

## Diastolic dysfunction: from the discovery to the latest updates

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Over a long period, chronic heart failure was primarily associated with impaired contractility of the left ventricular myocardium, which is a manifestation of systolic dysfunction. Based on modern ideas about the pathophysiology of CHF syndrome, systolic dysfunction is considered as one of the etiological factors along with changes in wall tension and the structure of diastolic filling, i.e. everything that is included in the concept of "LV remodeling".

**The objective** is to present a review of the key parameters of chronic heart failure and left ventricular diastolic dysfunction according to the latest updates.

The role and significance of diastolic dysfunction as the cause of chronic heart failure syndrome have only been determined over the past three decades, which can be explained by the difficulty of early diagnostics of diastolic dysfunction. The article describes the historical evolution of heart failure and left ventricular diastolic dysfunction estimation. It is important to note the high prevalence of diastolic dysfunction. The signs of myocardial diastolic dysfunction are detected in people with almost any heart disease. The universal review of the most important parameters which determine this disorder has been presented. It has been shown that Doppler echocardiography is now the noninvasive "gold standard" for estimation of diastolic dysfunction.

We have presented methods of treatment for diastolic dysfunction according to the 2017 American College of Cardiology/American Heart Association updated Guidelines for the management of heart failure

**Conclusions.** The experimental studies demonstrate that the survival of HF patients with a preserved EF depends not so much on its indices, but on the severity of DD. DD is a more prognostic marker of mortality rate in patients with HF than EF, which requires further study for better therapeutic efficacy.

**Ключові слова:**  
серцева  
недостатність,  
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### Діастолічна дисфункція: від відкриття до останніх оновлень

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Протягом тривалого часу хронічну серцеву недостатність пов'язували передусім із порушенням скорочувальної активності міокарда лівого шлуночка, що є проявом систолічної дисфункції. За сучасними уявленнями про патофізіологію синдрому хронічної серцевої недостатності, систолічну дисфункцію розглядають як один з етіологічних факторів разом зі змінами напруженості стінки та структури діастолічного наповнення, тобто всім тим, що входить у поняття «реконструкція лівого шлуночка».

**Мета роботи** – представити огляд ключових параметрів хронічної серцевої недостатності та діастолічної дисфункції лівого шлуночка відповідно до останніх оновлень.

У формуванні синдрому хронічної серцевої недостатності роль і значення діастолічної дисфункції визначають тільки протягом останніх трьох десятиріч, що може бути пояснено складністю ранньої діагностики діастолічної дисфункції. Показана історія розвитку серцевої недостатності та діастолічної дисфункції лівого шлуночка. Важливо відзначити високу поширеність діастолічної дисфункції. Ознаки діастолічної дисфункції міокарда виявляють в осіб майже з будь-яким захворюванням серця. Наведений огляд найбільш важливих параметрів, що визначають цей розлад. Нині неінвазивним «золотим стандартом» для оцінювання діастолічної дисфункції є доплерівська ехокардіографія.

Описано методи лікування діастолічної дисфункції, що засновані на оновлених рекомендаціях Американської колегії кардіологів/Американської асоціації серця в лікуванні пацієнтів із серцевою недостатністю 2017 р.

**Висновки.** Експериментальні дослідження показують: виживання хворих на серцеву недостатність зі збереженою фракцією викиду залежить не стільки від показників останньої, скільки від вираженості діастолічної дисфункції. Діастолічна дисфункція у хворих на серцеву недостатність є більш прогностичним показником смертності, ніж фракція викиду, яка потребує додаткових досліджень для кращого лікування.

### Диастолическая дисфункция: от открытия до последних обновлений

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В течение длительного периода хроническая сердечная недостаточность связывали прежде всего с нарушением сократимости миокарда левого желудочка, что является проявлением систолической дисфункции. Исходя из современных представлений о патофизиологии синдрома хронической сердечной недостаточности, систолическую дисфункцию рассматривают как один из этиологических факторов наряду с изменением напряжения стенок и структуры диастолического наполнения, т. е. со всем тем, что включается в понятие «ремоделирования левого желудочка».

**Цель работы** – представить обзор основных параметров хронической сердечной недостаточности и диастолической дисфункции левого желудочка в соответствии с последними обновлениями.

