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Review Article

CORONARY SLOW-FLOW PHENOMENON (CSFP) AND MYOCARDIAL INFARCTION WITH NON-OBSTRUCTIVE CORONARY ARTERIES (MINOCA) IN CLINICAL SYMPTOMS ONE PERSPECTIVE: LITERATURE REVIEW PAPER

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ABSTRACT

Cardiovascular diseases have become one of the most prevalent diseases around the world, and it is considered the main cause of death among all infectious diseases. The most common disease among them is coronary artery disease, which is distinguished by its characteristics in stenosis, obstruction, and cardiac ischemia. Their symptoms vary from chest tightness and pain to general weakness.

Patients with slow blood flow are characterized by the same clinical symptoms that accompany patients with coronary arteries, and those patients are detected after a cardiac catheterization, where the patient comes with symptoms similar to angina pectoris, and this condition is more common in young male smokers other than other groups of people. This group of patients is dominated by elevated total cholesterol, blood glucose, and body mass index levels.

This review paper will discuss and compare diagnostically between coronary slow-flow phenomenon (CSFP) and myocardial infarction with non-obstructive coronary arteries (MINOCA). And their accompanying primary clinical causes, psychological and moral secondary causes.

Keywords: Coronary slow-flow phenomenon (CSFP), Myocardial Infarction with Non-Obstructive Coronary Arteries (MINOCA), percutaneous interventional (PCI), Pericarditis Coronary artery disease (CAD

INTRODUCTION

Coronary slow-flow phenomenon (CSFP)[1]:

Is considered as an angiographic clinical entity, and characterized by delayed distal vessel opacification in the absence of significant epicardial coronary stenosis. CSFP is one type of myocardial ischemia, due to the lack of myocardial blood supply, clinical manifestations of myocardial ischemia, such as chest pain, chest tightness, pericardial discomfort, malignant arrhythmia, recurrent acute coronary syndromes and sudden death [1,2].

Previous literature explained that bacterial infection is an expected factor for coronary microvascular disease, small vessel heart disease, Endothelial dysfunction, early stage of coronary atherosclerosis, Inflammation, and Anatomical and psychological factors.

Myocardial Infarction with Nonobstructive Coronary Arteries (MINOCA):

Myocardial infarction with nonobstructive coronary arteries (MINOCA) is when the patient presented with acute myocardial infarction (AMI) symptoms with the absence of obstruction or stenosis < 50% in the coronary arteries on the diagnostic coronary angiography. In recent years, many cases of MINOCA myocardial infarction with nonobstructive coronary arteries disease have been diagnosed, as the causes of this disease were not clearly known, cardiologist doctors and clinical researchers believe that there are multiple possible pathological mechanisms converge in several causes.

Differential diagnosis:

The patient must have three criteria to be diagnosed as a MINOCA patient:

I. The patient must come with typical chest pain and diagnose as an AMI patient.
II. Coronary angiography must show no obstruction in the coronary arteries or stenosis has to be < 50%.
III. There is no clinical finding for other cardiovascular diseases that cause AMI, e.g., myocarditis and pulmonary embolism.[3]

Pathogenic factors:

MINOCA patients have aetiologic mechanism related to many factors can be divided into two types Epicardial causes include coronary artery disease, coronary plaque disruption, coronary dissection, coronary spasm, and microvascular causes includes Takotsubo syndrome (TTS), myocarditis, and coronary thromboembolism.

Also, MINOCA has some uncertain causes.

DISCUSSION

The diagnosis of CSFP is made via coronary angiography based on either a reduced Thrombolysis in Myocardial Infarction (TIMI) of grade two flow or an increased corrected TIMI frame count of greater than twenty-seven in one or more epicardial vessels (correct TIMI frame count) [1,2]. Which calculates coronary

blood flow velocity by counting the number of frames the coronary contrast agent transfers from the beginning of the coronary artery to its end.

There are currently several methods for the clinical diagnosis of slow blood flow in the coronary arteries, Doctor Wagans proposed a diagnosis by thrombolysis in myocardial infarction (thrombolysis in myocardial infarction, TIMI) TIMI is a measure of the velocity of coronary blood flow during the procedure of coronary angiography (CAG), where the classification is divided into three sections, TIMI 0-3, where TIMI 0 has no blood flow and TIMI 3 is a normal blood flow. Patients with slow blood flow are classified as TIMI 2 [12,16].

