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Research Progress on Pathogenesis and Clinical Treatment of Coronary Heart Disease Complicated with Depression

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Abstract

Coronary heart disease complicated with depression is one of the most common "psychosomatic heart diseases" in clinical practice. Its pathogenesis is complex and not yet fully clarified, and there is no specific drug available so far. This paper systematically reviews the pathogenesis of coronary heart disease complicated with depression and current clinical treatment methods, aiming to provide references for mechanism research and clinical treatment.

Keywords

Coronary Heart Disease Complicated with Depression, Pathogenesis, Clinical Treatment, Research Progress

1. Introduction

The concept of "dual-heart disease" was proposed relatively early, referring to the coexistence of cardiovascular diseases and mental illnesses. Cardiovascular diseases and psychological factors interact with each other, leading to complex pathophysiological changes. Coronary heart disease complicated with Depressive Disorder (CHD-DD) is one of the most common dual-heart diseases in clinical practice [1]. Statistics show that the incidence of depression in patients with coronary heart disease is about 15% - 30%, and the incidence of depression increases to 30% - 60% after an acute myocardial infarction. Moreover, the incidence of cardiovascular accidents in coronary heart disease patients with depression is significantly increased [2], which seriously affects the patients' quality of life and the prognosis of the disease. In this paper, with "Coronary heart disease complicated", "Depres-

sive Disorder" and "Coronary heart disease complicated with Depressive Disorder" as key words, about 140 relevant literatures from 2021 to 2025 were systematically retrieved from databases such as PubMed and CNKI. The pathogenesis and progress in clinical treatment were reviewed, so as to provide references for the research and treatment of CHD-DD in the future.

2. Pathogenesis of CHD-DD

2.1. Renin-Angiotensin System

As a key component of the renin-angiotensin system (RAS), angiotensin exerts crucial biological activities and occupies a central position in regulating multiple physiological and pathological processes, including cell proliferation and apoptosis, oxidative stress, and inflammatory responses [3]. Studies have revealed [4] that when angiotensin II (Ang II) is activated, the balance between Ang II and angiotensin-(1-7) (Ang-(1-7)) is disrupted, triggering a series of cascading reactions. These reactions lead to abnormal vascular proliferation, intensified inflammatory responses, accelerated cell apoptosis, and other changes, which accelerate the progression of atherosclerosis and ultimately induce coronary heart disease. In addition, studies on the serum of patients with coronary heart disease and depression have found that their serum levels of Ang-(1-7) are significantly lower than those in healthy individuals [5]. Research by Wei Yin *et al.* [6] has confirmed that Ang-(1-7) can significantly inhibit the proliferation of infantile hemangioma endothelial cells (Hem ECs), promote their apoptosis, and upregulate the expression of Mas receptor mRNA, thereby achieving the effect of protecting vascular endothelium. Given the extensive protective effects of RAS on vascular endothelium and the brain nervous system, it can be predicted that RAS may serve as a new entry point and a novel target for the clinical treatment of CHD-DD.

2.2. Platelet Dysfunction

As an indispensable part of the coagulation system, platelets also play a significant role in the pathogenesis of CHD-DD. Platelet activation and aggregation caused by various factors can activate the body's coagulation system, increasing the probability of thrombus formation in coronary arteries. Thrombus is precisely one of the core pathological processes of atherosclerotic coronary heart disease [7]. The main triggers for platelet activation are factors such as endothelial damage and inflammatory factors in the body, which induce the release of various procoagulant substances (e.g., ADP, thromboxane A2) that lead to platelet aggregation and thrombus formation. This, in turn, exacerbates atherosclerosis and contributes to the development of coronary heart disease [8]. Liao Dongsheng *et al.* [9] observed changes in serum levels of platelet-activating factor (PAF) and other indicators in 163 clinical CHD-DD patients. They found that PAF levels in CHD patients increased with the severity of depression, suggesting that PAF may be a key influencing factor for comorbid depression in CHD patients.

