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Review Article

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Research Progress on the Relationship between Serum Cystatin C and Heart Failure

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Abstract

Heart failure (HF) is caused by many factors that lead to myocardial damage, myocardial remodeling of ventricular overload, dysfunction of cardiac diastolic and systolic function, and insufficient blood volume of cardiac circulation. The process of myocardial remodeling is accompanied by myocardial cell ischemia, necrosis, apoptosis, progressive interstitial cell fibrosis and other pathological processes, which is a clinical syndrome in the final stage of various heart diseases, it has high morbidity and mortality, which is a serious threat to human health [1]. Early detection of HF and effective treatment to reduce its morbidity and mortality is particularly important. In recent years, it has been found that Cystatin C (Cys C) is closely related to the occurrence, development and prognosis of HF, and may be an independent predictor of HF. This article reviews the research progress on the relationship between serum Cys C and HF, as well as the pathogenesis, diagnosis, severity and prognosis of Cys C in HF.

Keywords: Heart Failure, Cystatin C, Ventricular Remodeling

Introduction

The incidence of cardiovascular disease in China is getting higher and higher, such as hypertension, coronary heart disease and other cardiovascular disease effective treatment, the survival time is prolonged so that chronic heart failure (CHF) is also increasing year by year. Although some progress has been made in the standardized diagnosis and treatment of CHF, and the mortality rate is lower than in the past, it is still at a high level [2]. Therefore, it is particularly important to find an ideal laboratory index for the early diagnosis of HF. At present, it is generally believed that B-type brain natriuretic peptide (BNP) or N-terminal-pre-B type brain natriuretic peptide (NT-proBNP) is an important marker for the diagnosis of HF, but many studies have shown that the diagnostic value of, BNP (or NT-proBNP) in CHF is far lower than that of acute heart failure, and is affected by age, body weight, renal function and other factors [3]. How to better detect and diagnose CHF earlier for early intervention, it is necessary to find more sensitive and specific reliable indicators. Some studies have found that the level of serum Cys C is related to the occurrence and development of CHF, can reflect the cardiac function of patients with CHF, and can be used as an important index of cardiac function in patients with CHF [4]. Therefore, Cys C has become the focus and focus of clinical research on HF.

Biological characteristics of Cys C

Cys C is a kind of cysteine protease inhibitor, which can inhibit the activity of cysteine protease. It is a protein encoded by CST3 gene. It consists of 122 amino acid residues with a relative molecular weight of 1.3x104. Cys C can be expressed in almost all nucleated cells in human body, and its secretion is constant and has no tissue specificity. It can freely pass through the glomerular filtration membrane [5-7]. Cys C is cleared through the kidney, is completely reabsorbed in the proximal convoluted tubule, and then catabolizes completely after reabsorption, it is not returned to the blood, but only a trace excretion in urine [8]. Its concentration is closely related to the degree of renal damage. Cys C is a sensitive and specific index for evaluating glomerular filtration function and is considered to be a sensitive index for early renal function damage [9,10]. In recent years, more and more studies have confirmed that Cys C is closely related to cardiovascular diseases such as hypertension, coronary heart disease and HF. In a study by detecting the level of serum Cys C in patients with hypertension and healthy people, it was found that the level of serum Cys C in all levels of hypertension was significantly higher than that in the healthy group, and the level of Cys C was positively correlated with the grade of hypertension, that is, the level of Cys C increased with the increase of hypertension grade [11]. A case-control study on the relationship between cardiovascular progress of Cys C and coronary

heart disease found that the level of serum Cys C was significantly correlated with the first ischemic cardiovascular event, suggesting that Cys C may be involved in the process of atherosclerosis and play an important role in the occurrence and development of coronary heart disease [12].

Clinical Study on Serum Cys C and CHF

Etiology and Pathogenesis: Scholars believe that serum Cys C may be involved in the occurrence and development of HF through the following four mechanisms.