The diagnosis of MINOCA is usually determined depending on several methods. First, according to the expected pathological mechanisms, it can include ECG, IVUS, OCT, FFR, and iFR for coronary artery disease. Or intracoronary nitrates for coronary artery spasm, Ventriculography, echocardiography, troponin, B-natriuretic peptide, and CMR for Takotsubo syndrome, CMR, EMB, viral serologies, and high c-reactive protein for myocarditis, thrombophilia screen, TTE, TOE. And finally, bubble contrast echography for coronary embolism.

Pathogenic theories:

Both diseases MINOCA and CSFP share almost the same pathogenic factors

Small vessel disease:

Small vessel disease is sometimes called coronary microvascular disease or small vessel heart disease. The small vessels have the same characteristics as the large coronary vessels. Thus, they could get occluded, spasm, or even have stenosis. However, the literature has contradictions in whether angiography in large vessels or small vessel dysfunction has been typically involved in the pathogenesis of CSFP. To prove this hypothesis, researchers reported fibromuscular hyperplasia, medial hypertrophy, myointimal proliferation, as well as endothelial edema, thickening, and degeneration in the coronary microvessels [4].

The coronary artery system includes the subepicardial coronary artery and the small blood vessels in the myocardium. Which usually refers to a volume vessel that does not produce resistance to blood flow. The small blood vessels in the myocardium are microvessels, which are composed of resistance blood vessels with a diameter of less than 400μm, which limit the flow of myocardial blood vessels when the large blood vessels function normally. [5,6]

Tambe et al. [1] proposed that small vessel occlusion may be the mechanism of CSFP when they proposed CSFP. Since then, researchers have proposed that the increase in microcirculation resistance may be the pathophysiological mechanism of MINOCA and CSFP. Fineschdi et al. [7] found that the study confirmed that the coronary artery resistance of CSFP patients increased significantly. In addition, some pathological phenomena such as degenerative diseases of microvessels may be related to MINOCA and CSFP [4, 8]. Coronary artery blood flow reserve (CFR) can be used to evaluate the hemodynamic level of the coronary circulatory system, specifically referring to the ratio of myocardial peak blood flow to resting blood flow [9], which can indirectly reflect the microvascular function of patients without coronary artery disease. Erdogan et al. [10]

found through research that the CFR value of CSFP patients was significantly lower than that of normal people, thus confirming that microcirculation lesions may be correlated with the occurrence of CSFP. In addition, Beltrame [11,12] study found that the coronary arteries of MINOCA and CSFP patients are in a state of spasm, so microvasospasm is also an important pathological factor of MINOCA and CSFP.

Endothelial dysfunction:

Is considered a type of non-obstructive coronary artery disease (MINOCA) in which there are no heart artery blockages, but the large blood vessels on the heart's surface constrict instead of dilating where the vessels wall had an impairment, Vascular endothelium plays a very significant role in regulating the function of vasodilation and contraction, cell adhesion, anti-thrombosis, vascular smooth muscle cell proliferation and inflammation, and it is also closely related to the development of atherosclerosis. Gunes et al. [13] conducted a flow-mediated dilation (FMD: a simple method to judge endothelial function) on CSFP patients and found that the brachial artery diastolic function decreased in CSPF patients. It is confirmed that the endothelial function of CSFP patients is impaired. In addition, the measurement of nitric oxide (NO), Endothelin-1 (Endothelin-1, ET-1), and other active substances secreted by the vascular endothelium found that CSFP patients have higher ET-1 concentrations, while NO The concentration is low [14], from which it can also be inferred that the endothelial function of CSFP patients may be impaired.

