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Review

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Modern Aspects of Diagnosis and Treatment of Dilated Cardiomyopathy With Remodeling of the Right Heart

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ABSTRACT Dilated cardiomyopathy (DCM) is the second most common cause of chronic heart failure, and a leading indication for heart transplantation. In the early stages of the disease, many patients are asymptomatic, but they have a high risk of developing life-threatening ventricular arrhythmias (VA) and sudden cardiac death (SCD). Modern methods of DCM diagnosis, such as MRI of the heart, speckle tracking and 3D echocardiography, have convincingly proved the development of structural and functional changes of the right heart (RH) in patients with DCM, their prognostic and therapeutic significance. By MRI of the heart, myocardial fibrosis (MF) is diagnosed, which occurs in the early stages of DCM. Progressive fibrosis is observed in one fifth of patients and is associated with a more than a 3-fold increase in the risk of death and complications of chronic heart failure (CHF). With adequate pharmacological and hardware treatment, reverse heart remodeling occurs in some patients. However, optimal and long-term drug therapy does not lead to MF regression even in individuals with improved left ventricular (LV) function. Remodeling of the RH, regardless of LV ejection fraction (EF), is a predictor of SCD, indicates the progression of the disease, foreshadowing an unfavorable outcome. The prevalence of RH remodeling has not been reliably determined; however, systolic dysfunction of the right ventricle was registered in 34-65% of patients with DCM. The annual and subsequent mortality of patients with DCM remains high.

MRI of the heart with contrast enhancement has become the gold standard for the diagnosis of DCM and crucial for the stratification of risk and prognosis of the disease. The treatment of patients with DCM is a complex process. Adequate drug and instrumental therapy in 40% of cases leads to reverse remodeling of the heart, which may be unstable.

Keywords: dilated cardiomyopathy, cardiac remodeling, right heart, risk stratification, myocardial fibrosis, myocardial deformity, treatment

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AF — atrial fibrillation
CHF — chronic heart failure
CI — confidence interval
CO — cardiac output
CRem — cardiac remodeling
CRT — cardiac resynchronization therapy
DCM — dilated cardiomyopathy
EchoCG — echocardiography
EDD — end-diastolic dimension
EDV — end-diastolic volume
EF — ejection fraction
ESV — end-systolic volume
HR — heart rate
HT — heart transplant
ICD — implantable cardioverter defibrillator
LBBB — left bundle branch block
LGE — late gadolinium enhancement
LV — left ventricle
MCS — mechanical circulatory support
MD — myocardial deformability
MF — myocardial fibrosis
MRI — magnetic resonance imaging
NUP — natriuretic peptide
RA — right atrium
RD — risk of death
RHC — right heart chambers
RV — right ventricle
SCD — sudden cardiac death
VA — ventricular arrhythmia

INTRODUCTION

Dilated cardiomyopathy (DCM) is a genetic or acquired myocardial disease characterized by dilation and systolic dysfunction of the left ventricle (LV) or both ventricles, and is not a consequence of ischemic heart disease or conditions leading to pressure or volume overload [1–3]. DCM is caused by heterogeneous causes, and varies in its phenotypic and clinical manifestations; it is a specific model of heart failure, which differs from chronic heart failure (CHF) of other etiologies, more often affecting the elderly population [4]. Conventionally, the disease is divided into stages: preclinical, early phase without clear phenotypic manifestations, and clinical phase [5]. At the stage of early diagnosis, patients are usually young (3rd–5th decade of life), many of them have no symptoms of CHF, but have a high risk of developing life-threatening ventricular arrhythmias (VA) and sudden cardiac death (SCD) [1, 5]. The pathogenetic substrate for the formation of cardiac remodeling (CRem) and the development of VA is myocardial fibrosis (MF) [4, 6]. MF is a key pathological change in DCM, which can be detected by late gadolinium enhancement (LGE). Characterization of the heart using comprehensive magnetic resonance imaging (MRI), including the presence and localization of LGE, is becoming a fundamental tool for diagnosing DCM [5, 7]. In the early stages of the disease, when the normal size and function of the LV are preserved, cardiac MRI allows identifying barely noticeable fibrous scars of the myocardium [2]. During long-term observation (median observation of 7.9 years) of patients with early-stage DCM, foci of MF were detected [6]. The results of the study confirm the fact that the early stage of the disease is not a benign condition, and MF characterization helps in risk stratification and selection of treatment tactics. DCM is a dynamic disease with high mortality, the second most common cause of CHF, and an indication for heart transplant (HT) [8]. With adequate pharmacological and instrumental treatment, some patients experience reverse remodeling of the LV with normalization of its size and function [9]. However, despite the apparent resolution of the disease, a significant proportion of patients die or have worse clinical and instrumental indicators [10].