В формировании синдрома хронической сердечной недостаточности роль и значение диастолической дисфункции стали определять лишь на протяжении последних трех десятилетий, что может быть объяснено трудностью ранней диагностики диастолической дисфункции. Показана история развития сердечной недостаточности и диастолической дисфункции левого желудочка. Важно отметить высокую распространенность диастолической дисфункции. Признаки диастолической дисфункции миокарда отмечают у лиц практически с любым заболеванием сердца. Представлен универсальный обзор наиболее важных параметров, определяющих это расстройство. Показано, что в настоящее время неинвазивным «золотым стандартом» для оценки диастолической дисфункции является доплеровская эхокардиография.

Представлены методы лечения диастолической дисфункции, основанные на обновленных рекомендациях Американской коллегии кардиологов/Американской ассоциации сердца в лечении пациентов с сердечной недостаточностью 2017 г.

**Выводы.** Экспериментальные исследования показывают, что выживаемость пациентов с сердечной недостаточностью с сохраненной фракцией выброса зависит не столько от показателей последней, сколько от выраженности диастолической дисфункции. Диастолическая дисфункция у пациентов с сердечной недостаточностью является более прогностическим показателем смертности, чем фракция выброса, которая нуждается в дальнейших исследованиях для лучшего лечения.

**Ключевые слова:**

сердечная недостаточность, желудочковая дисфункция, эхокардиография, диагностика, лечение, прогноз.

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Chronic heart failure (CHF) is a pathological condition when the heart, due to impairment of the pump function, can not provide the organs and tissues with the necessary amount of blood in accordance with the metabolic needs of the tissues. From a clinical point of view, CHF is a syndrome, the typical features of which are reduced tolerance to physical activity, fluid retention, progressive pattern and decreased life expectancy. Left ventricular (LV) diastolic dysfunction (DD) (LVDD) is characterized by alterations in LV diastolic filling / distension and is a strong predictor of cardiovascular events and heart failure (HF). Given the increased incidence, this pathology becomes one of the most serious problems of modern medicine with substantial financial costs [1,2].

## Aim

The objective is to present a review of the key parameters of chronic heart failure and left ventricular diastolic dysfunction according to the latest updates.

### *Historical evolution of HF and LVDD evaluation*

The studies of diastole and diseases that are associated with its changes started in 1877, when Francois-Franck concluded through studies that the maximal filling of the LF occurs during early diastole. In 1906, Henderson described three phases of diastole, and in 1921, Wiggers and Katz discovered that the left atrium (LA) had a significant influence in patients with altered LV. In 1927, Meek found in the experiment that the phase of active relaxation in diastole affects contractility of myocardium. In 1949, Wiggers almost completely described the basic state of myocardium in diastole – relaxation. In 1975, W. H. Gaasch found in a series of experimental and clinical studies the difference in diastole of healthy people and patients with cardiovascular pathology, using changes in LV pressure and volume. In 1983–1984, H. H. Echevernia, A. H. Doherty and R. Souter introduced the term “diastolic heart failure” into clinical practice [1–3].

Nowadays, the term “diastolic dysfunction” is in use. Diastole is disturbed also in systolic HF and considered to be more stressing with further worsening of exercise intolerance and determines the prognosis and systolic contraction disturbances, so HF is a common entity with both phenotypes [4,5]

The signs of myocardial DD are detected in people with almost any heart disease. Thus, in patients with arterial hypertension (AH), left ventricular diastolic dysfunction (LVDD) occurs in 50–90 % of cases and closely correlates

with the degree of increase in blood pressure (BP) and AH presence. The prevalence of LVDD in patients with type 2 diabetes mellitus (DM) without clinical manifestation of heart disease is found in 75 % of cases. The combination of type 2 DM with AH increases the frequency of LVDD signs detection. According to the results of a large epidemiological study, the presence of type 2 DM 5 times increases the risk of CHF in women and 2.6 times in men. Comorbid AH and obesity in patients with type 2 DM without ischemic heart disease (IHD) increase the probability of LVDD manifestation and left ventricle remodeling, which contributes to the development and progression of HF. In addition, type 2 DM is an independent predictor of CHF development. So, Borlaug B.A. and co-authors demonstrated in their study the presence of previously undiagnosed CHF in 28 % of patients with type 2 DM over 60 years of age [6,7].

