Cite as: Liu ZE, Guo JQ. Research progress and treatment status ofnon-ischemic cardiomyopathy [J]. Chin J Clin Res, 2024, 37(6):835-839,871.
DOI: 10.13429/j.cnki.cjcr.2024.06.004

Research progress and treatment status of non-ischemic cardiomyopathy

LIU Ze'en, GUO Jianqiang

Department of Cardiology, Affiliated Hospital of Inner Mongolia Medical University, Huhehaote, Inner Mongolia 010000, China

Corresponding author: GUO Jianqiang, E-mail: gjq161208@126.com

Abstract: Cardiomyopathy is a heart disease clinically characterized by enlargement of the heart, arrhythmia and heart failure alone or simultaneously. Ischemic cardiomyopathy is usually caused by coronary atherosclerotic lesions, but non-ischemic cardiomyopathy is different. It is caused by non-coronary atherosclerotic lesions which can cause heart failure, arrhythmia, and even sudden death. With the improvement of the diagnosis level, non-ischemic cardiomyopathy has been focused on. However, the pathogeny, diagnosis and treatment methods are still unclear in recent years, and the efficacy needs to be explored further. The article analyzes the pathogeny, diagnosis, current status of drugs and non-drug treatment, aiming to provide more reference materials for the early prevention of patients with non-ischemic cardiomyopathy and provide direction for the diagnosis and treatment of clinical patients.

Keywords: Non-ischemic cardiomyopathy; Dilated cardiomyopathy; Hypertrophic cardiomyopathy; restrictive cardiomyopathy; cardiac resynchronization therapy ; Bone marrow stem cell transplantation; Radiofrequency ablation

Non ischemic cardiomyopathy (NICM) is a kind of cardiogenic heart failure caused by structural and/or functional insufficiency of the heart due to non-coronary atherosclerosis. Compared to ischemic cardiomyopathy, NICM has the characteristics of insidious onset and lack of specificity in etiology. Its causes can be genetic, acquired, or secondary to systemic diseases. Currently, understanding of this condition remains incomplete, and diagnosis and treatment are still imperfect. This paper provides an overview of NICM in recent years, including etiology, diagnostic methods, and treatment, aiming to improve a theoretical basis.

1 Etiology of NICM

Dilated cardiomyopathy (DCM) is one of the most common causes of NICM, characterized by ventricular dilation and impaired contractile function. Despite advancements in treatment, the mortality of DCM remains high. DCM is a major indication for heart transplantation. Numerous clinical studies indicate that toxins, diabetes, arrhythmias, myocarditis, and pregnancy typically contribute to phenotype and outcomes. In recent years, there has been increasing attention to genetic factors and mutations. In some foreign NICM patients, autosomal dominant inheritance is often observed. Additionally, mutations in genes, particularly the absence of β-myosin heavy chain, have become a focus, suggesting a genetic cause for familial NICM [1]. Understanding the interplay between genetic and acquired diseases has been a recent research focus, indicating that environmental factors influence the expression of genetic backgrounds, thereby potentially improving the assessment of such patients and new treatment methods in the future.

Research over the past three decades has established hypertrophic cardiomyopathy (HCM) as an autosomal dominant genetic disease caused by pathogenic variants in genes encoding sarcomere proteins critical for contractile function [2]. The two most common disease genes involved are *MYBPC3* and *MYH7*, with pathogenic variants in these genes accounting for 70% to 80% of all genotype-positive HCM patients [3]. Features include left ventricular hypertrophy, myocardial fibrosis, enhanced oxidative stress and energy consumption, ultimately leading to heart failure and arrhythmias. Understanding the genetic basis of HCM heralds the era of precision medicine, with genetic testing leading to improved and precise diagnosis, allowing for effective genetic testing in at-risk family members and providing better-targeted therapies.

Restrictive cardiomyopathy (RCM), defined by increased myocardial stiffness, leads to restricted ventricular filling, with late-stage manifestations including heart failure, arrhythmias, and conduction abnormalities. Compared to HCM or DCM, RCM is less common. RCM is typically caused by cardiac amyloidosis, cardiac sarcoidosis, or cardiac hemochromatosis. Features include non-dilated left or right ventricles with diastolic dysfunction. Patients with diastolic dysfunction presenting with normal or near-normal systolic function and a restrictive filling pattern on echocardiography should be suspected of having RCM. Echocardiography is essential for confirming diastolic dysfunction, differentiating RCM from constrictive pericarditis. The prognosis of RCM is the poorest due to lacking of effective treatment methods. Currently, there are no specific treatments directly targeting RCM, and more approaches based on the etiology

are needed in the future [4].

In addition to the above three common causes, other etiologies include hypertensive heart disease, metabolic cardiomyopathy, valvular heart disease, as well as systemic inflammatory diseases, drug-induced cardiomyopathy, peripartum cardiomyopathy, and other idiopathic cardiomyopathies. Clear diagnosis of these conditions is crucial for treatment and prognosis. These cardiomyopathies primarily manifest as abnormalities in cardiac structure and function, such as myocardial hypertrophy, chamber dilation, and myocardial stiffness, leading to symptoms such as decreased cardiac contractile function, arrhythmias, and heart failure. Diagnosis of NICM requires comprehensive analysis through detailed medical history, physical examination, electrocardiography, echocardiography, cardiac magnetic resonance imaging, and other diagnostic methods. Treatment methods include pharmacotherapy, non-pharmacological treatments, as well as implantation of cardiac pacemakers or cardioverter-defibrillators, and heart transplantation, with specific treatment plans tailored to the patient's condition and specific type.

2 Diagnostic methods for NICM

2.1 Electrocardiography

Electrocardiography is one of the basic diagnostic methods for NICM and can display cardiac rhythm and cardiac enlargement. The electrocardiogram of NICM shows sinus bradycardia or tachycardia, premature or ectopic beats in the atrium or ventricle, mild or moderate prolongation of QRS complex duration, and changes in the shape and amplitude of T waves; There may also be manifestations of ventricular hypertrophy and dilation, such as ST segment changes, Q wave appearance, left deviation of the electrical axis, etc. It is important to note that ECG is not a specific indicator in the diagnosis of NICM, but it can be used during treatment to assess changes in cardiac electrical activity and the presence of arrhythmias. Regular ECG examinations can help physicians promptly detect changes in the patient's condition and take appropriate therapeutic measures. However, ECG is just one diagnostic method for NICM, and diagnosis and treatment need to be considered in conjunction with other examination results and clinical symptoms.

2.2 Echocardiography

Echocardiography can help differentiate different types of NICM. Ventricular enlargement due to myocardial pathology may differ from ventricular hypertrophy caused by hypertension or other causes. Echocardiography can display parameters such as ventricular wall thickness, interventricular septal thickness, and left ventricular end-diastolic diameter. NICM may present with left ventricular enlargement, significantly reduced systolic function, enhanced wall echogenicity, and segmental wall motion abnormalities. Combined with relevant medical history, this aids physicians in distinguishing between different types of cardiomyopathies, thereby improving accuracy and precision of clinical diagnosis. Echocardiography can also be used to monitor disease progression and treatment effects in NICM [5]. However, if clinical suspicion of NICM is high, further investigations may be conducted.