LV dilation has been described as a predictor of early VA, and its dysfunction leads to changes in the size of the right heart chambers (RHC), their contractility and diastolic function. Right ventricular (RV) dysfunction has a more prognostic significance than LV dysfunction. RV dilation and dysfunction have prognostic significance associated with deterioration of functional status and progressive LV failure [11]. RHC remodeling, regardless of the LV ejection fraction (EF), is a predictor of SCD [12], and indicates disease progression, predicting an unfavorable outcome [13]. The mechanism of

increased risk of VA in patients with RV dysfunction and non-ischemic LV dysfunction has not been studied [6].

More than two decades ago, the study of RV systolic function in patients with DCM was performed using invasive methods, such as thermodilution or contrast ventriculography, which were rarely used in clinics. Modern diagnostic methods (cardiac MRI, speckle tracking and 3D echocardiography (echoCG)) have convincingly proven the structural and functional changes of the RHC in patients with DCM, their prognostic and therapeutic significance [14–15]. Although the prevalence of RHC remodeling has not been reliably determined, according to some data, RV systolic dysfunction is registered in 34–65% of patients with DCM [16]. RV dysfunction is an independent prognostic marker of death, a predictor of life-threatening arrhythmias, rehospitalizations, and survival in patients without HT [13]. In individuals with LVEF less than 35%, the incidence of RV dysfunction is 30–70%. Such values of LV function are threshold for implantation of an implantable cardioverter defibrillator (ICD) [17].

Overload of the ventricles of the heart with systolic and diastolic dysfunction inevitably affects the work of the atria. Atrial fibrosis and atrial myopathy contribute to right atrium (RA) enlargement and dysfunction, which subsequently leads to decreased cardiac output (CO) and life-threatening cardiac arrhythmias [18]. Increased RA volume is an independent predictor of death, HT, rehospitalization, and development of atrial fibrillation/flutter (AF) [19].

The study of RHC indicators plays an important role in stratification of the risk of death (RD) of patients with DCM; and a comprehensive analysis of biatrial and biventricular myocardial deformation (MD) can contribute to improving RD stratification, and the implementation of new treatment recommendations [4, 20]. Thus, in the management of patients with DCM, early RD stratification, detection and prevention of cardiovascular complications are relevant.

The aim of the study was to investigate modern methods of diagnosis and treatment of DCM with structural and functional changes in the RHC and their prognostic significance.

PATHOPHYSIOLOGY OF CARDIAC REMODELING IN DILATED CARDIOMYOPATHY

In DCM, in response to myocardial injury or a genetic abnormality, CRem develops, characterized by dilation and impaired systolic function of not only the LV, but often the RV as well [19–20]. Molecular, cellular, and histological changes in the myocardium determine macroscopically the size, shape, and function of the cardiac muscle [3–4]. CRem is associated with activation of neuroendocrine, paracrine, and autocrine factors that increase after myocardial injury, against the background of LV wall tension and hemodynamic disorders. Pathophysiological changes in DCM include decreased stroke volume and CO, and increased end-diastolic pressure. Compensatory volume overload leads to an increase in preload, which contributes to an increase in afterload and, ultimately, to an increase in LV wall tension. Natriuretic peptides (NUP) are released in response to myocardial stretching and act as counter-regulatory hormones that promote natriuresis, diuresis, vasodilation, and are a marker of poor prognosis. An increase in the level of various inflammatory mediators (tumor necrosis factor α, interleukin, etc.) confirms the inflammatory genesis of DCM.