Atherosclerosis:

In previous studies of atherosclerosis intravascular ultrasound (IVUS) shows most patients with CSFP have longitudinally extended massive calcification throughout the epicardial coronary arteries Pekdemir *et al*. [15], Some researches result in recent years indicate that CSFP may be an early manifestation of coronary atherosclerosis. Because the coronary arteries are expanded compensatory in the form of reconstruction to maintain the area of the lumen in the early stage of coronary atherosclerosis, CAG often cannot find the early coronary artery lesions without stenosis in the lumen. Intravascular Ultrasound (IVUS) can directly visualize the structure of the blood vessel wall, so it can detect intimal hyperplasia and plaque formation. Cetin [16] found diffuse thickening of coronary artery intima and media in patients with CSFP through the application of IVUS technology. In addition, large-scale calcification of the entire epicardial artery longitudinal extension was found in 13 cases (68.49%) of CSFP patients, and local calcification was found in 6 cases (31.6%) of CSFP patients. In the measurement of coronary artery pressure, the test results showed that the pressure difference between the proximal and distal ends of CSFP patients was significantly increased, and the CFR was significantly reduced. Therefore, even if the coronary arteries of CSFP patients do not show obvious stenosis in routine angiography, diffuse intimal thickening, extensive vascular wall calcification and atherosclerosis may already exist, and the proximal end of the epicardial coronary artery in CSFP patients There is a pressure gradient between and the distal end. Based on these results, we believe that CSFP may be diffuse atherosclerosis involving both the microvascular system and epicardial coronary arteries. In addition, by taking the carotid artery intima-media thickness (CIMT) as an early indicator of atherosclerosis, Avsar et al. [17] confirmed that CIMT has a strong correlation with the number of corrected blood flow frames. It can

also indicate that CSFP may be an early manifestation of atherosclerosis.

Epicardial causes:

Coronary artery spasm, plaque disruption, and coronary dissection are major etiology and are highly estimated in MINOCA patients, their lipid-rich body and thin fibrous cap, making them vulnerable to rupture, the frequency of ruptured plaques in MI patients was estimated to be between 20% and 40%, and patients with plaque rupture had increased plaque burden, plaque volume and positive arterial remodeling, Coronary artery spasm (CAS) represent between 3% and 95% of MINOCA cases depending on the registry. Positive provocative tests with intracoronary, adenosine, or ergonovine portend a worse prognosis.

Inflammation:

Inflammation is the causative factor of many cardiovascular diseases. The increase of inflammatory markers in CSFP patients may indicate that inflammation is involved in the pathological process of CSFP. Inflammatory factor C-reactive protein (C-reactive protein, CRP) is the most important and sensitive non-specific inflammation marker in the human body, while high-sensitivity C-reactive protein (h-sensitivity C-reactive protein, hs-CRP) is more accurate and sensitive. Cetin [16] and other studies have shown that the blood of CSFP patients.

The level of CRP is significantly higher than that of people with normal coronary blood flow, and it is positively correlated with TIMI blood flow. At the same time, Li [18] et al. also confirmed through research that the serum CRP and Interleukin-6 (IL-6) concentrations in CSFP patients are higher, and the average TIMI blood flow count is positively correlated with serum CRP and IL-6 concentrations. The overexpression of Cell Adhesion Molecules (CAMs) induces leukocytes and vascular endothelial cells.

Adhesion of Endothelial Cell (EC) is the pathological change in the early stage of atherosclerosis, that is, the inflammatory reaction. Turhan et al. [19] found that Intercellular Adhesion Molecule-1 (ICAM-1), Vascular Cell Adhesion Molecule-1 (VCAM-1), intercellular adhesion molecules (Vascular Cell Adhesion Molecule-1, VCAM-1) in the plasma of CSFP patients.

The level of E-selectin was significantly higher than that of patients with normal coronary blood flow. In addition, Akpinar et al. [15] confirmed that the number of peripheral blood leukocytes and neutrophils in CSFP patients increased significantly, and Doan et al. [20] found that the Neutrophil/Lymphocyte Ratio (NLR) was significantly higher in CSFP patients. Patients with normal coronary blood flow. The above research results all indicate that patients with CSFP may be in a state of inflammatory activation. In addition, Kopetz et al. [21] found that CSFP patients with ACS have elevated hs-CRP in the acute phase, but the levels of creatine kinase isoenzyme and plasma cardiac troponin T have not changed, which may indicate that thrombosis and inflammation are involved Acute course of ACS in CSFP patients.

Abnormal platelet function and morphology, previous studies have shown that compared with normal coronary blood flow patients, platelet aggregation rate in CSFP patients has a significant increase [22], (Mean Platelet Volume, MPV) increased. Cin VG [23] confirmed through experimental studies that MPV levels are significantly related to coronary blood flow, and elevated MPV levels may be an independent predictor of

the presence of CSFP. In addition, patients with CSFP also have increased platelet count [4] and abnormal platelet function [22].