2.3 Endomyocardial biopsy (EMB)

EMB, as an invasive procedure, is the gold standard for both diagnosis and etiological assessment of NICM. With advancements in surgical instruments and the application of immunohistochemistry, viral gene sequencing, and other tissue analysis technologies in clinical settings, the frequency of EMB usage is increasing. Although specific clinical trials and guidelines are currently lacking, the clinical indications for performing EMB are based on expert opinion. A recent study found that EMB achieves a detection rate of 65% for NICM [5]. The primary concerns associated with EMB include the selection of heart specimens, the necessity of biopsying both ventricles, and risks such as tricuspid valve prolapse and cardiac perforation. Therefore, in patients clinically suspected of NICM, careful collection of medical history, clinical examinations, electrocardiograms, echocardiograms, etc., is essential to identify reliable clinical indications and the optimal timing for EMB, thereby minimizing risks and improving prognosis to maximize benefits.

2.4 Cardiac magnetic resonance (CMR)

While EMB is the gold standard, its invasive nature limits its clinical application, particularly in the study of NICM. Currently, non-invasive cardiac imaging techniques have become crucial for diagnosing myocardial diseases. CMR is considered the optimal diagnostic tool for assessing the morphology, function, and tissue phenotype of myocardial disease. It is regarded as the gold standard imaging modality for evaluating cardiac functional and morphological parameters such as wall thickness, left ventricular mass, and volume. CMR utilizes various pulse sequences to characterize myocardial tissue, with late gadolinium enhancement (LGE) remaining the most relevant tool for tissue characterization in CMR. Studies conducted by Brendel et al. have shown that LGE can assess myocardial viability and describe myocardial scar formation [6]. Recent research indicates significant differences in affected segments, thickness, and age between patients with and without LGE [7]. Thus, LGE plays a crucial role in the diagnosis and prognostic assessment of cardiomyopathy, and every patient suspected of cardiomyopathy should undergo MRI with LGE technology. However, the lack of standardized pulse

sequences remains a primary limitation of LGE technology.

3 Current status of clinical treatment research for NICM

In the past two decades, with the establishment and refinement of standardized treatment protocols, particularly the adoption of biological therapies such as β-adrenergic receptor blockers, angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), and aldosterone receptor antagonists (ARAs), collectively known as "guideline-directed medical therapy (GDMt)", significant advancements have been made in the management of non-ischemic cardiomyopathy (NICM) patients [8-10]. Additionally, non-pharmacological treatments like cardiac resynchronization therapy (CRT) have further improved prognosis, markedly reducing mortality rates and improving left ventricular function and/or structural abnormalities in some NICM patients [11]. These advancements have been characterized by improvements in left ventricular ejection fraction (LVEF) or fraction shortening (FS), sometimes accompanied by reductions in left ventricular end-diastolic diameter (LVEDD) or volume (LVEDV), indicative of "left ventricular reverse remodeling (LVRR)" [12-15]. From the first global classification of cardiomyopathies by World Health Organization's to the 2008 ESC classification, the classification of cardiomyopathy has been redefined, including DCM, HCM, RCM, arrhythmogenic right ventricular cardiomyopathy, and amorphous cardiomyopathy. The prognosis of different types of cardiomyopathies varies greatly. The following will provide specific explanations from drug treatment and non-drug treatment, providing some ideas for clinical doctors to intervene in this type of disease in the early stage.

3.1 Pharmacological treatment

3.1.1 Anti ventricular remodeling—β-receptor blockers

β-receptor blockers, as first-line treatment drugs for improving symptoms, are recommended routinely when no contraindications exist. In cases of heart failure with preserved ejection fraction (HFpEF) or reduced ejection fraction (HFrEF), medications like metoprolol or bisoprolol are utilized, starting with low doses and gradually increasing to the maximum tolerated dose (typically achieving a resting heart rate of 55-60 beats per minute). Early and appropriate use of β-receptor blockers has shown significant reductions in mortality, rehospitalization rates, and sudden death risks in NICM patients. For patients with concomitant arrhythmias, rhythm control becomes more important. Although amiodarone is generally preferred, combined use of β-receptor blockers can better control and improve prognosis.

3.1.2 Inhibiting renin-angiotensin system—ACEIs/ARBs

ACEIs not only has antihypertensive function, but also can delay and reverse ventricular remodeling, thereby preventing cardiac hypertrophy and improving endothelial and cardiac function. They significantly reduce hospitalization costs and mortality in HFrEF patients and are considered cornerstone drugs that should be initiated early in heart failure management, irrespective of severity. Due to their dose-dependent effects, starting with low doses and gradually doubling every two weeks until reaching target therapeutic doses is recommended. Regular monitoring of blood pressure, potassium levels, and renal function is essential to avoid abrupt discontinuation. For patients with poor ACEI tolerance, ARBs offer a viable alternative with similar benefits in hemodynamics. Milestone trials have demonstrated ACEI/ARBs can reduce heart failure mortality by 20%-30%. Additionally, the CHARM-added trial confirmed that adding ARBs on the basis of ACEIs significantly reduces cardiovascular disease and heart failure hospitalization risks, albeit increasing the likelihood of renal function deterioration and hyperkalemia. Therefore, treatment selection for HFrEF patients should be individualized based on specific clinical circumstances.

3.1.3 Sodium-glucose co-transporter 2 (SGLT-2) inhibitors

Initially developed as antidiabetic agents, SGLT-2 inhibitors have shown significant cardiovascular benefits independent of their glucose-lowering effects. Early cardiovascular trials in type 2 diabetes mellitus (T2DM) patients with high-risk of cardiovascular disease demonstrated a 30%-35% reduction in heart failure hospitalization risks. Unlike other more effective antihypertensive treatments that failed to reduce cardiovascular risks in T2DM patients, SGLT-2 inhibitors have emerged as agents with distinct cardioprotective roles. Recent meta-analyses indicated that early intervention with SGLT-2 inhibitors in T2DM patients with HFrEF not only improved ventricular remodeling but also significantly lowered cardiovascular disease mortality rates [16]. Although the exact mechanisms for survival benefits remain under investigation, SGLT-2 inhibitors are recommended for use in HFrEF patients with or without type 2 diabetes to enhance quality of life, improve clinical symptoms, and reduce heart failure-related hospitalization rates.

3.1.4 Aldosterone receptor antagonists

Aldosterone has numerous pathophysiological functions, including inducing central hypertension,

promoting tissue damage, inducing ventricular or severe arrhythmias, promoting sodium retention, and causing myocardial fibrosis. Mineralocorticoid receptor antagonists (MRA), such as spironolactone, can be used in patients with ascites and heart failure-related edema. They have been shown to significantly improve the prognosis of patients with HFrEF. The 2018 Chinese Guidelines for Diagnosis and Treatment of Heart Failure suggest that HFrEF patients should first use ACEI/ARB and β-receptor blockers in small doses, gradually increasing to the target dosage, and then use diuretics as needed. If the clinical symptoms do not improve and eGFR is ≥ 30 mL·min^{-1}·1.73m^{-2}, and blood potassium is<5.0 mmol/L, MRA intervention should be considered. Consideration of MRA intervention is based on the patient's clinical condition and presentation, not necessarily initiating treatment early. Often, spironolactone is used concurrently with loop diuretics. Eplerenone, a novel selective aldosterone receptor antagonist, significantly lowers blood pressure and can be added when blood pressure remains uncontrolled despite multiple antihypertensive medications.