The main cellular mechanism is apoptosis of cardiomyocytes, which leads to CRem, as well as pronounced dystrophic changes in the cellular structure of the myocardium. Ultrastructural remodeling consists of a change in the shape of the nucleus with marginal aggregation of heterochromatin clumps, an increase in the number of mitochondria, and the accumulation of lipid droplets and glycogen. The final stage is cardiomyocyte necrosis - irreversible destruction and lysis of organelles, accompanied by the ingrowth of collagen fibers into disintegrating cardiomyocytes. MF (determined by cardiac MRI) can occur in the form of focal replacement (scar) tissue, interstitial and perivascular fibrosis, which can run in parallel, and become a substrate for life-threatening arrhythmias and further impairment of the mechanical functions of the heart. Histologically, hypertrophy, atrophy of up to one third of myocytes, increased fibrosis, and changes in cytoskeletal elements are observed [2, 5]. Macroscopically, we note cardiomegaly reaching gigantic dimensions,

predominance of dilation of the heart chambers over hypertrophy, characteristic of eccentric hypertrophy, an increase in heart weight by 19.7-20.7% in various types of DCM compared to the conditional norm, an increase in myocardial density associated with the development of myofibrosis and interstitial edema [3, 21]. DCM is characterized by complex changes in the electrical properties of ventricular cardiomyocytes, predisposing to VA [22]. During four-chamber echoCG, the mean values of the LV end-diastolic volume (EDV) in stages I, IIA and IIB of CHF exceed the values in the control group by 51, 86 and 104%; and the mean values of the RV EDV - by 19, 37 and 63%, respectively. Thus, progression of CHF in patients with DCM is accompanied by an increase in the EDV of both ventricles; but LV dilation develops faster than that of the right ventricle. The mean values of the LV end-systolic volume (ESV) and RV ESV: at stage I of CHF, they exceed the norm by 2.3 and 2.1 times; at stage IIA — by 3.5 and 2.5 times; at IIB — by 3.9 and 4.2 times. This indicates that with the progression of CHF in patients with DCM, the LV and RV ESV increase almost proportionally. The increase in LV dilation is accompanied by an increase in the diastolic and especially systolic sphericity index. At stages I and IIA of CHF, the length of the LV remains virtually unchanged, and only at stage IIB does it increase slightly, indicating that it changes its spatial geometry and becomes more spherical. As the severity of CHF increases, the volume and length of the RV increase in parallel, mainly due to an increase in the transverse dimensions. The RV acquires a spherical shape due to the expansion of the free wall [23]. As a result of treatment, reverse CRem is possible, defined as an increase in LVEF by 10–50% from the initial value, and a decrease in the indexed end-diastolic dimension (EDD) of the LV by 10% (EDD of more than 33 mm/m2) [4].

RISK OF DEATH STRATIFICATION

Modern advances in genetic sequencing and cardiac imaging, especially in terms of MF and MD quantification, have enabled the identification of DCM patients with high RD. RD stratification was based on the degree of LV dysfunction and the presence of symptoms. Several prediction models incorporating clinical, cardiopulmonary, and blood laboratory variables have been developed to predict the risk of SCD. However, none of them turned out to be specific for DCM, and were not included in international guidelines [20].