1. Ventricular Remodeling: The pathological mechanism of ventricular remodeling includes not only myocardial hypertrophy, cardiomyocyte apoptosis, interstitial fibrosis, but also extracellular matrix remodeling [13]. It has been confirmed that ventricular remodeling is the basic pathological mechanism of the occurrence and development of HF. Some studies have shown that serum Cys C may be involved in the process of ventricular remodeling in patients with HF. The imbalance between myocardial collagen synthesis and degradation is the main reason for myocardial extracellular matrix remodeling. As a cysteine protease inhibitor, Cys C can inhibit the injury of elastic fibers, promote the degradation of collagen fibers and affect ventricular remodeling by inhibiting the activity of endogenous cysteine protease [14].
2. Oxidative Stress: Oxidative stress refers to the imbalance between the production of reactive oxygen clusters and the clearance of antioxidant defense system in the body, resulting in excessive production of reactive oxygen clusters and damage to biological macromolecules such as proteins and nucleic acids in tissues and cells [15]. Some studies have found that the level of Cys C is positively correlated with the level of oxidative stress such as glutathione. It is speculated that serum Cys C may participate in the occurrence of oxidative stress and mediate cardiomyocyte apoptosis, thus promoting the occurrence of HF [16].
3. Inflammatory Response Mechanism: HF as a complex syndrome, many pathophysiological mechanisms are involved in the occurrence and development of HF, including nerve, humoral, immunity and so on. Inflammation is an integral part of body balance and a complex tissue response to stressors, which plays a key role in the occurrence, development, severity and prognosis of HF. Some studies have shown that the level of serum Cys C is positively correlated with the levels of inflammatory factors such as hypersensitive C-reactive protein and matrix metalloproteinase-9 in human body [17]. Other studies have shown that Cys C may aggravate the progression of HF through inflammatory factors associated with fiber degradation, initiating inflammatory-related cascades, activating other factors of the interleukin family and activating a variety of cytokines [18].
4. Atherosclerosis: Atherosclerosis is characterized by the accumulation of local lipids and complex sugars in the intima, proliferation of fibrous tissue and calcareous deposition to form atherosclerotic plaques, weakening elasticity and increasing brittleness of the affected arteries, resulting in gradual narrowing or even complete occlusion of the involved arteries, resulting in serious complications. Some studies have shown that Cys C can regulate arterial wall proteolysis, participate in vascular wall matrix remodeling and promote vascular calcification [19-21]. Wang Wen hui et al, found that serum Cys C level is closely related to the degree of coronary sclerosis, and it has a high specificity in predicting the degree of coronary sclerosis, but its sensitivity is poor [22]. Serum Cys C can participate in the decomposition process of extracellular proteins in patients, and has a certain inhibitory effect on endogenous proteases, thereby damaging the vascular wall, destroying the balance between anti-proteolytic activity and arterial proteolytic activity, promoting the occurrence of atherosclerosis, and then inducing HF [23].