3.1.5 Diuretics

Due to inevitable fluid retention in heart failure, diuretics have been recommended in treatment of heart failure. Diuretics include loop diuretics, thiazide diuretics, and potassium-sparing diuretics, with decreasing strength in the order. According to the American Heart Failure Association guidelines, oral furosemide 20 mg is recommended for chronic heart failure. Long-term use of loop diuretics has been shown to significantly improve patient survival rates, especially when combined with other diuretics, though there is a risk of electrolyte imbalance. Therefore, treatment, whether alone or in combination, should be tailored based on the patient's symptoms, signs, weight, and urine output.

For NICM, treatment should be tailored to the type of cardiomyopathy. The above medications are foundational. For example, HCM requires reducing myocardial remodeling and improving arrhythmias, while DCM necessitates treatments such as anti-heart failure and anticoagulation. In severe heart failure, medications according to the AHA/ACC/HFSA heart failure management guidelines may include diuretics, vasodilators, recombinant human brain natriuretic peptide, or calcium channel blockers. Specific drug treatments for NICM depend on diagnosis and complications, with hopes for future standardized treatment protocols.

3.2 Non-pharmacological treatments

3.2.1 CRT

CRT is a new non-pharmacological treatment method. Since NICM often progresses to chronic congestive heart failure (CHF), drug therapy alone may be insufficient for patients at NYHA II or above, and cannot improve long-term quality of life, CRT has become a mainstream treatment. It enhances the synchrony of atrial and ventricular mechanical movements through pacing devices, reversing left ventricular hypertrophy, improving cardiac function, and preventing arrhythmias [16-17]. Initial single-point pacing may not predict the optimal pacing site well, with up to 40% of patients showing no response to CRT. Quadripolar or more leads can stimulate more left ventricular areas, improving CRT response in terms of hemodynamic improvement, left ventricular ejection fraction (LVEF) enhancement, and reduced asynchrony [18-19]. But in the future, a large number of multicenter samples are needed to prove the safety and effectiveness of multi-point pacing.

3.2.2 Bone marrow stem cell (BMC) transplantation

In recent years, BMC has shown clinical advantages. Bone marrow mononuclear cells (BMMC) play a significant role in the treatment of ischemic cardiomyopathy and acute myocardial infarction, although data for NICM are limited [20-21]. Stem cells have paracrine regulatory mechanisms in cytokine secretion and play a role in cell differentiation. Intracoronary application of BMC has been proven safe and significantly increases left ventricular ejection fraction post-treatment, with some cells remaining effective in the myocardium. Direct myocardial injection of BMMC is safe and improves ejection fraction of NICM, though clinical trials have shown controversial efficacy. A recent meta-analysis demonstrated significant improvement in left ventricular ejection fraction and reduced end-diastolic diameter with BMMC transplantation.

3.2.3 Radiofrequency ablation

NICM often leads to ventricular arrhythmias in the later stage of NICM. While implantable cardioverter-defibrillators (ICDs) effectively prevent sudden death, patient symptoms may recur, and antiarrhythmic drugs have side effects. Radiofrequency ablation remains highly effective in NICM patients, with randomized trials showing superior outcomes compared to drug therapy. It improves prognosis and reduces the need for heart transplantation and mortality rates. In 2019, HRS ventricular arrhythmia radiofrequency ablation experts recommended that NICM patients with recurrent persistent monomorphic VT and AAD were ineffective, contraindicated, or intolerant. Choosing radiofrequency ablation can help reduce the recurrence of VT and ICD shocks. But NICM is different from ICM. NICM is more complex, with higher ablation difficulty and lower success rate. According to the latest research report, the use of stereotactic body radiotherapy (SBRT) has a significant effect on the treatment of refractory ventricular tachycardia,

providing new ideas for future refractory arrhythmias.

4 Summary and outlook

NICM is a very dangerous heart disease, and its incidence is rising. At present, the treatment methods are not yet mature. Gene editing technology has become very advanced in recent years and can be used in the future to repair, modify, or regulate genes related to myocardial disease. This is of great significance for the treatment of some familial inherited NICM, and currently available drug therapies have a significant effect on improving the quality of life and prognosis of patients with this type of cardiomyopathy, but there are still limitations and shortcomings. In the future, we should continue to strengthen research on drug therapy, develop new molecules, and develop new technologies based on RNA interference. NICM may cause problems such as weakened ventricular wall movement or ventricular dilation, which are related to abnormal cardiac electrical signals. Future treatment directions can include bioelectrical control and repair technologies aimed at restoring ventricular function by controlling cardiac electrical signals. The occurrence of NICM is also related to the imbalance of neural regulation, so neural regulation therapy is a possible future direction. By adjusting the balance between the sympathetic and parasympathetic nerves, heart function can be improved and the risk of death in patients can be reduced.

In short, with the continuous development of medical technology, the treatment of NICM will also continue to improve and innovate. The future treatment direction needs to take into account factors such as technological level, biology, and clinical practice, and focus on improving treatment effectiveness while ensuring patient safety and comfort.