Anatomical and psychological factors:

The abnormal anatomical shape of the coronary artery's tree could cause the CSFP, some bifurcation is considered to be the reason for accumulating plaques and resulting in atherosclerosis which is one cause of CSFP. Stress is the most common cause of psychological problems that lead to heart weakness, Takotsubo is stress cardiomyopathy represents 1%-3% of all STEMI, with 5%-6% prevalence in female subgroups, and is characterized by apical ballooning of the left ventricle in the absence of occlusive CAD, although concomitant CAD is described in 10%-29% of Takotsubo syndrome (TTS)cases. Studies have shown that high levels of cortisol caused by long-term stress increase blood cholesterol, triglycerides, blood sugar and, blood pressure. These are common risk factors for heart disease. This pressure can also lead to changes that promote plaque deposition in the arteries.

Treatment theories:

At present, because the specific pathogenesis of CSFP is not clear, the treatment of CSFP is still inconclusive. According to the timing of CSFP treatment, it can be divided into CAG intraoperative treatment and postoperative treatment. CAG intraoperative treatment: administer nitroglycerin [24] or sodium nitroprusside [25] immediately when CSFP is found, and observe whether CSFP improves. Or intracoronary injection of nicorandil [26] can also improve CSF, CAG postoperative treatment: mainly oral medications, such as dipyridamole [27-28], nicorandil, trimetazidine [29-30], statins [31-32], beta-blockers [33], in recent years, studies have also found that Telmisartan [34] can improve CSFP by improving the vascular endothelial dysfunction of CSFP patient's symptom. In addition, studies have pointed out that Chinese medicine [35-36] treatment also has a certain effect in improving the symptoms of CSFP. Nowadays the treatment of CSFP mainly focuses on improving coronary blood flow speed and relieving chest pain symptoms, based on improving microvascular function, anti-inflammatory and maintaining the endocrine function of blood vessels, and anti-platelet, Improve microcirculation.

Since small vessel disease may be the mechanism of CSFP [1], improving microcirculation may be an effective treatment for CSFP patients. Because the sarcoplasmic reticulum of vascular smooth muscle is poorly developed, the calcium ions needed for vascular smooth muscle contraction mainly come from outside the cell, so vascular smooth muscle is more sensitive to calcium ion channel blockers. The use of calcium channel blockers such as verapamil [37] in clinical treatment can regulate the inflow of calcium ions on vascular smooth muscles, dilate coronary arteries, dilate large transport vessels and small resistance vessels, and increase coronary blood flow and the amount of collateral circulation, relieved. spasms of microcirculation. Nicorandil [38] is a potassium ion channel activator, which not only activates the potassium channel of the vascular smooth muscle cell membrane, promotes the outflow of potassium ions, makes the cell membrane super, thereby inhibiting the effect of calcium ion influx, but also releases NO to increase vascular smooth muscle Intracellular cyclic guanosinc monophosphate (cGMP) Studies have confirmed that

the injection of nicorandil, verapamil, and other drugs into the coronary arteries can improve the blood flow velocity in the coronary arteries [39-41].

In addition, studies have shown that injecting nicorandil during CAG can prevent the occurrence of CSFP [42]. In addition, due to the lack of active enzymes in the capillaries of coronary arteries that catalyze the production of NO, which is an active substance that can relax vascular smooth muscle, by nitrate drugs, many studies have confirmed that intra-coronary injection of nitroglycerin is ineffective in the treatment of CSFP patients [43, 44]. Dipyridamole [43] can act on microvessels with a diameter of less than 200μm, and has a certain expansion effect on small blood vessels, which can improve the blood flow of coronary arteries.

Anti-inflammatory treatment:

Researchers such as Li [18] and Turhan [19] have confirmed through studies that the inflammatory response may be closely related to the occurrence and development of CSFP, so the current clinical use of anti-inflammatory treatment to partially relieve the symptoms of CSFP. Statins are mainly used clinically as blood lipid regulating drugs. In addition, statins also have multi-effect effects, including improving vascular endothelial function, reducing plasma CRP, and reducing inflammatory reactions in the atherosclerotic process. In addition, statins also It can eliminate free radicals and exert antioxidant effects. The use of statins in CSFP patients can significantly improve the long-term Period blood flow velocity [45-47].

