RESEARCH PAPER

Myocardial Fibrosis in the Pathogenesis, Diagnosis, and Treatment of Hypertrophic Cardiomyopathy

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Abstract

Hypertrophic cardiomyopathy (HCM) is a type of hereditary cardiomyopathy caused by gene mutation. Its histological features include cardiomyocyte hypertrophy and disarray as well as myocardial fibrosis. Gene mutation, abnormal signal transduction, and abnormal energy metabolism are considered the main mechanisms of myocardial fibrosis. There is a strong correlation between myocardial fibrosis and the occurrence, development, and prognosis of HCM. We review the application of myocardial fibrosis in the diagnosis and treatment of HCM, focusing on research progress and the application of magnetic resonance imaging on the basis of the characteristics of fibrosis in the diagnosis and prognosis of HCM.

Keywords: Hypertrophic cardiomyopathy; myocardial fibrosis; review

Introduction

Hypertrophic cardiomyopathy (HCM) is one of the most common genetic cardiomyopathy diseases, and is characterized by asymmetric myocardial hypertrophy, with the greatest involvement most commonly of the left ventricle and the interventricular septum. However, myocardial hypertrophy cannot be explained only by abnormal loading conditions [1]. HCM is the leading cause of sudden cardiac death (SCD) in adolescents and athletes. The prevalence of HCM has been estimated to range from 0.16% to 0.29% in the global population [2].

In China, there are currently more than one million HCM patients, and the annual mortality rate ranges from 2% to 4% among hospitalized patients [3].

HCM is transmitted by an autosomal dominant pattern of inheritance in most cases. Autosomal recessive, X-linked modes of inheritance and mitochondrial inheritance have been described but are rare [1]. At present, 27 causal genes have been reported encoding sarcomere-associated proteins. Among the known causal genes, the β-isoform myosin heavy chain gene (*MYH7*) and the myosin-binding protein C gene (*MYBPC3*) are the two most common causes of HCM. Mutations not only impair Ca^{2+} cycling and sensitivity but also affect myocardial metabolism and energetics. Consequently, myocardial fiber disarray and myocardial fibrosis occur as well as myocardial hypertrophy. Histological

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analysis verifies that myocardial hypertrophy, disorder of myofibril arrangement, and fibrosis occur in HCM. Myocardial fibrosis is one of the significant characteristics of HCM, and its severity is closely related to the progression and prognosis. Bittencourt et al. [4] reported that myocardial fibrosis is the main risk factor for SCD in HCM patients. Late gadolinium enhancement (LGE) and T1 imaging as cardiac magnetic resonance imaging (CMRI) techniques are the recommended methods to assess the degree of myocardial fibrosis in patients with HCM. It is suggested that the presence and extent of LGE have a significant correlation with quantitative assessment of myocardial fibrosis. Therefore, it is used as an important method to diagnose and evaluate prognosis. However, the concrete role of myocardial fibrosis in the development and prognosis of HCM is still unclear.

In this review, we aim to introduce the association between myocardial fibrosis and the pathogenesis, diagnosis, and treatment of HCM. On the basis of the characteristics of fibrosis in HCM, we focus on the use of CMRI for diagnosis and prognosis.

The Mechanism of Myocardial Fibrosis in HCM

"Myocardial fibrosis" refers to dysregulated collagen metabolism in the extracellular matrix (ECM). The imbalance between synthesis and degradation of collagen leads to excessive deposition of collagen, which increases stiffness and decreases compliance [1]. Cardiac fibroblasts are the main components of the myocardial interstitium, and secrete ECM proteins and mediate the turnover of proteins. Therefore, increased collagen synthesis and cardiac fibroblast activation play a vital role in the pathology of myocardial fibrosis. It was observed that serum levels of propeptide of procollagen type I in HCM patients with pathogenic sarcomere gene mutations but normal cardiac morphology increased. This finding means fibrosis occurs early and precedes the presence of cardiac hypertrophy. Meanwhile, it also confirms that myocardial fibrosis is not secondary to myocardial hypertrophy. As discovered in cardiac tissues from 30 HCM patients undergoing transplantation, Galati et al. [5] reported that almost every cardiac tissue had 23–56% myocardial

fibrosis. There are many subtypes of myocardial fibrosis in HCM patients, including mainly perivascular fibrosis, interstitial fibrosis, and replacement fibrosis. Replacement fibrosis is most common, and is the basis of heart failure and arrhythmia in HCM patients. Young patients with SCD and elderly patients with advanced heart failure experience severer fibrosis. Increased myocardial fibrosis not only impairs cardiac diastolic function but also increases the propensity of heart failure and ventricular arrhythmias. However, the mechanism of myocardial fibrosis in HCM is still unclear.