Conflict of Interest None

References

[1] de Frutos F, Ochoa JP, Navarro-Peñalver M, et al. Natural history of MYH7-related dilated cardiomyopathy[J]. J Am Coll Cardiol，2022，80(15):1447-1461.
[2] Karatsai O, Lehka L, Wojton D, et al. Unconventional myosin VI in the heart: involvement in cardiac dysfunction progressing with age[J]. Biochim Biophys Acta BBA Mol Basis Dis, 2023, 1869(6): 166748.
[3] Marsili L, van Lint FV, Russo F, et al. MYH7 p.(Arg1712Gln) is pathogenic founder variant causing hypertrophic cardiomyopathy with overall relatively delayed onset[J]. Neth Heart J, 2023, 31: 300-307.
[4] Brodehl A, Gerull B. Genetic insights into primary restrictive cardiomyopathy[J]. J Clin Med, 2022, 11(8): 2094.
[5] Zuo CC, Xu W. Application of echocardiography combined with percutaneous left ventricular angiography in differentiating ischemic cardiomyopathy from dilated cardiomyopathy[J]. J Imag Res Med Appl, 2022, 6(11): 59-61. **[In Chinese]**
[6] Li L, Liu SY, Wu LM, et al. Clinical features of patients with complex ventricular arrhythmia and myocarditis: diagnostic value of endocardial myocardial biopsy[J]. Chin Circ J, 2023, 38(6): 669-674. **[In Chinese]**
[7] Huang DJ, Liu Y, Gao L, et al. miR-32-3p regulates myocardial injury induced by microembolism and microvascular obstruction by targeting RNF13 to regulate the stability of atherosclerotic plaques[J]. J Cardiovasc Transl Res, 2022, 15(1): 143-166.
[8] Zhang LS, Gao FB. Evaluation value of mr tissue tracking technique in dilated cardiomyopathy[J]. J Clin Radiol, 2023, 42(1): 168-171. **[In Chinese]**
[9] Terentes-Printzios D, Gardikioti V, Latsios G, et al. Aortic systolic blood pressure predicts periprocedural myocardial injury after transcatheter aortic valve implantation[J]. Eur Heart J, 2021, 42 Supplement_1: ehab724.2333.
[10] Sun RR, Chen TZ, Meng M. Hypereosinophilic syndrome presenting as acute ischemic stroke, myocardial infarction, and arterial involvement: a case report[J]. World J Clin Cases, 2022, 10(11): 3547-3552.
[11] Feng LL, Tian RF, Mu XD, et al. Identification of genes linking natural killer cells to apoptosis in acute myocardial infarction and ischemic stroke[J]. Front Immunol, 2022, 13: 817377.
[12] Iyer Nithin R, Thao LT, Kui Michelle SL, et al. Markers of focal and diffuse nonischemic myocardial fibrosis are associated with adverse cardiac remodeling and prognosis in patients with hypertension: the REMODEL study[J]. Hypertension, 2022: 79(8):1804-1813.
[13] Tat E, Ball C, Camren GP, et al. Impact of late gadolinium enhancement extent, location, and pattern on ventricular tachycardia and major adverse cardiac events in patients with ischemic vs. non-ischemic cardiomyopathy [J]. Front Cardiovasc Med, 2022, 9: 1026215.
[14] Ajufo E, Ayers CR, Vigen R, et al. Value of coronary artery calcium scanning in association with the net benefit of aspirin in primary prevention of atherosclerotic cardiovascular disease[J]. JAMA Cardiol, 2021, 6(2): 179.
[15] Chen HS, Jungen C, Kimura Y, et al. Ventricular arrhythmia substrate distribution and its relation to sympathetic innervation in nonischemic cardiomyopathy patients[J]. JACC, 2022, 8(10): 1234-1245.
[16] Wang KY, Yang Y, ZULIPIYE Ainaisi , et al. Efficacy and safety of four SGLT2 inhibitors in the treatment of heart failure with reduced ejection fraction: a network meta-analysis[J]. J Clin Cardiol, 2023, 39(1): 21-28. **[In Chinese]**
[17] Thibault B, Dubuc M, Khairy P, et al. Acute haemodynamic comparison of multisite and biventricular pacing with a quadripolar left ventricular lead[J]. Europace, 2013, 15(7): 984-991.
[18] Cojan-Minzat BO, Zlibut A, Agoston-Coldea L. Non-ischemic dilated cardiomyopathy and cardiac fibrosis[J]. Heart Fail Rev, 2021, 26(5): 1081-1101.
[19] Yang SW, Liu ZM, Hu YR, et al. A novel risk model for mortality and hospitalization following cardiac resynchronization therapy in patients with non-ischemic cardiomyopathy: the alpha-score[J]. BMC Cardiovasc Disord, 2020, 20(1): 205.
[20] Mehta VS, Elliott M, Sidhu B, et al. Multipoint pacing for cardiac resynchronisation therapy in patients with heart failure: a systematic review and meta-analysis[J]. J Cardiovasc Electrophysiol, 2021, 32: 2577-2589.
[21] Schiedat F, Bogossian H, Schöne D, et al. Long-term performance comparison of bipolar active vs. quadripolar passive fixation leads in cardiac resynchronisation therapy[J]. Front Cardiovasc Med, 2021, 8: 734666.

Submission received: 2023-08-09

· 研究进展 ·

非缺血性心肌病的研究进展及治疗现状

刘泽恩，　郭建强

内蒙古医科大学附属医院心血管内科，内蒙古 呼和浩特 010000

摘要：临床上把心脏扩大、心律失常和心力衰竭三者单独或同时存在为特征的心脏疾病称为心肌病。通常由冠状动脉粥样硬化病变引起的为缺血性心肌病，非缺血性心肌病与之不同，是指由非冠状动脉粥样硬化病变所致，可引起心力衰竭、心律失常、甚至猝死。但对其病因、诊断、治疗方法仍不甚明确，疗效有待进一步探索。本文分析了缺血性心肌病病因学、诊断方面，及当前药物及非药物治疗现状，为此类患者的早期预防提供更多参考资料，为临床上患者的诊断及治疗提供方向。

关键词：非缺血性心肌病；扩张型心肌病；肥厚型心肌病；限制性心肌病；心脏再同步化治疗；骨髓干细胞移植；射频消融术

中图分类号：R542.2　**文献标识码**：A　**文章编号**：1674-8182(2024)06-0835-05

Research progress and treatment status of non-ischemic cardiomyopathy

LIU Ze'en, GUO Jianqiang

Department of Cardiology, Affiliated Hospital of Inner Mongolia Medical University, Hohhot, Inner Mongolia 010000, China

Corresponding author: GUO Jianqiang, E-mail: gjq161208@126.com

Abstract: Cardiomyopathy is a heart disease clinically characterized by enlargement of the heart, arrhythmia and heart failure alone or simultaneously. Ischemic cardiomyopathy is usually caused by coronary atherosclerotic lesions, but non-ischemic cardiomyopathy (NICM) is different. It is caused by non-coronary atherosclerotic lesions which can cause heart failure, arrhythmia, and even sudden death. However, the pathogeny, diagnosis and treatment methods of NICM are still unclear, and the efficacy needs to be explored further. The article analyzes the pathogeny, diagnosis, current status of drugs and non-drug treatment of NICM, aiming to provide more reference materials for the early prevention of patients with NICM and provide direction for the diagnosis and treatment of NICM.

Keywords: Non-ischemic cardiomyopathy; Dilated cardiomyopathy; Hypertrophic cardiomyopathy; Restrictive cardiomyopathy; Cardiac resynchronization therapy; Bone marrow stem cell transplantation; Radiofrequency ablation

非缺血性心肌病(non-ischemic ardiomyopathy, NICM)是一种由于非冠状动脉粥样硬化而导致的心脏结构和/或功能不全而导致的心源性心力衰竭。与缺血性心肌病相比，NICM 发病隐匿、病因缺乏特异性，其病因可以是遗传性、获得性或继发性全身性疾病，目前对该疾病的认识仍不全面，关于诊断和治疗尚不完善，本文对近年来 NICM 从病因学、诊断方法、治疗等作一综述，旨在提升患者的获益。

1　NICM 的病因

扩张型心肌病(dilated cardiomyopathy, DCM)是 NICM 常见的原因之一，其特征是心室扩张和收缩功能障碍。尽管在治疗方面取得了进展，DCM 的死亡率仍然很高，它是心脏移植的主要原因之一。近年来关于遗传因素和基因突变逐渐得到了关注，一些国外 NICM 患者，通常出现常染色体上显性遗传，此外，基因突变也成为了焦点，相关学者认为 β-肌球蛋白的缺失是家族性 NICM 的病因[1]。关于遗传性疾病和获得性疾病之间的相互作用一直是最近研究的焦点，这表明环境因素影响遗传背景的表达，因此在未来可能会更好地评估这类患者和新的治疗方法。