Since previous studies have shown that compared with those with normal coronary blood flow, the platelet aggregation rate of CSFP patients is significantly higher [28], MPV [48], platelet counts [4], and platelet function abnormalities [4] and platelet function abnormalities [22]. Through these studies, it can be inferred that platelets may be involved in the occurrence and development of CSFP, and the currently commonly used clinical drugs for the treatment of CSFP also contain aspirin. However, in clinical studies at home and abroad, the effect of antiplatelet therapy on the long-term prognosis of CSFP patients has not been clarified. Therefore, the effect of antiplatelet therapy on CSFP needs to be further studied.

Diagnosing CSFP became easier to distinguish among other diseases but on another hand, it's still not much clear about the cure medical treatment of CSFP, in clinical ablation anti-anginal agents are of limited clinical value. It was shown that dipyridamole and mibefradil have positive effects on the dilation of arteries muscle [29], the most important of these are statins its shown great benefits on CSFP patients due to their effects on cholesterol [30-49].

For MINOCA patients, there are no clinical guidelines for this clinical syndrome system. Early identification of the etiology or pathogenesis of MINOCA patients is the key to optimize MINOCA treatment. Thrombosis and thromboembolism play an important role in the pathogenesis of MINOCA with plaque rupture. In 2016, experts from the European Society of Cardiology ESC position working group suggested that patients with suspected or confirmed plaque rupture should receive dual antiplatelet therapy for 1 year, and then maintain long-term or even lifelong single antiplatelet therapy. For atherosclerotic lesions in the coronary artery, statins are recommended. For the treatment of spontaneous coronary artery dissection, the current study found that most SCAD patients are not complicated with atherosclerotic diseases, and the

routine application of statins and antiplatelet aggregation therapy are not recommended. Clinically, conservative treatment is generally advocated for patients with spontaneous coronary artery dissection, because coronary intervention and stent implantation may cause the risk of expanding the scope of dissection. [41]

For myocardial bridge patients with chest pain and other symptoms, β receptor blockers and calcium channel blockers are recommended, and nitrates are avoided. [42] For patients with severe symptoms and recurrent attacks, try the surgical treatment. A coronary stent implantation is unconventional. [44] Takotsubo cardiomyopathy is usually characterized by acute reversible left heart failure [45]. At present, there is no diagnosis and treatment guide for the TCM system. Clinically, empirical treatment is routinely used: for example, patients with left ventricular outflow tract obstruction use cardiac high selectivity β Angiotensin-converting enzyme inhibitors can be used in patients with receptor blockers, avoiding the routine application of sympathetic drugs, and persistent left ventricular dysfunction Mechanical support therapy such as left ventricular assist devices and short-term anticoagulant therapy for patients at risk of thrombosis 72731 previous studies have confirmed that nitrates and calcium channel blockers can effectively treat coronary artery spasm and effectively prevent adverse cardiovascular events induced by coronary artery spasm 46741 patients with myocarditis, Clinically, it is mainly used to improve myocardial metabolism and antiviral treatment. If it is combined with acute left ventricular dysfunction, it is usually used in treatment β Receptor blockers and ACEI drugs. Clinically, about 50% of patients with myocarditis can effectively alleviate their symptoms within 2-4 weeks, but 12-25% of patients may deteriorate into fulminant heart failure in a short time, or even develop dilated cardiomyopathy in a late-stage, requiring left ventricular assistance device or heart transplantation.[50]

The specific etiology of MINOCA patients is complex, and treatment for the etiology is the key. However, because the specific etiology cannot be determined in the early stage, and there is no targeted clinical guide at present, its treatment scheme is often based on the experience of clinicians. A Swedish study of 9136 MINOCA patients reported that the use rates of receptor blockers, ACEI / ARB, statins, and ADP receptor antagonists were 83.4%, 64.1%, 84.5%, and 66.4% [14] respectively. A recent study in the United States involving 2690 AMI patients aged 18 to 55 reported that the discharge medication of MINOCA patients was significantly lower than that of MIC patients in aspirin (98.6% vs 93.7%), ß receptor blockers (98.3% vs 85.9%), ACEL / ARB drugs (73.3% vs 50.2%) and statins (96.9 vs 73.49%). [12]. An Italian study reported that the use rate of receptor blockers (78% vs 63.3%) and ACEI inhibitors (57.7% vs 66.4%) in MINOCA patients during 6-month follow-up were significantly higher than those in the control group.[51]

Prognosis:

There are great differences in the prognosis of MINOCA patients. This paper will review the long-term and short-term prognosis of MINOCA and CSFP patients.