Patients with DCM, who have suffered sudden cardiac arrest, have LVEF of 35% or more in 70–80% of cases [24]. In mild to moderately reduced LVEF, decreased RVEF is a predictor of arrhythmic events [25]. RV dysfunction is an independent prognostic marker of death, predictor of life-threatening arrhythmias, rehospitalizations, and survival in patients without HT [26–27]. In individuals with LVEF <35%, the incidence of RV dysfunction is 30–70%. Such changes in LV function are threshold for ICD [17]. Assessment of RVEF in patients with DCM may be an important part of ICD candidate selection [28]. At the same time, RVEF is a predictor of the development of shock activation or death from ICD [29].

Currently, cardiac MRI is actively used for RD stratification in DCM. LGE has been the subject of several meta-analyses, the results of which indicate that the presence of contrast-enhancing lesions is an independent predictor of cardiovascular mortality and VA [7]. LGE is detected in 30% of patients with DCM, and predicts SCD in patients with LVEF greater than 40% who do not meet current guideline criteria, and can be used to select for ICD. The presence of LGE is virtually the only independent predictor of arrhythmic events in DCM with LVEF >35%. Patients with LGE and LVEF >35% had a significantly higher risk of arrhythmia compared with non-gadolinium-enhanced patients with LVEF between 21 and 35% [30]. In the MINICOR (Multi-Modal International Cardiovascular Outcomes Registry) study, LGE pattern in MRI was associated with a 1.5-fold increase in all-cause RD, the risk of HT, and the use of an LV bypass device (odds ratio (OR) 1.45, 95% confidence interval (CI) [1.03–2.04]), and with a 1.8-fold (OR 1.82, 95% CI [1.20–3.06]) risk of SCD and ICD [31]. MF Progression, assessed by the degree of LGE, is associated with a poor prognosis [32]. MF is a stable risk marker in patients with DCM, and does not regress with optimal drug therapy even in individuals with improved LV function. Progressive fibrosis is observed in one fifth of patients, and is associated with a more than 3-fold increase in RD. Thus, serial assessments of MF using MRI may improve risk

stratification in patients with DCM. Patients with an implantable cardiac device require cardiac MRI the most to prevent serious cardiac events. Currently, devices with the "Safe MRI Mode" setting have appeared, which allows scanning during device operation without risk to the patient's health and the implanted device [33]. The results of a multicenter study of patients with DCM using cardiac MRI showed that MD parameters of both ventricles are significant predictors of adverse outcomes [34]. The Cardiovascular Magnetic Resonance GUIDEd management of mild-moderate left ventricular systolic heart failure (CMR GUIDE HF) trial (NCT01918215) is currently underway to determine whether ICDs improve outcomes in populations with ischemic or nonischemic cardiomyopathy (LVEF 36 to 50%) with 2 or more LGE segments.

Another method of RD stratification is the determination of MD using MRI, which is expressed as a percentage change in myocardial length (shortening in the longitudinal/circumferential directions and elongation in the radial direction). MD allows detection of minor anomalies in relatives of patients with sarcomeric mutations but with normal LVEF and LV volume. With a 1% worsening of global longitudinal strain, the all-cause RD increases (OR: 2.10; $p<0.001$) regardless of LVEF and the presence or degree of LGE [15].

Numerous studies have found the importance of clinical and laboratory data in risk stratification of patients with DCM. Thus, brain NUP and N-terminal pro-brain NUP are associated with all-cause mortality, and a troponin T value of more than 18 ng/L is a prognostic factor for all-cause mortality in non-ischemic heart failure [20].

RIGHT HEART DYSFUNCTION AND ITS DIAGNOSIS

The RA plays an important role in the interaction of the heart chambers and the systemic blood flow. Normal mechanical function of the RA ensures sufficient blood return to the heart and prevents venous congestion. In DCM, systolic and diastolic dysfunction of the LV causes RV overload worsening its diastolic function, increases functional tricuspid regurgitation which progresses to RV failure. The dilation of the RA chamber and its dysfunction further contribute to the reduction of CO. Neurohormonal imbalance in fibrous stretching of the RA is manifested by excessively defective synthesis of atrial NUPs. Processes such as atrial dyssynchrony, fibrosis, and dilation lead to the progression of atrial myopathy and interatrial block, and ultimately to AF [18]. Interstitial MF is a hallmark of AF-induced atrial remodeling, and is associated with chamber dilation, spherical deformation, and decreased atrial function, which further contribute to the development of AF.