过去三十年的研究已经确定肥厚型心肌病(hypertrophic cardiomyopathy, HCM)是一种常染色体显性遗传疾病，由编码对收缩功能至关重要的肌节蛋白的基因中的致病变异引起[2]。涉及的两个最常见的疾病基因是 *MYBPC3* 和 *MYH7* 基因，这两个基因的致病变异占所有基因型阳性 HCM 患者的 70%~80%[3]。特征是左心室肥厚、心肌纤维化、氧化应激增强和能量消耗，最终导致心力衰竭和心律失常。对 HCM 遗传基础的了解增加预示着在精准医学的时代，基因检测使诊断更精确，在有风险的家庭成员中进行有效的基因检测，能够提

DOI: 10.13429/j.cnki.cjcr.2024.06.004

通信作者：郭建强，E-mail: gjq161208@126.com

出版日期：2024-06-20

QR code for English version

供更好的靶向治疗。

限制性心肌病(restrictive cardiomyopathy, RCM)的定义是心肌僵硬增加而导致的心室充盈受限,疾病后期会发生心力衰竭、心律失常和传导障碍等。与 HCM 或 DCM 相比,RCM 不太常见。RCM 通常由于心脏淀粉样变性、心脏结节病、心脏血色素沉着症导致。特征是左心室或右心室不扩张并伴有舒张期功能障碍。对于心脏收缩功能正常或接近正常、超声心动图上有限制性充盈模式的舒张期功能障碍的患者,应怀疑为 RCM。超声心动图对于确定舒张期功能障碍,区分 RCM 和缩窄性心包炎是必不可少的。但由于缺乏治疗,RCM 的预后是最差的,目前还没有已经明确直接针对 RCM 的治疗方法,未来还需要更多的方法来根据病因具体治疗[4]。

除了上述三种常见的病因以外,还存在高血压性心脏病、代谢性心肌病、瓣膜性心脏病等;还有全身性炎性疾病、药物毒性心肌病、围产期心肌病及其他原因不明的心肌病。对其明确的诊断是治疗及预后的关键。此类心肌病的主要表现为心肌结构和功能异常,如心肌肥厚、心腔扩张、心肌僵硬等,会导致心脏收缩功能下降、心律失常、心力衰竭等症状。诊断 NICM 需要经过详细的病史、体格检查、心电图、心脏超声、核磁共振等多种检查手段综合分析。治疗方法包括药物治疗、非药物治疗及植入心脏起搏器或心律转复除颤器、心脏移植等,具体治疗方案需要根据患者的病情和具体类型进行制定。

2　NICM 的诊断方法

2.1　*心电图*　作为诊断 NICM 的基本检查方法之一,可以显示心脏节律和心脏肥大等特征。心电图示窦性心动过缓或过速,也可能表现为心房或心室的早搏或异位搏动。心电图示 QRS 波群的时限可能有轻度或中度的延长,T 波的形态和振幅可能有改变。心电图可能显示心室肥厚和扩张的表现,如 ST 段改变、Q 波出现、电轴左偏等。心电图在 NICM 的诊断中并非特异性指标,在治疗过程中,心电图可以用于评估心脏电活动的变化和是否存在心律失常等问题。定期进行心电图检查可以帮助医生及时发现病情的变化,采取相应的治疗措施。需要注意的是,心电图只是 NICM 的一种诊断方法,诊断和治疗需要结合其他检查结果和临床症状综合考虑。

2.2　*心脏超声*　心脏超声还可以帮助医生区分不同类型的 NICM。心肌病变导致的心室肥大可能与高血压或其他原因引起的心室肥厚有所不同。心脏超声可以显示心室壁厚度、室间隔厚度、左室舒张末期内径等参数,NICM 可出现左室扩大,收缩功能明显减低以及室壁回声增强、室壁运动节段性降低,结合相关病史,有助于医生对不同类型的心肌病进行区分,能够提高临床的正确率及准确率。心脏超声还可以用于监测 NICM 的病情进展和治疗效果[5]。若临床医生高度怀疑 NICM,可能会进行进一步检查。

2.3　*心内膜下心肌活检*(endomyocardial biopsy, EMB)　EMB 是一种有创检查手段,目前仍然是确诊和病因学诊断的金标准,随着操作器械的不断更新以及免疫组化、病毒基因测序和等组织分析技术应用于临床,EMB 的使用频率也在提升。虽然现在缺乏具体的临床试验和指南,但进行 EMB 的临床适应证是基于专家意见的。最近的一项研究发现,EMB 对于 NICM 的检出率达到了 65%[6]。与 EMB 最直接明显的问题是如何选择心脏标本、是否需要双心室活检以及存在三尖瓣脱垂、心脏穿孔等风险。因此在临床疑似 NICM 的患者中,需要仔细收集病史、临床检查、心电图、超声心动图等,找到可靠的临床适应证以及最佳时机,才能规避风险,得到较好的预后,以此得到最大的获益。

2.4　*心脏磁共振*(cardiac magnetic resonance, CMR)　虽然 EMB 是金标准,但由于其有创,在临床上的应用不多,对 NICM 研究有一定的局限性。目前,无创的心脏成像技术已经成为诊断心肌疾病的一个重要手段。CMR 可能是评估心肌病的形态、功能和组织表型的最佳诊断工具。它被认为是评估心脏功能和形态学参数(如壁厚、左心室质量和体积)的金标准成像方式。CMR 能够通过组合不同的脉冲序列来表征心肌组织。然而,在所有不同的 CMR 技术中,晚期钆增强(late gadolinium enhancement, LGE)仍然是 CMR 与组织表征最相关的工具。Brendel 等研究发现 LGE 可用于评估心肌病的存活能力和描述心肌瘢痕形成[6]。最新的研究表明,采用 LGE 的患者受累节段数、厚度及年龄与非 LGE 患者有明显的不同[8]。说明此类特征可能在 CMR 是常见的特点。因此 LGE 在心肌病的诊断和预后评估中起着关键作用,每一位疑似心肌病的患者都应进行 LGE 技术的 MRI 检查。但缺乏脉冲序列的标准化是 LGE 技术的主要局限性。

3　NICM 临床治疗研究现状

在过去 20 余年间,随着标准化治疗方案的确立和完善,尤其是 β 肾上腺素能受体阻滞剂、血管紧张素转化酶抑制剂(angiotensin converting enzymeInhibitor, ACEI)或血管紧张素受体阻断剂(angiotensin receptor blocker, ARB)及醛固酮受体拮抗剂(aldosterone receptor antagonist, ARA)等在内的生物治疗模式,即所谓“指南指导的药物治疗(guideline-directed medical therapy, GDMt)”方案的推广和应用[8-10]。以及心脏再同步化治疗(cardiac resynchronization therapy, CRT)等非药物治疗措施的进展,显著改善了 NICM 患者的预后,不仅明显降低了其病死率,而且改善了部分 NICM 患者的左心室功能障碍和/或结构异常[11]。具体表现为左心室射血分数(left ventricular ejection fraction, LVEF)或缩短分数(fraction shortening, FS)的提高,伴或不伴有左心室舒张末期内径(left ventricular end-diastolic diameter, LVEDD)或容积(left ventricular end-diastolic volume, LVEDV)的缩小,即发生了所谓的“左心室逆重构(left ventricular reverse remodeling, LVRR)”[12-15]。从 WHO 撰写全球第一个心肌病分类指南到 2008 年 ESC 分类描述区分了原发/继发心肌病概念,对心肌病的分型重新进行了定义,包括 DCM、HCM、RCM、致心律失常性右室心肌病、未定型心肌病等。不同类型的心肌病预后有很大的区别,以下将从药物治疗及非药物治疗做具体阐述,为临床医生对该