Up to last year, 2016 Guidelines of the European Society of Cardiology and the Heart Failure Association for the diagnosis and treatment of acute heart failure (AHF) and CHF were in use. Patients with HF were previously divided into 3 major classes based on changes in the LV ejection fraction (EF): CHF with reduced (less than 40 %) EF (HFrEF), formerly called systolic heart failure; CHF with mid-range (40 % to 49 %) EF (HFmrEF), so-called “gray zone”; CHF with preserved (50 % or more) EF (HFpEF).

While the current updated version, proposed by a group of experts in 2017, is of great interest [8,9] due to significant changes. Based on these Guidelines, the 2013 update included only two categories of patients with cutoff value for EF of 40 % for the definition of HF with preserved or reduced EF.

The majority of patients with HF and preserved LVEF usually have diastolic dysfunction, which is considered as one of HF causes in such patients [9,10].

However, patients with a reduced LVEF may also have diastolic dysfunction, while mild systolic dysfunction (SD) is present in some patients with a preserved LVEF.

The incidence of diastolic myocardial dysfunction as a cause of CHF increases dramatically with age. The prevalence of preserved LV systolic function among patients with CHF of older age groups is widely represented in the medical literature. As a result of a clinical study conducted by I. A. Sharoshina it was found that LV systolic function is preserved in more than 60% of patients with CHF of 60 years old and older, and it occurs in 47 % of patients with CHF at the age of 66–75 years old and in 64 % – over 75

years old. Given the data of National Heart Failure Project, CHF with preserved systolic function of the left ventricle in the US is observed in 50 % of women over 65 years old and a third of men of the same age [12].

Approximately 1–2 % of the adult populations in developed countries have HF, with a prevailing risk >10 % among patients over the age of 70 years old. Among the people older than 65 years old with newly diagnosed exertional dyspnea, unrecognized HF (mainly HFpEF) is detected in one of the six. The risk of HF occurring at the age of 55 is 33 % for men and 28 % for women. The number of patients with HFpEF varies from 22 % to 73 %, depending on the age of detection, sex of the studied population, old myocardial infarction. Recent data based on examination of hospitalized patients suggest that the HF incidence is lower in HFrEF than in HFpEF. HFpEF, apparently, has other epidemiological and etiological reasons than HFrEF. Patients with HFpEF are older and women with concomitant hypertension and atrial fibrillation (AF) are more common among them, while MI occurs in a smaller percentage [11, 13–15].

LV diastolic function is the ability of the LV to be filled with the amount of blood that is necessary to maintain adequate cardiac output at an average venous pulmonary pressure of no more than 12 mm Hg. Diastolic filling of the heart is regulated by a variety of cardiac and extracardiac factors.

Filling of the ventricles with blood in a healthy person is typically divided into two phases: the phase of rapid (active) filling during early diastole and the phase of slow (passive) filling during late diastole ending with the atrial systole. Atrial systole is no more than 25 % in cardiac output in preserved diastolic relaxation and normosystole, which allows it to be considered as only an additional pump for ventricles filling. However, with the progression of CHF, the systole of the atria assumes a fundamentally important compensatory role [16, 17].

Relaxation of the myocytes causes a rapid isovolumic pressure drop in the blood remaining in the LV chamber, during the first phase of diastole known as isovolumic relaxation. When the pressure of the blood in the LV falls below the pressure of the LA, the mitral valve opens causing the LV chamber to fill with blood during early diastole. The latter depends on both the pressure in the atrium itself and the rate of ventricular myocardium relaxation, which leads to pressure equalization between the atrium and the ventricle. An increase in IVRT indicates a slowdown in energy-dependent cellular relaxation, and the decrease corresponds to an increase in the filling pressure. The rapid filling of the ventricle with blood is an integral part of relaxation, as the ventricle can not expand without the blood entering it. The active, energy-dependent part of the relaxation represented by the rate of actin-myosin dissociation and the passive one, non-energy-dependent part of the relaxation represented by stretching the elastic structures of the myocardium, compressed during systole, determine the process of relaxation. When the ventricle relaxes during the 1st phase, ionic fluxes and a new force arise, which moves the actin and myosin filaments in the opposite direction, providing the fibers elongation. Because of this, relaxation is as active process as one (hence the term "active relaxation"). It has been proved that with a gradual disruption of energy production, myocardial relaxation changes appears earlier than the indices of systolic function decrease. After the mitral

valve opening, the ventricle relaxation increasingly depends not on cellular active relaxation, but on the blood flow, which is regulated by the filling pressure and the atrioventricular valve orifice area.