For the short-term prognosis of MINOCA patients, most of the research results show that the short-term prognosis of MINOCA patients is better than that of MICAD patients. The literature review is as follows:

the results of Larsen et al show that the cardiogenic mortality 30 days after discharge in MINOCA patients is lower than that in MICAD group [43]. The HORIZONS-AMI study showed that the major adverse cardiovascular events 30 days after discharge in MINOCA patients were lower than those in MICAD group (1.6% vs 57%). A systematic review showed that MINOCA patients had a significant reduction in all-cause mortality compared with MCAD patients, including a 63% reduction in hospital mortality [2]. A prospective study in Sweden in 2017 showed that the short-term mortality of MINOCA patients was lower than that of MCAD patients [15]. The COAPT study showed that MINOCA patients had a lower in-hospital all-cause mortality than MICAD patients (2.7% vs 0.8%) 3. A New Zealand study of 897 MINOCA patients reported that all-cause mortality in the MICAD group was lower than that in the MICAD group (0.2% vs 1.5%). Some studies have shown that the short-term prognosis of MINOCA patients is similar to that of MICAD patients. For example, a study of 2442 NSTEMI patients showed that the cardiac mortality of MINOCA patients in one month after discharge is similar to that of MICAD patients. [53] A Korean study reported that the incidence of major adverse cardiovascular events in the two groups was similar to that in the MINOCA group 1 month after discharge. [54]

For the prognosis of CSFP, there are few studies on the prognosis of CSFP patients, and the prognostic conclusions are not consistent. Some studies have shown that CSFP patients have a better prognosis [55], and some studies have shown that CSFP patients have obvious filling defects on radionuclide scans [50]. According to reports, a young man [51] who was only 20 years old suffered from ventricular fibrillation due to the appearance of CSFP, and finally died suddenly. This CSFP patient had only a history of smoking without other traditional risk factors for heart disease, chest echocardiography The image and electrophysiological examination was completely normal, the stress myocardial perfusion imaging showed reversible myocardial ischemia in the anterior and inferior walls of the left ventricle, and the angiography showed CSFP. In addition, Fragasso et al. [56] conducted a 14-year follow-up on 5 patients with CSFP. All of these patients showed myocardial hypoperfusion through single-photon emission computed tomography. In the end, 1 patient died and 4 patients developed CAD. None of the patients died, and no patients developed significant CAD. Due to frequent chest pain or chest discomfort, CSFP patients are often accompanied by mental anxiety, depression, and Anxiety can not only lead to an increase in mortality [54,57-58], it is also related to the occurrence of cardiovascular disease [59]. The outcomes of these studies indicate that the long-term prognosis of CSFP patients they are much useful and needs to have more clinical and laboratories research to reach the clear pathological and management of CSFP.

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CONCLUSION

1. Although the scientific and medical community has made great efforts to explore CSFP, so far, there is no consensus on the drug treatment plan of CSFP, and there are still many controversies in its

pathophysiological mechanism, diagnosis, management, and prognosis.

2. Some research results in recent years believe that CSFP may be the result of a variety of pathological mechanisms: CSFP is microvascular disease, or an early stage of atherosclerosis, or it is due to impaired endothelial function and inflammation. Caused by platelet dysfunction.
3. Although some researchers have a long-term follow-up of CSFP patients The results showed a good prognosis [55], the study only included 7 CSFP patients. Therefore, in the future, a larger sample size of multi-center, prospective, and controlled design studies of CSFP is needed to further clarify the specific pathophysiological mechanism and long-term prognosis of CSFP, so as to better manage the risk of CSFP patients, and according to different risk stratification, corresponding treatment strategies are formulated to maximize the quality of life of CSFP patients, reduce the mortality rate, and improve the prognosis of CSFP.
4. CSFP in the coronary arteries is an integral part of MINOCA diseases, and more research and studies must be done to find a treatment that is more appropriate for CSFP disease and the patient's life.

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