类疾病早期干预提供一些思路。

3.1　*药物治疗*

3.1.1　抗心室重构——β 受体阻滞剂　β 受体阻滞剂是改善症状一线治疗药物,当无禁忌证时,应常规使用,在合并心力衰竭的情况,无论是射血分数保留的心力衰竭(heart failure with preserved ejection fraction, HFpEF)亦或是射血分数降低的心力衰竭(heart failure with reduced ejection fraction, HFrEF)均可选用美托洛尔、比索洛尔等,根据心率血压等从小剂量开始,逐渐增加至最大耐受剂量(患者能够耐受情况下静息心率达到 55~60 次/min)。相关研究显示,早期的合理使用,能明显降低 NICM 的死亡率、再住院率及猝死风险。对于合并心律失常的患者,节律的控制反而变得更重要,尽管胺碘酮一般是首选,但在联合使用 β 受体阻滞剂后能够更好地控制,并改善预后。

3.1.2　抑制肾素系统——ACEI/ARB　ACEI 不仅有降压功能,而且还能够延迟和逆转心室重构,从而阻止了心脏肥厚的发生,提高了血管内皮功能和心功能,也可以明显降低 HFrEF 患者的住院费用和死亡率。ACEI 是基石药物,只要确定了心力衰竭患者,无论严重程度,都应该早期使用。因 ACEI 类药物呈剂量依赖性,小剂量使用对血流动力学影响小,应从小剂量开始,每隔两周加倍,直到达到治疗靶剂量。同时定期检测血压、血钾及肾功能、避免突然停药。由于一些患者对 ACEI 反应性较差,ARB 耐受性好,长久应用可改善血流动力学,应用方法及不良反应监测同 ACEI,一项具有里程碑的试验显示,ACEI/ARB 可将心力衰竭死亡率降低 20%~30%。此外 CHARM-added 试验还证实了 ACEI 基础上加用 ARB 后,能显著降低心血管疾病和心力衰竭住院风险,同时也会加剧肾功能恶化和增加高钾血症发生的概率。因此对于 HFrEF 患者,在治疗选择上,应根据实际情况选择合理的药物。

3.1.3　钠-葡萄糖协同转运蛋白 2(sodium-dependent glucose transporters 2, SGLT-2)抑制剂　SGLT-2 抑制剂首先是作为一种降糖药物应用的,尤其是针对 2 型糖尿病患者。早期心血管试验结果表明,在心血管疾病高危的乙型糖尿病患者中,心力衰竭住院风险降低 30%~35%。其他更有效的降压治疗未能降低 2 型糖尿病患者的心血管风险,提示 SGLT2 抑制剂具有独立于降糖能力的心脏保护作用。一项荟萃分析显示,在同时合并 HFrEF 的 2 型糖尿病患者,早期的干预治疗,能很好改善心室重构,同时能显著降低心血管疾病的死亡率[16]。SGLT2 抑制剂可使整个射血分数范围内的心力衰竭获益,但 SGLT2 抑制剂可使生存获益的确切机制尚未完全确定。但仍推荐伴或不伴 2 型糖尿病的 HFrEF 患者使用 SGLT2 抑制剂,提高生活品质及改善临床症状,降低因心力衰竭的住院率及死亡率。

3.1.4　醛固酮受体拮抗剂　醛固酮具有诸多病理生理功能,其能够诱发中枢性高血压,促进组织损害,诱导室性或严重心律失常,促进钠潴留,促使心肌纤维化。醛固酮受体拮抗剂(mineralcorticoid receptor antagonist, MRA)螺内酯可用于腹水和心源性水肿的患者,其已经被证实可显著提升 HFrEF 患者的预后。《2018 中国心力衰竭诊断和治疗指南》指出 HFrEF 患者宜先小剂量应用 ACEI/ARB 和 β 受体阻滞剂,并逐步提高至目标用量,再根据需要应用利尿药。如果临床症状不改善,且 eGFR≥30 mL·min^{-1}·1.73 m^{-2},血钾<5.0 mmol/L,则考虑使用 MRA 干预,也就是说在临床工作中,根据患者的现实情况及临床表现考虑是否使用 MRA,并不是越早进行使用越好,事实上很多时候都是在使用袢利尿剂的同时使用了螺内酯。依普利酮是一种新型选择性醛固酮受体拮抗剂,能显著地降低血压,在联合多种降压药物后血压未达标,加用依普利酮可使血压有明显的降低。与 ACEI 和 β 受体阻滞剂同时应用治疗对 HFrEF 可提高患者生活品质和降低死亡率。

3.1.5　利尿剂　由于心力衰竭会不可避免地导致体液潴留,因此利尿剂一直以来就是心力衰竭治疗中的推荐药物,利尿剂可分为袢利尿剂、噻嗪类利尿剂和保钾利尿剂,这三类利尿剂的作用强度依次降低。根据美国心力衰竭协会指南建议,慢性心力衰竭口服利尿剂治疗建议呋塞米 20 mg 开始。研究显示,长期使用袢利尿剂能明显提高患者生存率,同时联合利尿剂治疗,可能会使心力衰竭或肾衰竭的多重受益。但也同时存在电解质紊乱的风险。因此不管是单用还是联合用药,均需要根据患者心力衰竭症状、体征、体重、尿量来选择最佳方案。

由于 NICM 的治疗更需要根据心肌病的类型,选择合理的治疗手段,以上两种药物只是基础治疗,比如 HCM 在药物治疗方面更需要去减少心肌的重构,改善心律失常,而 DCM 患者需要抗心力衰竭、抗凝等。如果合并严重的心力衰竭,根据心功能分期,按照 AHA/ACC/HFSA 心力衰竭管理指南合理用药,包括可能需要用利尿剂,或者扩血管药物,对于顽固的心力衰竭,还可以用人重组脑利钠肽,或者钙离子拮抗剂,因此对于 NICM 临床上需要根据诊断,明确心肌病的类型及所导致的并发症对因治疗,希望在未来会有更标准化的药物治疗方案。