The phase of passive filling consists of diastasis (the static equilibrium state of the LV during mid-diastole when the LV and LA are relaxed and static) and atrial systole [18].

Further changes in pressure and volume in late diastole occur passively, under the influence of the blood "pumping". During this period, the ventricle filling depends on the ventricle chamber stiffness, the pressure in the atrium and its contractility, as well as on the heart rate, pericardial conditions, preload and afterload. In its turn, the stiffness of the ventricular chamber myocardium depends on the mechanical properties of the cardiomyocytes, connective tissue stroma, bloodstream and the ventricle geometry (the walls volume to the chamber volume ratio). Passive properties of the myocardium begin to determine LV filling already in early diastole, but maximally affect the filling process in the phase of diastasis and atrial systole. Further the LV blood supply occurs by inertia, against the pressure gradient, i.e., with deceleration. Increased lengthening of early diastolic LV filling indicates a slowing of passive relaxation and a reduced lengthening indicates a high filling pressure. Approximately at mid-diastole, there is no atrioventricular pressure gradient (the phase of diastasis), and mitral inflow is practically absent until the systole of the atria. The value of the maximal atrial systolic velocity depends on the LA preload (LA filling by the moment of atrial contraction) and the stiffness of the left ventricular myocardium. It is difficult to affect the stiffness of the ventricle. Apparently, it is a question of such measures as a decrease in the degree of hypertrophy, surgical treatment of pericarditis, attempting to influence the degree of fibrosis severity [19].

If the active relaxation is entirely determined by the cardiomyocytes properties, then the stiffness of the myocardium largely depends on the state of interstitium. At the heart of increased myocardial stiffness there is an excessive deposition of fibrous tissue in the myocardium (processes of collagen synthesis predominate over its degradation) [20].

LVDD is the inability of myocardial muscle fibers to relax during diastole, resulting in insufficient blood in the LV. In order to compensate for the lack of blood in the ventricles and their weak work, LA at the same time begins to work with increased strain and tries to draw in as much blood as possible. As a result, this leads to an overload of the atrium and an increase in its volume. Proceeding from the latter, by LVDD is meant such damage to the heart muscle which requires an increased pressure in the pulmonary veins and the LA to adequately fill the LV cavity. In case of LVDD, the LV filling is slowed down, delayed or insufficient resulting in signs of pulmonary or systemic congestion development [21]. In its pure form, DD occurs in less than 20 % of all cases.

Disturbance of the diastolic properties of non-hypertrophied myocardium may be due to interstitial fibrosis development in it and is observed after 45 years old as a variant of the age norm. This type of diastole changes is common for the aging heart (even in the absence of any cardiovascular disease) due to the naturally occurring disorders caused by normal aging of distensibility, stiffness and compliance of the LV myocardium, because of changes

in tissues (primarily an increase in the content of collagen and osteopontin), a decreased receptor function, endothelial dysfunction, etc. [22].

Disorders of LV diastolic function due to ischemia and / or cardiosclerosis are now generally recognized in IHD patients including those without a history of myocardial infarction (MI). The inhibition of myocardial relaxation resulting from reduced blood supply to the myocardium, in turn, worsens myocardial ischemia. Reduction in the rate and completeness of active diastolic relaxation takes a leading role in DD pathogenesis. Therefore, myocardial fibrosis, its hypertrophy, ischemia, as well as the increase in afterload in AH are classified as the main pathogenetic factors that contribute to DD development. Myocardial hypertrophy is a consequence of such diseases as hypertrophic cardiomyopathy, hypertension; aortic valve stenosis. The result of the above factors interaction is an increase in calcium ions concentration in cardiomyocytes, decrease in the compliance of the LV myocardium, disorder of cardiac muscle relaxation, change in the normal ratio of early and late LV filling, increase in the end-diastolic volume (EDV). In addition, the causes of hemodynamic disorders can be such diseases as: constrictive pericarditis – a thickening of the pericardium resulting in heart chambers compression; primary amyloidosis – deposition of amyloid causes atrophy of muscle fibers and a decrease in myocardial elasticity; coronary vessels pathology leading to chronic coronary heart disease, and the development of myocardial rigidity (stiffness) due to cicatricle changes.