The results of the RA study using MRI demonstrated a significant decrease in MD in patients with DCM. The value of RA MD in patients with CHF is an independent predictor of adverse clinical events; and the RA volume index is considered an independent predictor of death, HT, and rehospitalization [19]. In DCM with severe impairment of RA function, an elevated RA area index and its impaired MD indicate an unfavorable prognosis, and lack of response to cardiac resynchronization therapy (CRT) [35].

RV myopathy is a multifactorial process and depends on the etiology of DCM. Biventricular disease is observed in 30–40% of patients with DCM, and the same myopathic process affects both ventricles [14]. Predictors of RV dysfunction include low LVEF and ventricular systolic coupling across the interventricular septum, i.e. the size, shape, and compliance of one ventricle affect the other [13]. Due to ventricular systolic interdependence, impairment of systolic function of the interventricular septum results in decreased RV systolic function. The RV muscle consists mainly of longitudinal muscle fibers; during systole, the tricuspid valve ring moves to the apex, uncoordinated contraction in the longitudinal direction occurs, which leads to a decrease in RV function. With eccentric hypertrophy and deterioration of systolic function, RV dyssynchrony develops, which is a marker of the maladaptive stage of CHF. Patients with severe RA dilation have significant RA dyssynchrony and poor pump function.

Decreased global LV contractility results in decreased ventricular systolic interaction and decreased RV contractility, even if the RV is not involved in the pathological process causing LV systolic dysfunction [13]. As the LV becomes more spherical, the septal fibers become less oblique, which dramatically reduces their mechanical

advantage and further impairs RV contractile function. Ultimately, this leads to clinical right ventricular failure. In addition to the ventricular systolic interaction, when the RV enlarges and stretches the pericardium, the diastolic pressure in the pericardium and RV increases significantly, which leads to limitation of LV filling by the pericardium (pericardial limitation) and the RV through the interventricular septum. This is the so-called diastolic ventricular interaction, which plays a secondary role in determining RV dysfunction with LV overload [14]. RV dysfunction has become an independent predictor of serious adverse cardiac events (OR 3.2, 95% CI [1.3–7.6]; p=0.009) along with RA area and patient age [36]. Patients with RV dysfunction are more often males with a high functional class of CHF and AF. A decrease in LVEF and AF increases the likelihood of RV dysfunction by 1.06 times.

In patients with DCM, biventricular and biatrial MD is impaired [18, 37, 38]. Speckle echocardiography tracking of LV MD has emerged as an independent predictor of adverse outcomes. It was proposed to measure LV MD regularly to assess the prognosis of DCM. A strong relationship was found between atrial and ventricular stress and functional parameters, including LVEF and LAEF. Due to the complex anatomy of the RV, assessment and detection of its early dysfunction is difficult. Evaluation of the prognostic significance of RV parameters showed the influence of RVEF and its global longitudinal MD on the frequency of hospitalizations, prediction of cardiac death, and death from all causes. The prognostic value of longitudinal RV MD was higher than that of other traditionally used echocardiographic indices of RV systolic function [39].

