomes is still unclear, as some studies already after six months have seen no significant differences of hemodinamic parameters between the patients treated with immunoadsorption and not (23), whereas in one study reduced rates of hospitalization for heart failure three years after immunoadsorbtion have been documented (24). However, quite recently data have been published that in patients with DCM, immunoadsorption with subsequent immunoglobulin substitution modulates myocardial gene expression of desmin which is known to be upregulated in HF (25). Thus, this treatment method, and especially its cost effectiveness, still remain controversial.

PATHOGENESIS OF HEART FAILURE DUE TO DILATED CARDIOMYOPATHY

Neuroendocrine system

The progression of HF is consistent in patients with different etiologies, as it is ultimately driven by very similar biologically active molecules, regardless of the inciting cause (26). Compensatory mechanisms that are activated after the initial decline in the pumping capacity of the heart are able to modulate LV function within the physiologic range. Therefore the functional capacity of the patient at the beginning is preserved or depressed only minimally.

The early activation of the sympathetic nervous system (SNS) and salt-water retaining renin-angiotensin-aldosterone system (RAAS) preserve cardiac output by increasing heart rate and contractility and expanding the plasma volume. In order to reduce wall stress hypertrophy develops. To counteract the excessive vasoconstriction resulting from excessive activation of SNS and RAAS, the family of vasodilatory molecules, including natriuretic peptides, prostaglandins (PGE2, PGEI2) and nitric oxide, is activated (26–28). Yet for a longer time all these compensatory mechanisms show adverse affects, such as altered gene expression, resulting in changes in cardiac myocytes, growth and remodelling and apoptosis. Angiotensin II through collagen deposition is thought to enhance myocardial fibrosis. Excessive adrenergic stimulation has a toxic effect on the myocytes and results in their necrosis. It has been documented, that in transgenic mice overexpression of beta1-adrenoreceptors causes myocyte hypertrophy, followed by fibrosis and heart failure, whereas overexpression of beta2-adrenoreceptors was generally better tolerated or even beneficial, although it also remains controversial (29–34).

Changes at the myocyte level

Altered expression of genes causes defects of their encoded proteins or regulatory mechanisms and further enhances myocardial contractile dysfunction. These phenomena may be divided into two groups: changes in intrinsic and in modulated heart function. The intrinsic heart function means the contraction and relaxation of the myocardium in the resting state, which is not influenced by hormonal or neural factors. Modulated heart function might be stimulated or inhibited by extrinsic factors (neurotransmitters, cytokines, autocrine / paracrine substances and hormones). It is very important for the response to the changed physiologic conditions or physical stimuli (28).

The changes in intrinsic function in the failing heart comprise an altered length-tension relation, a blunted force-frequency response and signals responsible for the abnormal cellular and chamber remodelling (28). Side-to-side slippage of myocytes within the wall and their lengthening relatively to their transverse diameter further enhance mural thinning and cavitary dilation, thereby the wall stress, which is one of the determinants of myocardial oxygen consumption, also increases (28, 35–37). Moreover, myocyte energy production is inadequate due to deficiencies in subcellular ion flux mechanisms or the myosin ATPase cycle (28, 38). All this places the heart at energetic disadvantage and further contributes to contractile dysfunction.

Most of the changes in the modulated heart function occur in beta-adrenergic signal transduction (39). Four types of beta-adrenoreceptors have been identified: beta-1, beta-2, beta-3 and beta-4. The first two, and especially beta-1, are recognised as important in HF pathogenesis. Despite many similarities, these two receptors have distinct genetic and pharmacological characteristics. Beta1-adrenoreceptors stimulate c-AMP production by interacting exclusively with G stimulatory proteins, whereas beat2-aderenoreceptors can couple with both stimulatory and inhibitory G proteins. Furthermore, beta1-adrenoreceptor-mediated responses are mainly

related to c-AMP production, whereas beta2-adrenoreceptor-mediated signalling is more complex and not entirely defined. Numerous studies have shown downregulation of beta1-adrenoreceptors in failing heart with the desensitization of the remaining receptors (29, 40, 41). This, together with the changes in G stimulatory proteins and c-AMP, affects the ability of beta-adrenergic stimulation to increase heart rate and contractility and thereby influences myocardial reserve and exercise responses. Although beta2-adrenoreceptor levels are reported to remain unchanged in HF, there are data that stimulation of these receptors is arrhythmogenic, mediated by sarcoplasmic reticulum (SR) Ca overload-induced spontaneous SR Ca release and aftercontractions (32). Moreover, it has been suggested that patients with HF with the Thr164*Ile* polymorphism of beta2-adrenoreceptors have a lower exercise capacity (33) and may have a higher mortality or progression to transplantation (34).