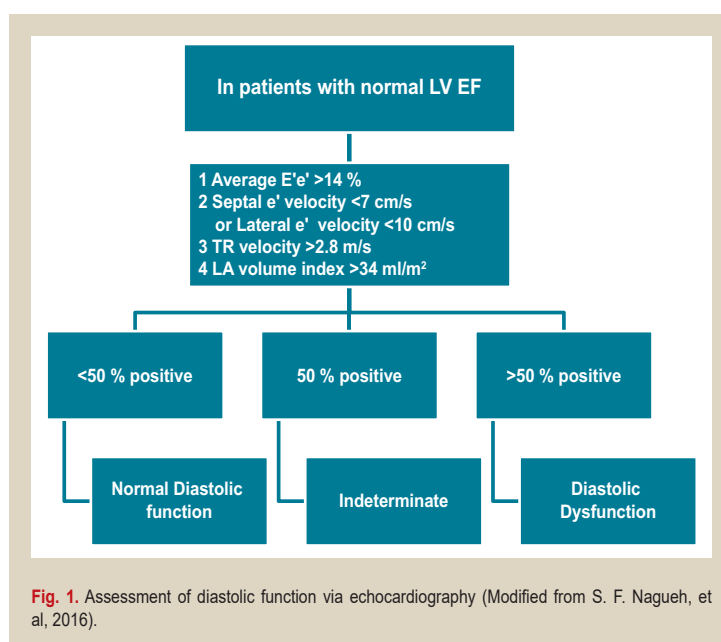
Due to compensatory pulmonary hypertension development, right heart preload is increased, DD of both ventricles is formed. The risk factors are such conditions as obesity and diabetes. Restrictive lesions of the myocardium (Loeffler's endocarditis and endomyocardial fibrosis or Davies disease), which can reduce the process of relaxation, or diastole. This muscle is adversely affected by harmful habits such as alcohol abuse and smoking, caffeine addiction also causes an additional heart load. The environment has a direct impact on this vital organ state.

So, the term "diastolic dysfunction" means clinically significant changes in LV filling. A classic standard for this pathology detection is an invasive intervention – heart catheterization [23].

Nowadays, the noninvasive "gold standard" for DD estimation is Doppler echocardiography [24]. Echocardiographic assessment of LV diastolic function is an integral part of the routine evaluation of patients presenting with symptoms of dyspnea or HF. Echocardiography is the most important diagnostic method in HF patients, as long as physical examination, electrocardiogram and X-ray do not give sufficient information to identify systolic or diastolic form of HF. Assessment of LV diastolic function is an integral element for the echocardiographic evaluation of each patient (Fig. 1).

#### Classification and Diagnostic criteria

There are three grades of LVDD: DD with impaired relaxation and normal LV filling pressures (grade I), pseudo-normalization (grade II) and DD occurs when LV relaxation is impaired along with markedly elevated LV filling pressures (grade III) (Table 1) [24,25]. These are stages of myocardial diastolic dysfunction progression. In the absence of appropriate medical and preventive measures, the first grade



of impairment goes to the second, and the second – to the third. It is particularly difficult for diagnosis the second grade of impairment – pseudonormalization. The first two grades may not be accompanied by symptoms, while the last grade corresponds to a severe degree of CHF with marked symptoms.

Grade I – LVDD is classified as mild. Now this grade of DD is usually called a delayed LV relaxation. This is the initial stage of pathological changes in the myocardium and it can be termed as hypertrophic, which is the most common type. It occurs absolutely asymptotically at the earliest stages of development and that is its insidiousness, since the patient does not presume a disorder in the heart work and does not seek medical help. The hypertrophic type is associated with slow ventricular relaxation in diastole and is characterized by a decrease in the ability to pump blood from the pulmonary artery into the ventricle in the filling stage. The main volume of blood in this case comes during the atria contraction. This is due to the lack of myocardial elasticity. We should note that the diastolic pressure in the LV can remain at normal level. With Type I there is no HF dysfunction, and this type is diagnosed only with the help of echocardiography.

One of the causes of LVDD is hypertension in which there is a disorder of active relaxation and compliance, increased myocardial mass and stiffness, an increase in ventricles weight due to their walls thickening. The factors leading to DD development worsen the process of relaxation, reduce the elasticity of the LV walls mainly due to hypertrophy (thickening) of myocardium development. In arterial hypertension, the disorder of relaxation is detected in 90 % of patients with LV hypertrophy and in 25 % without it. Significant DD is sometimes observed in patients with a very mild and focal thickening of the ventricular wall without obstruction.