Genetic Basis

As a typical genetic disorder of cardiac myocytes, three-fifths of HCM patients have genetic mutations; mutation of a single gene encoding sarcomere structural proteins is most common. Of all mutations, *MYH7* and *MYBPC3* mutations are responsible for approximately three-quarters of patients with HCM. Mutations in the genes that encode troponin I (*TNNI3*), troponin T (TNNT2), tropomyosin α1 chain (*TPM1*), and myosin light chain 3 (*MYL3*) account for less than 10% of cases. Mutations in the genes encoding telethonin, ankyrin repeat domain 1 (*ANKRD1*), phospholamban (*PLN*), and junctophilin 2 (*JPH2*) can also lead to HCM, but such mutations are rare.

The presence of myocardial fibrosis might be the primary defect of sarcomere gene mutations. In mice carrying a sarcomere mutation, researchers revealed that genes involved in the formation of ECM are significantly upregulated early [6]. Mutations could stimulate the proliferation of noncardiomyocytes and induce an increase in the expression of fibrogenic molecules, accounting for pathological remodeling of myocardial tissue [7]. Therefore, compared with negative genetic test patients, genotype-positive individuals have severer ventricular hypertrophy, microvascular metabolism dysfunction, and myocardial fibrosis [8]. At the same time, mutations could affect the process of transcription and translation, which results in the abnormal structure and function of sarcomeric proteins. In autosomal dominant cases, a small number of gene mutations lead to premature truncation of the encoded protein, and the ubiquitin-proteasome system will degrade the misfolded protein [9]. However,

the specific mechanism of cardiac myocyte–specific mutations in the sarcomere gene to increase myocardial fibrosis still needs more research.

Ca²⁺ Pathway

Ca^{2+} pathway disorder is one of the main pathways leading to myocardial fibrosis in HCM [10]. On the one hand, sarcomere gene mutations can increase Ca^{2+} sensitivity and slow down the release of Ca^{2+} from troponin C, which prolongs the attenuation of Ca^{2+} transients and increases the concertation of Ca^{2+} in the diastolic phase. On the other hand, sarcomere gene mutations can account for ATP depletion, impair the function of sarcoplasmic reticulum Ca^{2+}-ATPase (SERCA), and reduce the rate of recovery of Ca^{2+} from cytoplasm during the diastolic phase. Consequently, the overload of Ca^{2+} in the cytoplasm and sarcoplasmic reticulum is aggravated, which could result in calmodulin-dependent protein kinase II (CaMKII) being continuously activated. CaMKII can regulate the expression of genes involved in myocardial remodeling, and promote the differentiation of cardiac fibroblasts, the production of collagen, and increase of ECM [11]. In an animal experiment, researchers found that *TNNC1* mutation increased Ca^{2+} sensitivity and activated the calcineurin and mitogen-activated protein kinase kinase 1 (MEK1)/extracellular signal–regulated kinase (ERK) signaling pathways, resulting in cardiomyocyte enlargement and centripetal hypertrophy. Besides, studies show that increased Ca^{2+} sensitivity can shorten the effective refractory period in ventricular myocytes and significantly increase the risk of arrhythmia [12].

Transforming Growth Factor β

Transforming growth factor β (TGF-β) is the most effective fibrogenetic cytokine, and can promote the differentiation of fibroblasts to activated myofibroblasts. Similarly, it is the key mediator in the activation and fibrosis of fibroblasts [13]. Besides, TGF-β can activate the TGF-β/SMAD pathway to promote the development of fibrosis [14].

Renin-Angiotensin-Aldosterone System

Experimental data in transgenic mice that express mutant cardiac troponin T (cTnT-Q92) show that angiotensin II can not only aggravate myocyte disarray and interstitial fibrosis but can also increase the level of aldosterone significantly [15]. Several studies conclude that angiotensin II can decrease the activation of matrix metalloproteinase 1 and the expression of TGF-β1 through type I angiotensin receptor, and can stimulate the synthesis and release of aldosterone [16].