Nevertheless, the inhibition of modulated heart function is also abnormal in heart failure as a result of the reduced parasympathetic drive (7, 28).

Changes at the myocardium level

At the myocardial level, firstly the myocyte loss contributes to pump dysfunction in heart failure. Myocyte loss can occur via toxic mechanisms, producing necrosis, or by programmed cell death, producing apoptosis (7). There is experimental evidence that myonecrosis might be triggered by elevated levels of circulating or tissue norepinephrine, or by excessive stimulation with angiotensin II or endothelin (42, 43). Moreover, heart failure is characterized by a 232-fold increase in apoptotic myocyte death in spite of the enhanced expression of the anti-apoptotic gene product Bcl-2 in the cells (35). It has been proved in *in vitro* and *in vivo* models that apoptosis can be triggered by multiple factors taking part in the pathogenesis of heart failure, such as myocardial stretch, norepinephrine, TNFα, oxidative stress, angiotensin II. Yet all the currently available assessments of myocyte apoptosis in failing hearts have been performed on explanted hearts from heart transplantation recipients, many of whom were receiving inotropic support. As catecholamines are also known to provoke apoptosis, it remains unclear whether apoptosis occurs only in end-stage HF or whether it contributes to progression of cardiac remodelling and systolic dysfunction (26).

Increased collagen deposition has been reported in the end-stage idiopathic DCM (44, 45). After myocyte death, the deposition of fibrillar collagen takes place in the extracellular matrix. This "replacement fibrosis" as well as perivascular fibrosis around the intramyocardial blood vessels can be triggered by angiotensin II, endothelin and aldosterone (6, 7), and it is thought to contribute to increased ventricular stiffness which reduces myocardial compliance and further impairs its function (44). Alterations of myocardial collagen fiber orientation have also been reported in progressing DCM, which might be even more important for myocardial mechanics than the absolute amount of myocardial collagen (46). Gradual replacement of type III collagen with more tensile type I collagen, occurring in progressing HF (47), is also thought to contribute to cavitary dilation. Moreover, recently data have been published that the extent of myocardial fibrosis detected by late gadolinium enhancement by cardiac Magnetic Resonance Imaging predicts adverse outcomes in non-ischemic cardiomyopathy (48, 49).

However, despite an increased collagen deposition, increased plasma levels of collagen degradation products have been reported in patients with HF secondary to DCM (50). It appears that within the failing myocardium the activity of collagenolytic enzymes, known as metalloproteinases (MMPs), increases. The MMPs are the family of zinc-dependent enzymes, each capable of degrading several extracellular matrix (ECM) and non-ECM substrates. They are involved in normal tissue remodelling events, as well as in pathological conditions (tumour metastases, arthritis, inflammation, cardiovascular disease). From 25 different MMPs, six are expressed in heart and are responsible for the majority of physiological ECM degradations. Their role in the progression of cardiac disease and heart failure is now being intensively investigated. For example, cardiac-specific overexpression of MMP-1 and MMP-9 leads to a progressive degradation of the ECM, which accounts for the LV wall thinning, dilation and HF. Their impact on LV remodelling is also illustrated by the fact that in Framingham Heart substudy increased plasma MMP-9 levels were associated with LV dilation (51). Oxidative stress, TNF and other cytokines and peptide growth factors that are expressed in the failing myocardium are capable of activating MMPs (26, 44). Besides, the levels of endogenous tissue inhibitors of metaloproteinases (TIMPs) are shown to be decreased in progressing HF (52).

Drugs inhibiting MMPs have been developed. Firstly, they were targeted for indications such as cancer and rheumatologic disorders, and later animal studies on their impact on LV remodelling emerged. Unselective MMP inhibitors were successfully used in animal models for LV remodelling; later, selective MMP inhibitors were developed, which advanced from animal to clinical studies. Yet, although in animal models of LV remodelling they were successful, no benefit was seen in clinical studies conducted (53, 54).

Changes in left ventricular geometry and architecture

There are two different opinions about the role of LV remodelling. Some investigators view it as the end-organ response to long-lasting neurohormonal stimulation and to changes occurring at the myocardial level; others suggest that LV remodelling might contribute independently to the progression of heart failure and first of all by the increase in LV wall stress (55, 56).