Grade II – LVDD is characterized as moderate or pseudo normal. In grade II, due to insufficient relaxation of the LV and a reduced volume of blood flow from it, the LA takes on a compensatory role and begins to work hard enough for

**Table 1.** Doppler indices values for the grade of DD differentiation [24,25]

	Normal	Grade I	Grade II	Grade III
LV relaxation	Normal	Impaired	Impaired	Impaired
LAP (left atrial pressure)	Normal	Low or normal	Elevated	Elevated
Mitral E/A ratio	$\geq 0.8$	$\leq 0.8$	$> 0.8$ to $< 2.0$	$> 2$
Average E/e' ratio	$< 10$	$< 10$	10–14	$> 14$
Peak TR velocity (m/sec)	$< 2.8$	$< 2.8$	$> 2.8$	$> 2.8$
LA volume index	Normal	Normal or increased	Increased	Increased

two. Ventricles filling occur due to the difference in pressure. The second type of dysfunction can be characterized by clinical symptoms of HF and signs of pulmonary congestion.

Grade III, or restrictive type of dysfunction, is the terminal stage of DD formation. This is a serious disorder, which is characterized by a sharp decrease in the LV walls elasticity, its excessive stiffness, high pressure in the LA, a severe clinical course of congestive HF. In grade III, severe worsening resulting in pulmonary edema and cardiac asthma are common. And these conditions are seriously life threatening and often lead to death without proper emergency treatment. In a restrictive type of DD, LV remodeling reaches such a degree that the SD does not play the same basic role as at the initial stage. This type of diastolic LV filling disorder is an important predictor of cardiovascular mortality and cardiac transplantation.

In patients who experienced acute myocardial infarction (AMI), a feature of disadaptive LV remodeling is the tendency to develop a restrictive type of LV diastolic filling. It has been established that exercise tolerance and quality of life of CHF patients (functional class according to NYHA) are more correlated with restrictive DD than with SD. Therefore, restrictive type of DD detection, regardless of systolic LV function and other adaptive-compensatory mechanisms in CHF, indicates a more severe course of CHF. LVDD has the worst prognosis in CHF patients.

At the early, initial stages of LVDD development, a patient may not have any complaints. In 45 % of DD cases, an asymptomatic course is observed. It is not uncommon for cases of DD to be diagnosed by additional methods of examination like an accidental finding. At later stages of the disease, when clinical manifestations are caused by increased pressure in the LA cavity and pulmonary arteries, patients may experience the following complaints.

Dyspnea. Initially, this symptom is present only with physical exertion, but in progression of the disease, dyspnea may appear with a slight exertion and patients are breathless at rest.

Palpitation. An increase in heart rate is not common for this heart disorder. In many patients, the heart rate reaches submaximal values even at rest and increases significantly during work, walking and excitement. There are sensations of interruptions in the heart work, chest pain, accompanying heart rhythm disturbances, most often, atrial fibrillation. A common complaint among patients with this pathology is a feeling of chest compression, shortness of breath.

There is a dry cough worsened by lying supine and at night. Such patients are often treated for bacterial or viral infection month after month misdiagnosing as having bronchitis or another lung pathology. In fact, there is a disorder of diastolic function with manifestations of circulatory insufficiency.

Fatigability and the inability to perform previously well tolerated physical activity. Patients are surprised to note that easily tolerable earlier physical exertions are now heavy for them, accompanied by health deterioration and fatigue.

Lower extremity edema. As noted above, LVDD is a pathophysiological disorder underlying of HFpEF syndrome and therefore the evaluation of DD is of fundamental importance for the diagnosis. Taking into account the 2016 Guidelines of the European Society of Cardiology and the Heart Failure Association for the diagnosis and treatment of acute heart failure (AHF) and CHF, to improve the diagnosis of HF with a slight decrease in EF and preserved EF, a clinical diagnosis (history, symptoms, electrocardiographic changes) should be confirmed by the presence of cardiac dysfunction at rest or using stress testing. Electrocardiography (ECG) – is an aid in the diagnosis and allows identifying the signs of myocardial ischemia and myocardial hypertrophy. Abnormal ECG data increase the likelihood of having HF, but these data are not very specific, therefore ECG are recommended to exclude HF and not to confirm it. In case of CHF, the determination of natriuretic peptides (NUP) concentration is recommended. When the of brain natriuretic peptide NUP (BNP), N-terminal fragment of the NUP precursor (NT-proBNP)  $\geq 125$  pg/ml, echocardiography is indicated. If it is not possible to determine NUP in routine practice, an EchoCG is also recommended to confirm the diagnosis of HF. On average, the serum concentration of NUP is lower in HF patients with preserved LVEF than that in HF patients with reduced LVEF [25].