Diagnosis of HCM at the Progressing Stage

Although the diagnosis of HCM is based mainly on genetic testing, with deepening research, it is being realized that myocardial fibrosis, oxidative stress, microcirculation ischemia, and hemodynamic abnormalities also play an important role in the development of HCM. Therefore, proteomic analysis and imaging based on this are increasingly being applied in clinical phenotypic studies, especially in patients with HCM at the progressing stage. Myocardial fibrosis is closely related to advanced heart failure, arrhythmia, SCD, and so on. Therefore, CMRI and specific biomarkers have a significant prospect for evaluation of myocardial fibrosis and risk stratification.

Cardiac Magnetic Resonance Imaging

Although most HCM patients have a good prognosis, a minority have adverse events, such as SCD, heart failure, and ventricular arrhythmia. Because of the diversity of phenotypes and clinical manifestations, we cannot thoroughly identify patients who are at risk of having a bad prognosis. There remains a clinical need to identify accurate and simple tools for risk stratification. Myocardial fibrosis plays a vital role in the development of HCM. Consequently, detecting the presence of fibrosis can help us diagnose HCM early and evaluate the prognosis. CMRI, as the gold standard imaging technique to assess cardiac fibrosis and edema as well as inflammation, characterizes the phenotypes of HCM in detail and has become the gold standard for evaluation in patients with HCM. CMRI provides a comprehensive evaluation of wall thicknesses, both ventricles, and cardiac volumes, with spatial and

temporal resolution in all planes. Massera et al. [17] reported the effectiveness of CMRI in detecting cardiac hypertrophy was greater than that of other imaging methods, with a 1.4% detection of left ventricular hypertrophy among assumed healthy people.

CMR can identify the phenotypic expression of HCM and give us a more accurate assessment of the stage of HCM. Replacement fibrosis is common in HCM patients, diffusion of gadolinium into the interstitial space between cells needs more time compared with normal myocardium, resulting in accumulation and delayed clearance. Consequently, the concentrations of gadolinium are increased, and there is obvious enhancement in tissues with fibrosis. The myocardial scars shown by LGE are usually located at the insertion of the left and right ventricles or in the most hypertrophic area of the myocardium. LGE can be used to identify the area of myocardial fibrosis and comprehensively evaluate the morphological structure and function. Chan et al. [18] demonstrated that LGE limited to the insertion areas of the right ventricle to the ventricular septum was related to low risk of adverse events (including SCD), but this unique LGE pattern by itself cannot be recognized as a marker to predict adverse prognosis in HCM. Meanwhile, gadolinium pooling in the left ventricle to the ventricular septum does not reflect myocyte death and repair with replacement fibrosis or scarring, but according to Bittencourt et al. [4] the presence of LGE outside interventricular insertion points was associated with increased risk of SCD or its equivalent as well as overall mortality.

Adabag et al. [19] found that patients with LGE have a sevenfold higher risk of developing non-persistent ventricular tachycardia than patients without LGE (relative risk 7.3, 95% confidence interval 2.6–20.4, $P < 0.0001$) and that a weight of myocardial scar more than 7 g on LGE can predict the risk of ventricular tachycardia with a sensitivity of 75% and a specificity of 82%. Similarly, Sakamoto et al. [20] pointed out that the spatial distribution of LGE highly relates to depolarizing and repolarizing electrical damage in high-risk HCM with malignant ventricular arrhythmia. Chan et al. [21] reported that the extent of LGE is associated with the progression of HCM ($P < 0.001$). Bittencourt et al. [4] confirmed the association of myocardial fibrosis and other risk markers with critical arrhythmic outcomes in HCM and stressed the need for new prediction models in diagnosing and treating these patients.