It is important to note that RVEF alone provides an adequate assessment of the true global pumping function of the RV. 3D echocardiography is a method capable of directly measuring RV EDV and RV ESV, and reliably calculating RVEF. RV volumes obtained by 3D echocardiography correlate with RV volumes obtained by cardiac MRI and with volumes obtained by cardiac catheterization using volume thermodilution. 3D echocardiography has proven to be the most reliable method, overestimating RVEF by only 1.16% [40]. Based on large cohort studies of healthy volunteers, normative RV volumes and EF have become available, including reference values for age, body size, and gender. RVEF greater than 45% is indicated as the lower limit of normal. A recent study introduced classifications of RV systolic dysfunction: mild (40–45%), moderate (30–40%), severe (<30%), and confirmed their prognostic value [40–41]. 3D echocardiography allows specialists to evaluate RV MD in all planes and different directions (longitudinal, circumferential and radial deformation) similar to cardiac MRI. Patients with DCM and cardiovascular events (death, nonfatal circulatory arrest, rehospitalization) had impaired global RV longitudinal strain (-10.5±4.5% vs. -14.3±5.2%, p=0.009), RV free wall longitudinal strain (-12.9±8.7% vs. -17.5±7.1%, p=0.046), and RV ejection fraction (38±8% vs. 47±9%, p=0.001), compared to individuals without events. Patients with RVEF greater than 43.4% had a more favorable outcome compared to patients with RVEF less than 43.4% (p<0.001) [42]. MD is a predictor of mortality that correlates with RVEF, indicating the superiority of MD obtained using 3D echocardiography over other methods of its determination. Thus, availability, portability, accuracy and safety make 3D echocardiography one of the most versatile methods for assessing RV function.

Cardiac MRI is the gold standard for diagnosis and evaluation of the RV, the volumes and function of which can be measured with high accuracy and reproducibility (IIa class indications). Due to the ability to analyze myocardial tissue in addition to calculating volumes and systolic function, MRI allows us to differentiate the etiology of DCM, assess prognosis and RD. MRI is able to detect tissue abnormalities (fatty infiltration, LGE), which allows specialists to differentiate physiological from pathological RV remodeling. In DCM, MRI revealed an asymmetrical enlargement of the ventricles with a predominance of larger LV volumes; decreased LV and RV function; subepicardial or myocardial LGE pattern associated with the risk of SCD [43]. Regional MD assessed by cardiac MRI predicts the development of VA. Independent predictors of all-cause mortality are indexed LV EDV (with MRI>120.5 ml/m2), and the presence of more than three segments with MF, which increases the risk of VA.

Assessment of RV dyssynchrony is a promising new approach to assess RV dysfunction and disease prognosis. RV dyssynchrony is associated with RV remodeling, dysfunction, poor hemodynamics, and an increased risk of adverse clinical events [44]. In patients with nonischemic CHF, compared with ischemic CHF, there was marked RV dyssynchrony (44.3±17.8° vs. 35.8±15.8°, P=0.003), larger RV volumes (EDV: 302±98 vs. 243±83 ml, P<0.001; ESV: 199±86 vs. 138±69 ml, P<0.001), and lower RVEF (36±13% vs. 46±15%, P<0.001). Complete left bundle branch block (LBBB) may further worsen the degree of RV dyssynchrony. RV dyssynchrony is 'mitigated' by a sharp reduction in RV afterload, and is a potential therapeutic target; its assessment helps in risk stratification and decision making regarding the prevention and treatment of DCM.

PROGNOSIS

As a result of an integrated treatment strategy based on evidence-based therapy, early diagnosis and structured monitoring, the prognosis of DCM has improved over the past two decades. CRem is a dynamic process, and LV reverse remodeling is associated with a favorable outcome. However, patients with DCM should not be considered cured; they should be closely and systematically monitored to detect early signs of disease progression, and treatment should be continued indefinitely. The prognosis of DCM and the likelihood of LV reverse remodeling are influenced by RV function, functional mitral regurgitation, and the presence of LBBB. RHC remodeling in DCM is a hallmark of progressive disease, and is an independent prognostic marker of death, hospitalization for CHF, HT-free survival, and a predictor of arrhythmic events. RVEF<43%, determined by 3D echocardiography, can predict worse cardiovascular outcome in patients with DCM [42]. A 10% decrease in RVEF increases all-cause RD by 39.6% (95% CI, [16.4–67.4]), P=0.0003, and increases all-cause mortality or the need for HT by 4 times [44]. ICD reduces 1-year mortality in patients with DCM only to 23% [45]; but in patients with RV systolic dysfunction, all-cause mortality is significantly reduced (HR 0.41 (95% CI, 0.17–0.97), p=0.04) compared to patients without RV dysfunction (HR 1.87, 95% CI [0.85–3.92], p=0.12). In patients with RV dysfunction, ICD implantation reduced all-cause RD by 55%, whereas in patients without RV dysfunction, ICD implantation had no effect. ICD appears to significantly reduce the risk of SCD in patients with reduced RV function. ICD improved survival in biventricular failure when compared with outcomes of patients with LV systolic dysfunction only (P=0.001) [29].