It is important to note that there is no single sufficiently accurate and reproducible EchoCG parameter that could be used to diagnose LVDD. Diagnosis of early LVDD helps prevent irreversible changes. Two-dimensional EchoCG in combination with Doppler-echocardiogram, which allows to obtain a real-time image of the myocardium and to estimate its hemodynamic functions, is applicable to accessible and informative methods for diagnosis verification. By investigating the characteristics of transmitral blood flow, the dynamics of LV filling are assessed to study its functional state. For this purpose, using the impulse Doppler EchoCG, the early peak velocity –  $V_e$ , the late peak velocity –  $V_a$ , the late diastolic filling velocity –  $A$ , and the peak early filling velocity –  $E$  are measured. The indices  $V_e/V_a$  and  $E/A$  are calculated. To determine the time of LV isovolumetric relaxation (IVRT) and deceleration half time of the early filling period (DTE), a continuous-wave Doppler ultrasound is used. These indices values in a healthy patient are:  $V_e/V_a$  – 0.9–1.5,  $E/A$  – 1.0–2.0, IVRT  $< 100$  msec, DTE  $< 220$  msec. Peak of diastolic waves corresponding to early ( $e'$ ) and late ( $a'$ ) filling of the LV is measured by pulsed wave tissue Doppler imaging. In early diagnosis of LVDD, the tissue Doppler-EchoCG method in pulse-wave mode is a good supplement to the conventional Doppler EchoCG of the transmitral flow in the absence of pronounced changes in its geometry, since the results obtained with the help of this method do not depend on hemodynamic conditions.

At young age (up to 45 years old), healthy individuals are characterized by relatively high values of these indices, often at the upper limits of the norm. As a rule, in persons over 45 years of age, the values of these indices are at the lower limit of the norm. Values of the  $V_e/V_a$  and  $E/A$

indices for diastolic function disorders are usually reduced, and the IVRT is prolonged (transmitral blood flow type A, blood flow with atrial systole predominance). Patients with pseudo-normal transmitral blood flow (restrictive transmitral blood flow of type B), which indicates more significant disorders of LV function, constitute an exception. It is also characterized by high values of the  $V_e/V_a$  and E/A indices and IVRT shortening. In the clinic, this variant of DD is less common [9].

Radionuclide ventriculography and evaluation of active and passive diastolic properties of the myocardium during the catheterization of the ventricular cavity with the definition of its volume dynamics are the most informative. But these techniques have limitations inherent in all invasive procedures. With the help of new Doppler echocardiography methods of the heart echolocation (digital color kinesis), an assessment of focal diastolic function of myocardium, its individual segments, has become available, but it is also very expensive. Therefore, Doppler echocardiography remains available and the most common method.

Chest X-ray examination allows to determine the degree of cardiomegaly, if there is a hypertrophy and is used to detect signs of pulmonary hypertension.

MRI of the heart is not a routine method of examination, but is more informative than heart ultrasound and is sometimes prescribed for controversial cases diagnosis.

#### *Treatment modalities*

The patient and the doctor need to be clearly aware that even asymptomatic ventricular myocardial dysfunction requires an administration of medications. Given the prevalence of heart DD, there has been an understanding of the need for its correction in patients with both cardiovascular diseases (eg, AF, hypertension, IHD, pulmonary hypertension) and other non-cardiovascular diseases (DM, chronic renal disease (CRD), iron deficiency anemia, chronic obstructive pulmonary disease (COPD), and obesity). The optimal directions of diastolic HF treatment have not yet been developed; there is no proven treatment for patients with HFpEF, which would reduce the morbidity and mortality of these patients. Since these people are usually elderly patients with severe symptoms, an important goal of management in such patients is to reduce symptoms and improve their quality of life.