3.2　*非药物治疗*

3.2.1　CRT　CRT 是非药物治疗的新手段,由于 NICM 后期一般都会进展到慢性充血性心力衰竭(chronic congestive heart failure, CHF),因此对于 NYHA Ⅱ 级或以上的患者药物治疗的效果不佳,无法提升远期的生存质量,CRT 就成为了非药物治疗的主流手段,通过起搏装置加强心房和心室的同步性机械运动,大量的研究表明 CRT 在治疗 NICM 方面的疗效更好,能够逆转左室肥厚、改善心功能、防止心律失常的发生[16-17]。最初的单点起搏并不能很好地预测最佳起搏位置,由于受到心室激动顺序及时间的影响,使高达 40%的患者对 CRT 无反应,四极导联或更多导联能够刺激更多的左心室区域提高对 CRT 的反应。有研究首次报道,与传统的双室起搏相比,这种新的左心室起搏方式在血流动力学改善、LVEF 的提供和减少不同步方面具有优势[18-19]。但未来还需要大量的、多中心的样本证明多点起搏的安全性及有效性。

3.2.2　骨髓干细胞(bone marrow mononuclear cells, BMMC)移植　在过去的几年中,BMMC 的应用在临床中显示出优势。骨髓单个核细胞在缺血性心肌病和急性心肌梗死的治疗中具有重要作用。然而,在 NICM 中的研究数据较少[20-21]。干细

胞对细胞因子的分泌具有旁分泌调节机制,在细胞转分化中发挥作用。经冠状动脉内途径应用 BMMC 被证明是安全的,并且在治疗后显示 LVEF 显著增加,在 BMMC 的冠状动脉内应用中,一小部分移植细胞在心肌中保持有效。一些研究发现,直接心肌内注射 BMMC 是安全的,并且能提升 NICM 的射血分数。关于 BMMC 的疗效,以往的临床试验一直存在争议。最新的一项荟萃分析显示,BMMC 移植能明显提升 LVEF 及减少 LVEDD。

3.2.3　射频消融术　NICM 后期很容易导致室性心律失常,虽然植入式复律除颤器(implantable cardioverter defibrillator, ICD)能有效地防止猝死,但患者症状可能会复发,同时抗心律失常药物也有一定的副作用,射频消融术在 NICM 患者中还是非常有效的,一项随机试验显示,射频消融带来的效果远优于药物,能够很好的改善患者预后,降低心脏移植及死亡率。2019 年《HRS 室性心律失常导管消融专家共识》推荐:NICM 患者反复持续性单形性室性心动过速、抗心律失常药无效、禁忌或不耐受,选择射频消融有助于减少室性心动过速的复发和埋藏式心脏复律除颤器电击。但 NICM 与 ICM 不同,NICM 更加复杂,消融难度更高,消融成功率更低,根据最新研究报道,采用立体定向体部放疗(stereotactic body radiotherapy, SBRT)对治疗难治性室性心动过速有很显著的效果,为未来难治性心律失常提供了新思路。

4　结　论

NICM 是一类非常危险的心脏疾病,发病率不断上升。目前治疗方法尚未成熟。基因编辑技术近年来已经非常先进,在未来可以用于修复、改变或调节与心肌疾病相关的基因。这对于治疗一些家族遗传性 NICM 具有重要意义,目前可选择的药物疗法对于改善此类心肌病患者的生存质量和预后已有明显作用,但仍存在限制和不足。未来应继续加强药物疗法研究,开发新型分子、基于 RNA 干扰的新技术等。NICM 可能导致心室壁运动减弱或心室扩张等问题,这些问题与心脏电信号的异常有关。未来的治疗方向可以包括生物电控制和修复技术,旨在通过控制心脏电信号来恢复心室功能。NICM 的发生也与神经调节失衡有关,因此神经调控治疗是一个可能的未来方向。通过调整交感神经和副交感神经的平衡,可以改善心脏功能并降低患者的死亡风险。

总之,随着医疗技术的不断发展,NICM 的治疗也将不断完善和创新。未来的治疗方向需要兼顾科技水平、生物学和临床实践等因素,注重提高治疗效果同时保证患者的安全和舒适度。

利益冲突　无

参考文献

[1] de Frutos F, Ochoa JP, Navarro-Peñalver M, et al. Natural history of MYH7-related dilated cardiomyopathy[J]. J Am Coll Cardiol, 2022,80(15):1447-1461.

[2] Karatsai O, Lehka L, Wojton D, et al. Unconventional myosin VI in the heart: involvement in cardiac dysfunction progressing with age [J]. Biochim Biophys Acta BBA Mol Basis Dis, 2023, 1869(6): 166748.

[3] Marsili L, van Lint FV, Russo F, et al. MYH7 p.(Arg1712Gln) is pathogenic founder variant causing hypertrophic cardiomyopathy with overall relatively delayed onset[J]. Neth Heart J, 2023, 31: 300-307.

[4] Brodehl A, Gerull B. Genetic insights into primary restrictive cardiomyopathy[J]. J Clin Med, 2022, 11(8): 2094.

[5] 左璨粲,许卫.超声心动图联合经皮左心室造影对鉴别缺血性心肌病与扩张型心肌病的应用研究[J].影像研究与医学应用,2022,6(11):59-61.
Zuo CC, Xu W. Application of echocardiography combined with percutaneous left ventricular angiography in differentiating ischemic cardiomyopathy from dilated cardiomyopathy[J]. J Imag Res Med Appl, 2022, 6(11): 59-61.

[6] 李乐,刘尚雨,吴灵敏,等.复杂室性心律失常合并心肌炎患者的临床特点与心内膜心肌活检的诊断价值[J].中国循环杂志,2023,38(6):669-674.
Li L, Liu SY, Wu LM, et al. Clinical features of patients with complex ventricular arrhythmia and myocarditis: diagnostic value of endocardial myocardial biopsy[J]. Chin Circ J, 2023, 38(6): 669-674.

[7] Brendel JM, Holtackers RJ, Geisel JN, et al. Dark-blood late gadolinium enhancement MRI is noninferior to bright-blood LGE in nonischemic cardiomyopathies[J]. Diagnostics (Basel), 2023, 13(9): 1634.

[8] 张莉莎,郜发宝.MR 组织追踪技术对扩张性心肌病的评估价值[J].临床放射学杂志,2023,42(1):168-171.
Zhang LS, Gao FB. Evaluation value of mr tissue tracking technique in dilated cardiomyopathy[J]. J Clin Radiol, 2023, 42(1): 168-171.

[9] Terentes-Printzios D, Gardikioti V, Latsios G, et al. Aortic systolic blood pressure predicts periprocedural myocardial injury after transcatheter aortic valve implantation[J]. Eur Heart J, 2021, 42 Supplement_1: ehab724.2333.

[10] Sun RR, Chen TZ, Meng M. Hypereosinophilic syndrome presenting as acute ischemic stroke, myocardial infarction, and arterial involvement: a case report[J]. World J Clin Cases, 2022, 10(11): 3547-3552.

[11] Feng LL, Tian RF, Mu XD, et al. Identification of genes linking natural killer cells to apoptosis in acute myocardial infarction and ischemic stroke[J]. Front Immunol, 2022, 13: 817377.

[12] Iyer Nithin R, Thao LT, Kui Michelle SL, et al. Markers of focal and diffuse nonischemic myocardial fibrosis are associated with adverse cardiac remodeling and prognosis in patients with hypertension: the REMODEL study[J]. Hypertension, 2022, 79(8):1804-1813.