Diagnosis and Judgment of Severity

CHF is caused by abnormal cardiac structure or function impaired ventricular filling or ejection of a complex set of clinical syndromes, its main clinical manifestations of limited tolerance for breathing problems and activity, water sodium retention (congestion and peripheral edema of the lungs), various effects on the body's physiological function, seriously affect the patient's quality of life [24]. The diagnosis of HF is mainly based on the clinical manifestations such as dyspnea, varicose jugular veins, hepatomegaly, droop edema, aussaltation and odour, diastolic troponin, as well as echocardiography, electrocardiography, BNP, NT-proBNP, invasive hemodynamics and other auxiliary examinations [25]. Symptom and sign specificity of HF is poor, ultrasound electrocardiogram, X-ray and invasive hemodynamics and other auxiliary examinations also have certain limitations, and subject to objective conditions. BNP and NT-proBNP are currently recognized as important indicators for the diagnosis of HF and judgment of the severity of HF, but because BNP and NT-proBNP are affected by many factors, and the level of BNP and NT-proBNP in some patients is not proportional to the severity of HF, there are limitations in the early diagnosis of HF with BNP and NT-proBNP [26,27]. In order to detect HF early and improve the diagnostic accuracy of HF, it is necessary to search for HF markers with better specificity and higher sensitivity. Studies have shown that there is no significant difference in serum Cys C level in patients with HF caused by different etiology, and there is a positive correlation between serum Cys C and NT-proBNP [28]. Matana et al, found that serum Cys C level can be used in the diagnosis and risk stratification of HF [29]. A foreign study involving 4384 patients aged ≥65 years and without previous HF studied the relationship between serum Cys C level and HF by measuring the level of serum Cys C [30]. The study was followed for eight to nine years and showed that 17 percent of patients developed HF. Therefore, Cys C may be a new diagnostic index of HF, especially for severe HF, and can be used as an important supplement of NT-proBNP. Multi-index detection of combined Cys C may improve the diagnostic rate of HF, and also point out a direction for future research. The study also found that Cys C level increased with the increase of cardiac function grade, suggesting that Cys C level was correlated with the severity of HF, suggesting that Cys C could be used to evaluate the severity of HF. In addition, studies by other scholars have found that high level of serum Cys C is also closely related to left ventricular hypertrophy and diastolic dysfunction, which is a useful indicator for the detection of asymptomatic cardiac structural abnormalities [31]. Elevated serum Cys C level is associated with the occurrence of elderly patients with retained ejection fraction and may reflect the severity of HF. Serum Cys C is one of the markers of worsening HF and can be used as an independent predictor of HF [32].

Prognosis

In recent years, researchers have extensively studied whether Cys C can be used to evaluate the prognosis of patients with HF. A prospective study of elderly patients with HF followed up for 6 years found that serum Cys C> 1.30mg/L is one of the important indicators to predict the occurrence of acute HF or death in elderly patients with HF within one year, and the level of serum Cys C is an independent predictor of death in patients with HF, which can be used as a new index to evaluate the prognosis of patients with HF [21]. Another study shows that combined detection of Cys C and NT-proBNP can better stratify the risk of severity and predict adverse vascular events in patients with HF [33]. Combined detection of Cys C and NT-proBNP is a powerful method to predict the prognosis of patients with acute HF. The levels of serum Cys C and NT-proBNP increased with the severity of the disease in patients with CHF. The patients with high levels of Cys C and NT-proBNP had a poor prognosis. Some scholars believe that Cys C and NT-proBNP can evaluate and predict the prognosis of patients with cardiovascular disease [34,35]. The levels of Cys C and NT-proBNP increased with the severity of CHF, and they are independent risk factors affecting the prognosis of patients with HF. Patients with higher levels of Cys C and NT-proB-NP have a poor prognosis. Some scholars have pointed out that the short-term prognosis of patients with ischemic HF is also different according to the level of serum Cys C.

Discussion

According to clinical studies, the level of serum Cys C is closely related to the occurrence, development and prognosis of cardiovascular disease with the increase of the level of serum Cys C, the incidence of cardiovascular events increases, and directly affects the prognosis of patients. therefore, as an independent risk factor for HF, the level of serum Cys C is better than other conventional indexes such as creatinine in the evaluation of prognosis. The level of serum Cys C will not be affected by age, sex and other factors, so we can have a more comprehensive understanding of whether patients have CHF.As a sensitive indicator of early renal damage, whether the relationship between Cys C and cardiac insufficiency is related, or whether it independently participates in the disease development of HF, or promotes each other in a vicious circle, there is no consensus on the mechanism and pathophysiological process of Cys C and CHF. In addition, a large number of studies are needed to confirm whether Cys C can assist in determining the cause of CHF, and whether Cys C is better than NT-proBNP in the diagnosis of HF is unknown. All the above problems need to be further studied.

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