The increase in LV end-diastolic wall stress occurs as a result of the increase in LV size and change in its geometry from ellipsical to a more spherical shape. Given that the load of the ventricle at end-diastole contributes to the afterload

that the ventricle faces at the onset of systole, it follows that LV dilation itself increases the work and also oxygen utilization. This increase in afterload, created by LV dilation together with LV wall thinning occurring during the remodelling, contributes to a decrease in cardiac output (26, 57). The high end-diastolic wall stress might lead to episodic hypoperfusion of the subendocardium, with a resultant worsening of LV function (26, 58) and increased oxidative stress, with a resultant activation of genes sensitive to free radical generation (e. g. TNFα and interleukin-1beta).

Moreover, in the dilated spherical ventricle, the papillary muscles are pulled apart, which results in incompetence of the mitral valve and the development of "functional mitral regurgitation" (59). First of all, this causes the loss of forward blood flow, and secondly the regurgitant flow further overloads the ventricle.

The complex changes occurring at the myocyte, myocardial and ventricular levels, such as myocyte loss, their stretching and slippage, excessive fibrosis and extracellular matrix degradation, might result in the loss of normal fiber arrangement in the myocardium, and the latter is significant for the complex adaptations related to optimal energy transfer from the myocardium to the blood in the normal heart (60). Abnormal fiber orientation can contribute to the loss of synchronicity and homogeneity of systolic function. Studies have been published, demonstrating that in idiopathic DCM the LV wall motion is not always diffusely hypokinetic and that regional heterogeneity of left ventricular function is frequently present (61–68); moreover patients with HF have a more pronounced intraventricular dyssynchrony than normal subjects (62, 67, 69), which is an independent long-term predictor of cardiac events (64) and which can be diminished by beta-blocker therapy (69) or cardiac resynchronization therapy. The new echocardiographic modalities, such as tissue Doppler imaging or two-dimensional strain imaging, as well as magnetic resonance tomography allow an exact evaluation of ventricular synchronicity.

It seems that when the deleterious changes in cardiac function and remodelling are advanced enough, they become self-sustaining and are capable of driving disease progression independently of the neurohormonal status of the patient.

CONCLUSIONS

Although the heterogeneity of possible DCM etiologic factors and the complexity of HF due to DCM pathogenesis might seem confusing, its understanding is important. It enables a better interpretation of diagnostic methods, a more reasonable usage of HF drugs, and gives directions for further investigations, for developing novel therapeutic methods and drugs.

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DILATACINĖS KARDIOMIOPATIJOS NULEMTO ŠIRDIES NEPAKANKAMUMO PATOGENEZĖ

S a n t r a u k a

Įvadas. Šiame straipsnyje pristatoma dilatacines kardiomiopatijos vieta naujosiose kardiomiopatijų klasifikacijose, aptariamos šios būklės patogenezės naujovės.

Dilatacinės kardiomiopatijos vieta naujosiose kardiomiopatijų klasifikacijose. Dilatacinės kardiomiopatijos ir visų kitų kardiomiopatijų įvairiapusiškumas atsispindi dviejose neseniai pasiūlytose kardiomiopatijų klasifikacijose. Šių klasifikacijų, kurių vieną parengė Amerikos širdies asociacija, o kitą – Europos kardiologų draugija, skirtumai ir aptariami straipsnyje.

Dilatacinės kardiomiopatijos etiologija ir patogenezė. Pastaruoju metu pasirodė daug naujos informacijos apie sudėtingą šios būklės patogenezę. Šiuo metu jau pritariama, kad, dilatacinei kardiomiopatijai progresuojant į širdies nepakankamumą, svarbi yra ne tik simpatinė nervų sistema ir beta1-adrenoreceptoriai, bet ir reninio-angiotenzino-aldosterono sistema. Čia svarbų vaidmenį atlieka ir autoimunitetas, genetiniai defektai, metalomatrikso proteinazės, suintensyvėjęs kolageno kaupimasis bei jo degradacija, beta2-adrenoreceptoriai ir daug kitų veiksnių. Būtent jie ir tampa taikiniais naujų gydymo būdų bei vaistų, kurie šiuo metu yra intensyviai kuriami.

Išvada. Dilatacinė kardiomiopatija yra laikoma dažniausia lėtinio širdies nepakankamumo priežastimi.

Raktažodžiai: dilatacinė kardiomiopatija, širdies nepakankamumas