Although LGE as a noninvasive assessment can evaluate myocardial fibrosis, it cannot evaluate myocardial fibrosis quantitatively and identify diffuse fibrosis [22]. T1 imaging can identify diffuse myocardial fibrosis and quantitatively evaluate the degree of fibrosis. This technique is based on each tissue having its own specific T1 relaxation time, and the T1 relaxation time may be different in the same tissue with different pathophysiological conditions. In HCM patients without significant left ventricular hypertrophy, the T1 value on plain scan increased, which suggests that it can be used as an examination method for early diagnosis [23]. The enhanced T1 value is obtained after injection of gadolinium. Extracellular volume (ECV) fraction, calculated by enhanced T1, can distinguish whether fibrosis is caused by myocardial ischemia or nonischemia. Therefore, T1 mapping can distinguish HCM from other diseases that also cause ventricular hypertrophy, such as hypertensive cardiomyopathy, aortic valvular disease, cardiac deposition disease, and physiological cardiac hypertrophy associated with high-level athletes. Professional athletes have physiological myocardial hypertrophy after long-term intensive exercise, which is difficult to distinguish from cardiac hypertrophy caused by HCM. ECV fraction can solve the difficulty because ECV fraction increases with the progression of left ventricular hypertrophy in patients with HCM [24]. Inversely, in athletes engaging in long-term strenuous exercise, ECV fraction decreases with the increase of ventricular wall hypertrophy [25].

Compared with dense scars, the formation of interstitial fibrosis is a reversible dynamic process. We presume that novel therapies targeted for interstitial fibrosis have the prospect to change pathophysiological processes, finally blocking the progression and reducing the risk of arrhythmias and heart failure in HCM [26].

Current Treatment Methods for HCM

Medication

The main purpose of the clinical treatment of HCM is to improve quality of life and prevent SCD and other life-threatening complications. β-Adrenoceptor blockers and non-dihydropyridine calcium channel blockers are the main drugs for the treatment of HCM at present. With the comprehensive knowledge of the pathogenesis of HCM, aiming at the prevention of hypertrophy and fibrosis has become a new strategy.

Mavacamten

Mavacamten is an inhibitor of the specific myocardial contractile protein myosin, and reduces the binding time of myosin and actin, thereby reducing myocardial contractility and alleviating the pressure difference of the left ventricular outflow tract. This small-molecule muscle nodal protein inhibitor inhibits the activity of the ATPase of the myosin head and has shown good results in both basic and phase II clinical trials [1].

Angiotensin-Receptor Blockers

The role of the renin-angiotensin-aldosterone system in the process of myocardial fibrosis has been described in detail. For HCM patients without outflow tract obstruction, angiotensin-receptor blockers may alleviate the adverse effects of early myocardial fibrosis. An animal experiment has found that losartan can inhibit the expression of type I collagen and TGF-β1 in the heart of cTnT-R92Q mice, so losartan may be a potential drug to reverse or alleviate interstitial fibrosis [15]. Similarly, valsartan can inhibit the synthesis of type I collagen in patients with HCM, which may reduce fibrosis. A valsartan phase II placebo-controlled trial is currently under way to include HCM mutant carriers (NCT01912534) with mostly asymptomatic or mild early symptoms [27].

Spironolactone

Aldosterone is a mediator of myocardial fibrosis and is associated with cardiac hypertrophy, myocardial fibrosis, and disorders in HCM. In the genetically engineered HCM mutant mouse model, spironolactone can normalize myocardial collagen content, reduce myocardial cell structural disorder, and improve diastolic function [28]. However, the results of a recent clinical trial showed that the use of spironolactone did not reduce the markers of myocardial fibrosis in patients with HCM [29].

Statins

In the HCM transgenic rabbit model, statins can significantly reduce interstitial fibrosis and reduce diastolic dysfunction [30]. However, in a placebo-controlled randomized double-blind trial, in the group of patients with HCM who received 80 mg atorvastatin for 9 months no significant increase in left ventricular mass was found [31]. Considering the heterogeneity of the causes and genetic background of HCM, the inhibitory effect of statins on cardiac hypertrophy may be limited to several types of HCM, so larger sample size studies are needed to further confirm its effectiveness.

Resection of Interventricular Septal Myocardium

For HCM patients with high outflow tract pressure gradient, interventricular septal myocardial resection is the gold standard for symptomatic treatment. It includes mainly the classical Morrow operation and the modified extended Morrow operation. The degree of left ventricular outflow tract obstruction is reduced and cardiac function is recovered after the operation.