According to the 2017 Guidelines of the experts of the European Society of Cardiology, diuretics should be prescribed to patients with congestive HF due to DD. Diuretics tend to reduce congestion, if there are any, but they should be used with caution, so as not to cause an excessive decrease in LV preload and a drop in cardiac output. It is proven that diuretics reduce the symptoms of HF, regardless of LVEF [9].

Dehydration therapy in the active phase (in the presence of congestive phenomena) is performed with the excess of the excreted urine over the water intake no more than 1.0–1.5 liters per day in order to avoid electrolyte, hormonal, arrhythmic and thrombotic complications.

Such diuretics as furosemide, torasemide, bumetanide cause a more intense but less prolonged diuresis than thiazide ones (bendroflumethiazide, hydrochlorothiazide, metolazone, indapamide), although they can act synergistically and their combination can be used for resistant edema treatment. However, due to adverse effects, these

combinations should be used with caution. Torasemide has advantages over furosemide in terms of the strength of action, degree of absorption (convenience of ingestion), duration of action (better tolerability, with a lower incidence of urination), a positive effect on neurohormones (less electrolyte disturbances, less progression of myocardial fibrosis and improved diastolic filling of the heart) and reliably reduces the risk of repeated hospitalizations due to CHF exacerbation. The goal of diuretics is to achieve and maintain euvolemia (the «dry weight» of the patient) with the lowest available doses. The dose of diuretics should be adjusted according to individual needs during the treatment process. After reaching euvolemia, diuretics are prescribed daily in minimum doses, allowing to maintain a balanced diuresis (torasemide or furosemide). To maintain the optimal acid-base balance, preservation of sensitivity to loop diuretics and normalization of renal blood flow, a 4–5-day course of carbonic anhydrase inhibitor acetazolamide (0.75/day) is recommended every 2 weeks. In patients with euvolemia / hypovolemia without symptoms, diuretics can be temporarily withdrawn [26].

LVDD, the treatment of which depends on the degree of disease, primarily affects the processes of hemodynamics. Therefore, the therapy plan is based on the correction of this process disorders. Theoretically, to improve the diastolic function we should use drugs that reduce LV hypertrophy, improve active relaxation and increase LV compliance. To the methods of hemodynamic disorders correction should include the following medical measures: control of BP; heart rate reduction; water-salt metabolism maintaining to reduce preload, as well as remodeling of cardiac geometry (reducing the thickening and returning the walls of its chambers to normal) [26].

In persons with LVDD, it is important to treat AH (predominantly systolic), as evidenced by indirect research data. In this regard diuretics, angiotensin-converting enzyme (i-ACE) inhibitors, angiotensin II receptor blockers (ARBs), mineralocorticoid receptor antagonists (ARM) are effective, but beta-blockers (BB) less effectively reduce systolic BP. In recent studies, it has been shown that ARBs (olmesartan) should not be administered to patients with HFpEF if they receive I-ACE and BB [9,25].

The optimal frequency of ventricular contraction (VCR) in patients with LVDD and concomitant AF has not been determined, moreover, excessive VCR control may be harmful. It is yet to be fully determined which drugs should be preferred: digoxin, BB or calcium channel blockers (CCB) lowering heart rate, or their combinations. Verapamil and diltiazem should not be combined with BB. The data available to date are not sufficient to recommend patients with HFpEF ablation of pulmonary veins or AV node.

Patients with angina pectoris should be managed in the same way as patients with HFpEF. In patients with LVDD, exercise tolerance is reduced, which, as a rule, is accompanied by an increase in BP in response to exercise and chronotropic insufficiency. Combined endurance-resistance training is safe for patients with HFpEF and exercise tolerance increasing (due to increased peak oxygen consumption), improves the score on the scale of physical functioning and diastolic function [9,25].

2017 American College of Cardiology/American Heart Association updated Guidelines for the management of patients with HF recommended using an angiotensin re-

septor–neprilysin inhibitor (ARNI) (valsartan/sacubitril) and a sinoatrial node modulator (ivabradine) [9].

## Conclusions

Over the past decade, experimental studies have rejected the previous concept that the prognosis for HF patients with preserved LVEF is better than that for patients with reduced EF. Evidence shows that the survival rate of HF patients with preserved EF depends not so much on its indices, but on the severity of DD. DD is a more prognostic marker of mortality than EF in HF patients which requires further study for better therapeutic efficacy.

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