TREATMENT

Management of patients with DCM includes conventional approaches to the treatment of CHF, such as drugs [9], devices, and HT [5, 8]. The main goal of treatment of patients with DCM is to slow CHF progression, improve quality of life and prognosis. Treatment should include rapid optimization of volume status, restoration of perfusion pressure, improvement of contractility and cardiac rhythm, and, in case of refractory RV failure, mechanical circulatory support (MCS) or HT [2].

With adequate pharmacological and hardware treatment (for 6 months to 2 years), 40% of patients with DCM experience reverse LV remodeling, which is associated with a long-term prognosis; of these, 15% of cases show normalization of LV size and function, which persists for 10 years of observation. However, with a longer follow-up period (15 years), the condition deteriorates again in 5% [5]. Optimal medical therapy (9 months) can increase LVEF by 20% in one third of patients with DCM [46]. In the process of LV reverse remodeling, which was observed after an average of 24 months (odds ratio: 2.49; 95% CI [1.17–5.3]; p=0.018), normalization of RV function occurs. However, over time, in response to drug therapy, MF persists, and does not regress in size [32]. This fact highlights the distinction between fibrosis and LVEF as risk markers in the selection of patients for ICD. In this regard, assessment of myocardial scar should be included as a major criterion for patient selection for ICD placement [47].

In contrast to the treatment for CHF with systolic dysfunction, the principles of treatment for DCM with RV failure are poorly known. Most recommendations are based on either retrospective or small randomized trials. The goals of treatment for RV failure are to optimize myocardial preload, afterload, and contractility. Maintenance of sinus rhythm and sequential contraction of the atria and

ventricles is particularly important in RV failure, since AF and high-degree atrioventricular block can have serious hemodynamic consequences. Ventricular interdependence is also an important concept to consider when selecting therapy. Excessive volume load can increase pericardial pressure, and decrease LV and CO preload via ventricular interaction. On the other hand, hypovolemia may decrease RV and CO preload. Nevertheless, general recommendations for patients with right ventricular failure do not differ from those for patients with left ventricular CHF. It is important to recognize the factors that lead to clinical deterioration. These include non-compliance with medication or diet; selective drug intake; systemic factors such as sepsis, anemia, hypoxemia and hypercapnia; cardiovascular factors such as arrhythmia, myocardial ischemia, pulmonary embolism; sleep disorders, apnea, psychoemotional stress.