Interventional Therapy

Percutaneous interventricular septal ablation can be performed in patients with high surgical risk. By injection of absolute ethanol, the septal branch of the coronary artery is occluded, which decreases myocardial ischemia, necrosis, and contractility of the hypertrophic interventricular septum, widens the left ventricular outflow tract, and reduces the pressure gradient of the left ventricular outflow tract. After the operation, there is an increase in the levels of serum matrix metalloproteinases and a decrease in the levels of tissue inhibitors of matrix metalloproteinases and other cytokines that promote fibrosis, which means that myocardial fiber degradation

is accelerated and myocardial positive remodeling occurs. However, the use of alcohol during the operation may lead to nontarget myocardial infarction and may increase long-term mortality after the operation.

Left Ventricular Assist Device Implantation

Risk stratification and selection of patients with HCM for prophylactic implantable cardioverter defibrillator (ICD) treatment is still evolving, including novel risk markers and predictive scoring strategies. Nowadays the SCD risk markers in HCM include mainly left ventricular apical aneurysm, LGE, and systolic dysfunction (ejection fraction less than 50%) [1]. Primary-prevention ICD decision-making in HCM patients can always be complicated and full of challenges because of the low SCD event rates observed. What is more, the relatively young age of patients with HCM considered for SCD prevention means that the growth factor should be considered. So decisions regarding primary-prevention ICD therapy should incorporate a discussion with patients that includes the risk of SCD and the benefit that ICD therapy provides in protecting against life-threatening ventricular tachyarrhythmias balanced with complications associated with long-term device therapy. HCM patients who have experienced a cardiac arrest or hemodynamically significant ventricular tachycardia or ventricular fibrillation remain at higher risk of future life-threatening ventricular tachyarrhythmias and should be considered for secondary-prevention ICD therapy. Meanwhile, which type of ICD to implant is also a very important consideration. We need to consider both the pros and the cons, including single-chamber or dual-chamber or cardiac resynchronization therapy devices, a transvenous ICD versus a subcutaneous ICD, and the number of defibrillation coils when using a transvenous approach. Patients with HCM receiving ICDs are usually younger than those with ischemic and even nonischemic cardiomyopathies, and the rates of lifelong complications are likely to be higher in those with HCM [1].

Therefore, for HCM patients, whether to implant an ICD and when to implant it as well as which type of ICD should be implanted requires a specific analysis and a joint decision based on the patient's willingness.

Gene Therapy

HCM is primarily caused by gene mutation, so gene therapy is theoretically the most promising method of HCM therapy. It includes mainly gene silencing, gene replacement, trans-splicing, and exon jumping [32].

Gene silencing is the most direct treatment, selectively reducing the expression of mutant alleles encoding dominant-negative proteins. Experiments have been performed in *Myh6*-mutated HCM mice. The constructed inhibitor was introduced into mice by an adenovirus vector, which can reduce the level of mutant transcription and inhibit myocardial hypertrophy and fibrosis [33]. In RNA trans-splicing, the splicer can connect two distinct exons of precursor messenger (mRNA) to produce chimeric mRNA (i.e., using a foreign RNA sequence to replace one or more exons of mutant pre-mRNA). It can also be used in the treatment of HCM. As a result, two distinct RNA constructs covering the first and second halves of *MYBPC3* mRNA can repair all mutations in the gene, and if this can be successfully used clinically, it is expected to treat 40–60% of HCM patients [34, 35].

Increased sensitivity of myofilament to Ca^{2+} and Ca^{2+} overload promote the occurrence of myocardial fibrosis. SERCA2a and phospholamban play a role in maintaining the stability of calcium circulation. Pela et al. [36] performed SERCA2a gene replacement through a viral vector, upregulated the expression of the SERCA2a gene, increased the ratio of SERCA2a to phospholamban, improved the diastolic function of cardiomyocytes, and finally delayed the progress of myocardial hypertrophy and myocardial fibrosis.

Summary

Myocardial fibrosis is the basis of heart failure and arrhythmia in patients with HCM. We now know that gene mutation, abnormal signal transduction, and energy metabolism are all involved in the

occurrence of fibrosis. The emergence of CMRI techniques such as LGE and T1 imaging based on myocardial fibrosis has increased the accuracy of diagnosis and risk stratification. However, at present, the treatment of myocardial fibrosis is still in the exploratory stage, and there is not enough evidence to prove that it plays a definite role in reversing myocardial fibrosis.

Funding

None.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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