[13] Tat E, Ball C, Camren B, et al. Impact of late gadolinium enhancement extent, location, and pattern on ventricular tachycardia and major adverse cardiac events in patients with ischemic *vs*. non-ischemic cardiomyopathy[J]. Front Cardiovasc Med, 2022, 9: 1026215.

(下转第 871 页)

tion increased only endothelium-dependent relaxation in sprague-dawley rats fed a high-salt diet by enhancing abdominal aorta endothelial nitric oxide synthase gene expression[J]. Clin Med Insights Cardiol, 2020, 14: 1179546820902843.

[18] Cheng LL, Wang L, Guo MY, et al. Clinically relevant high levels of human C-reactive protein induces endothelial dysfunction and hypertension by inhibiting the AMPK-eNOS axis [J]. Clin Sci (Lond), 2020, 134(13): 1805-1819.

[19] Chi ZX, Le TPH, Lee SK, et al. Honokiol ameliorates angiotensin Ⅱ-induced hypertension and endothelial dysfunction by inhibiting HDAC6-mediated cystathionine γ-lyase degradation[J]. J Cell Mol Med, 2020, 24(18): 10663-10676.

[20] Dangudubiyyam SV, Mishra JS, Zhao HJ, et al. Perfluorooctane sulfonic acid (PFOS) exposure during pregnancy increases blood pressure and impairs vascular relaxation mechanisms in the adult offspring[J]. Reproductive Toxicol, 2020, 98: 165-173.

[21] 熊金丹,颜福根,李家志,等.早期高压氧联合康复训练对高血压脑出血钻孔置管引流术后患者神经功能康复及预后的影响研究[J].中国医师进修杂志,2021,44(6):553-558.
Xiong JD, Yan FG, Li JZ, et al. Effect of early hyperbaric oxygen combined with rehabilitation training on neurological rehabilitation and prognosis of patients with hypertensive intracerebral hemorrhage after borehole drainage[J]. Chin J Postgrad Med, 2021, 44(6): 553-558.

[22] 李霞,折盼,马晓媛.抗阻力锻炼结合穴位按摩对高血压脑出血患者生理指标的影响[J].贵州医药,2020,44(3):384-386.
Li X, She P, Ma XY. Effect of resistance exercise combined with acupoint massage on physiological indicators in patients with hypertensive intracerebral hemorrhage [J]. Guizhou Medical Journal, 2020, 44(3): 384-386.

[23] Wilson C, Zhang X, Lee MD, et al. Disrupted endothelial cell heterogeneity and network organization impair vascular function in pre-diabetic obesity[J]. Metabolism, 2020, 111: 154340.

[24] Yang X, Niu N, Liang C, et al. Stimulation of epithelial sodium channels in endothelial cells by bone morphogenetic protein-4 contributes to salt-sensitive hypertension in rats[J]. Oxidative Med Cell Longev, 2020, 2020: 3921897.

[25] Yoshida M, Nakamura K, Miyoshi T, et al. Combination therapy with pemafibrate (K-877) and pitavastatin improves vascular endothelial dysfunction in dahl/salt-sensitive rats fed a high-salt and high-fat diet[J].Cardiovasc Diabetol, 2020, 19(1): 149.

[26] Yoshitomi H, Zhou JX, Nishigaki T, et al. *Morinda citrifolia* (Noni) fruit juice promotes vascular endothelium function in hypertension via glucagon-like peptide-1 receptor-CaMKKβ-AMPK-eNOS pathway[J]. Phytother Res, 2020, 34(9): 2341-2350.

[27] Zhou TT, Wang ZW, Guo MT, et al. Puerarin induces mouse mesenteric vasodilation and ameliorates hypertension involving endothelial TRPV4 channels[J]. Food Funct, 2020, 11(11): 10137-10148.

[28] 张园园,冯慧,开绍江,等.有氧结合抗阻训练对原发性高血压患者血压变异性及血液相关指标的影响[J].中华物理医学与康复杂志,2019,41(5):348-352.
Zhang YY, Feng H, Kai SJ, et al. Aerobic exercise combined with mild to moderate circulatory resistance exercise can improve blood pressurevariability and other circulatory indexes of persons with hypertension[J]. Chin J Phys Med Rehabil, 2019, 41(5): 348-352.

[29] Park SH, Farooq MA, Gaertner S, et al. Empagliflozin improved systolic blood pressure, endothelial dysfunction and heart remodeling in the metabolic syndrome ZSF_1 rat[J]. Cardiovasc Diabetol, 2020, 19(1): 19.

[30] Pingili Ajeeth K, Jennings Brett L, Kamalika M, et al. 6β-Hydroxytestosterone, a metabolite of testosterone generated by CYP1B1, contributes to vascular changes in angiotensin Ⅱ-induced hypertension in male mice[J]. Biol Sex Differ, 2020, 11(1): 4.

收稿日期:2023-06-12　**修回日期**:2023-08-10　**编辑**:王娜娜

(上接第 838 页)

[14] Ajufo E, Ayers CR, Vigen R, et al. Value of coronary artery calcium scanning in association with the net benefit of aspirin in primary prevention of atherosclerotic cardiovascular disease[J]. JAMA Cardiol, 2021, 6(2): 179.

[15] Chen HS, Jungen C, Kimura Y, et al. Ventricular arrhythmia substrate distribution and its relation to sympathetic innervation in nonischemic cardiomyopathy patients[J]. JACC, 2022, 8(10): 1234-1245.

[16] 王凯阳,杨燕,祖丽皮耶·艾乃斯,等.4 种 SGLT2 抑制剂治疗射血分数降低的心力衰竭有效性和安全性的网状 meta 分析[J].临床心血管病杂志,2023,39(1):21-28.
Wang KY, Yang Y, Zulipiye Ainaisi , et al. Efficacy and safety of four SGLT2 inhibitors in the treatment of heart failure with reduced ejection fraction: a network meta-analysis [J]. J Clin Cardiol, 2023, 39(1): 21-28.

[17] Thibault B, Dubuc M, Khairy P, et al. Acute haemodynamic comparison of multisite and biventricular pacing with a quadripolar left ventricular lead[J]. Europace, 2013, 15(7): 984-991.

[18] Cojan-Minzat BO, Zlibut A, Agoston-Coldea L. Non-ischemic dilated cardiomyopathy and cardiac fibrosis[J]. Heart Fail Rev, 2021, 26(5): 1081-1101.

[19] Yang SW, Liu ZM, Hu YR, et al. A novel risk model for mortality and hospitalization following cardiac resynchronization therapy in patients with non-ischemic cardiomyopathy: the alpha-score[J]. BMC Cardiovasc Disord, 2020, 20(1): 205.

[20] Mehta VS, Elliott M, Sidhu B, et al. Multipoint pacing for cardiac resynchronisation therapy in patients with heart failure: a systematic review and meta-analysis[J]. J Cardiovasc Electrophysiol, 2021, 32: 2577-2589.

[21] Schiedat F, Bogossian H, Schöne D, et al. Long-term performance comparison of bipolar active *vs*. quadripolar passive fixation leads in cardiac resynchronisation therapy[J]. Front Cardiovasc Med, 2021, 8: 734666.

收稿日期:2023-08-09　**编辑**:王海琴