Beta-blockers, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, aldosterone antagonists, and angiotensin II receptor enkephalinase inhibitors affect the pathophysiological mechanism of CHF (sympathetic nervous system, renin-angiotensin-aldosterone system, and NUP system). In DCM, the level of circulating catecholamines is elevated, indicating hyperactivity of the sympathetic nervous system, which aggravates LV dysfunction. Slowing the heart rate (HR) improves LV filling, and can maintain the balance of myocardial oxygen supply and demand, reducing mortality and cardiovascular events. Carvedilol, which has unique vasodilatory and antioxidant properties, is the most effective drug among beta-blockers. In improving LVEF, carvedilol, verapamil, and trimetazidine have shown the greatest efficacy. Ivabradine, increasing the activity of the parasympathetic nervous system and improving the autonomic regulation of the cardiovascular system, prevents RD. In early DCM, non-dihydropyridine calcium channel blockers such as verapamil and diltiazem can preserve systolic function and diastolic filling, improving myocardial performance [8, 48]. In patients with biventricular failure, angiotensin-converting enzyme inhibition increases heart rate, and decreases RV EDV and filling pressures. β-blocking with carvedilol or bisoprolol improves RV systolic function. The risk of thromboembolic complications in patients with RV failure has not been reliably established. Although clinical practice varies, anticoagulants are generally recommended for patients with evidence of intracardiac thrombus, documented thromboembolic events (pulmonary embolism or paradoxical embolism), and patients with paroxysmal or persistent AF/ flutter.

For primary and secondary prevention of SCD, an ICD is used. The implantable device is needed in patients with DCM with a history of sustained ventricular tachycardia who have survived cardiac arrest [28]. CRT is used to restore the physiological contraction sequence of the cardiac chambers [35]. Biventricular pacing or CRT improves symptoms and survival in selected patients with systolic CHF. The study of RV resynchronization is in its infancy; and afterload reduction with sildenafil improves RV synchrony [44]. Results of a multicenter study demonstrated that CRT was associated with an improvement in LVEF in patients with right ventricular failure.

An alternative option in patients with end-stage CHF is long-term mechanical circulatory support (MCS)/LV assist devices as a targeted therapy or as a bridge to HT [8]. MCS has become an increasingly used strategy for the management of patients with both acute and chronic ventricular failure. For patients with advanced CHF refractory to guideline-based pharmacologic, device-based, and surgical therapies (CRT, ICD, transcatheter or surgical treatment), long-term MCS using an LV assist device, with or without additional temporary or long-term RV support, has had a good track record. Most long-term MCS devices are intended for the LV. In patients with DCM, the 2-year survival rate was over 80%, and was similar to the early survival rates after HT. Treatment outcomes of patients with MCS for right ventricular failure have shown that 42–75% of patients recover. Cases of patients with DCM treated with a paracorporeal LV assist device have been described. Recently, volume-reducing ventriculectomy, such as the Batista procedure, has become widely used for idiopathic DCM due to organ shortages. In patients with RV failure refractory to medical therapy, mechanical support with an RV assist device can be used as a bridge to HT or

recovery. The most common indications for the use of an RV assist device are severe RV failure associated with LV bypass, prospective HT. HT is the final stage of treatment for patients with DCM, and may be considered in selected patients with progressive refractory RV failure.

Cell therapy for DCM aims to combat cardiomyocyte loss and the progression of myocardial dysfunction. Clinical trials of cell therapy for DCM, especially when combined with additional cytokine therapy such as granulocyte-colony stimulating factor, have shown positive results in improving cardiac function and symptoms.

CONCLUSION

In dilated cardiomyopathy, the main cause of cardiac remodeling and life-threatening arrhythmias is myocardial fibrosis, which is determined in asymptomatic patients at an early stage of the disease. Involvement of the right heart chambers in the pathological process in patients with dilated cardiomyopathy is a predictor of adverse outcome (arrhythmic events, severe heart failure, rehospitalizations, heart transplantation, and death). Modern diagnostic methods have made it possible to study the right heart parameters, but they have not been introduced into routine practice. Contrast-enhanced cardiac magnetic resonance imaging is the gold standard for diagnosing dilated cardiomyopathy, and the definitive examination for risk stratification and prognosis of the disease. Evaluation and characterization of myocardial fibrous scar should be included as the main criterion for patient selection for implantable cardioverter defibrillator placement. Treatment of patients with dilated cardiomyopathy is a complex process. Adequate drug and instrumental therapy in 40% of cases leads to reverse remodeling of the heart, but without regression of areas of myocardial fibrosis, which indicates a continuing risk of complications and death.

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