2.3. Synergistic Mechanism of Inflammatory Response, Immune Activation, and Oxidative Stress

Inflammation and oxidative stress are closely interrelated in the occurrence and progression of CHD-DD, and they exert a synergistic effect by jointly affecting key links such as vascular endothelial dysfunction. The inflammatory response plays a central role in the development of CHD-DD: in patients with coronary heart disease and depression, the levels of inflammatory factors including C-reactive protein, interleukin family, interferon, and tumor necrosis factors are significantly elevated, and they are positively correlated with disease progression [10]. Mental illnesses can exacerbate inflammation by triggering stress response pathways, accelerating atherosclerosis, and thus increasing the risk of coronary heart disease in patients with depression. In this process, the transcription factor nuclear factor-κB (NF-κB) pathway and inflammatory factors form a positive feedback loop: NF-κB initiates immune responses by inducing the transcription of inflammation-related genes; meanwhile, various cytokines bind to receptors on target cells to trigger signal cascades, which further promote the nuclear translocation and activation of NF-κB, forming an inflammatory amplification cycle [11]. Therefore, inflammatory factors can serve as important indicators for evaluating the therapeutic efficacy of CHD-DD. Oxidative stress participates in the disease process through multiple mechanisms, and one of its core effects is inducing vascular endothelial dysfunction—a hallmark pathological change in vascular diseases. Specifically, oxidative stress can drive the occurrence and development of coronary artery disease by promoting lipid peroxidation, exacerbating inflammatory responses, and directly damaging vascular endothelium. Its effects can be confirmed by markers such as malondialdehyde (MDA) and glutathione peroxidase (GSH-Px) [12]. Additionally, the levels of oxidative stress markers (e.g., peroxides, low-density lipoprotein antibodies) in the plasma of depressed patients are increased, suggesting that oxidative stress may contribute to the pathogenesis of depression by involving neurodegenerative processes [13]. Notably, oxidative stress and inflammatory response can promote each other: oxidative stress can activate inflammatory signaling pathways (such as the NF-κB pathway), while reactive oxygen species released during the inflammatory process can further enhance oxidative stress. Together, they exacerbate the pathological progression of CHD-DD through mechanisms like impairing vascular endothelial function and accelerating atherosclerosis.

2.4. Hypothalamic-Pituitary-Adrenal (HPA) Axis Theory

The hypothalamic-pituitary-adrenal (HPA) axis plays a key role in the body's response to stress and regulation of physiological and psychological homeostasis, and is one of the important components of the neuroendocrine system. Relevant studies have pointed out [14] that the dysfunction of the HPA axis is likely to be one of the important biological bridges connecting coronary heart disease and mental disorders. Patients with depression exhibit significant emotional disorders

and mental disturbances. These adverse emotional responses can trigger the body's stress response, leading to overactivation of the HPA axis, which results in elevated cortisol levels in the blood. In turn, this affects and reduces the sensitivity of the HPA axis, thereby disrupting the balance between the sympathetic and parasympathetic nervous systems, accelerating the progression of metabolic syndrome, and becoming an important factor in the development of atherosclerosis [15].

2.5. Autonomic Nervous Dysfunction

2.5.1. Sympathetic Nervous Dysfunction

The sympathetic nervous system (SNS) is a complex network integrating autonomic regulation, neuroendocrine responses, and behavioral adaptation. Its core function lies in maintaining the body's homeostasis, participating in emotional expression, and coping with stressful situations [16]. Catecholamines are the signature substances for sympathetic nerve activation. When the body is in a state of anxiety and depression, the circulating levels of these substances in the body will increase significantly. This elevation in circulating levels is followed by a series of physiological reactions, such as a continuous increase in heart rate and a gradual rise in blood pressure. At the same time, it will also promote a reduction in coronary artery blood flow, while the resistance of systemic blood vessels increases accordingly. Such a series of physiological effects will increase the risk of coronary heart disease. In addition, excessive activation of the sympathetic nervous system can lead to metabolic disorders of neurotransmitters such as serotonin (5-HT) and dopamine (DA). The reduction of neurotransmitters induces or exacerbates the occurrence of depression [17].

2.5.2. Heart Rate Variability Dysfunction

Heart rate variability (HRV) refers to the fluctuation in the time intervals between consecutive heartbeats, which arises from the precise regulation of the sinoatrial node by the autonomic nervous system [18]. HRV not only reflects the balance state of the autonomic nervous system but also indicates the real-time activity of the sympathetic nervous system (SNS). When patients are in a state of depression, the body's stress perception mechanism may weaken the comprehensive regulatory capacity of the SNS and simultaneously induce excessive activation of the hypothalamic-pituitary-adrenal (HPA) axis. This series of reactions inhibits the release of γ-aminobutyric acid (GABA) and promotes the secretion of adrenocorticotropic hormone (ACTH), ultimately disrupting the balance of the autonomic nervous system, which is specifically manifested by a significant decrease in HRV [19]. The reduction of HRV is not only an independent predictor of mortality risk in heart disease patients but also an independent variable affecting anxiety and depression in coronary heart disease patients. Moreover, it is a key risk factor that exacerbates anxiety and depression symptoms and influences the prognosis of coronary heart disease [20].

2.6. Abnormal Neurotrophic Factors

Neurotrophic factors, especially brain-derived neurotrophic factor (BDNF), play an extremely critical role in the pathological process of CHD-DD. A decrease in BDNF levels has been confirmed to affect vascular endothelial function, alter thrombus size and stability, thereby participating in the processes of atherosclerosis and thrombosis [21]. The occurrence of depression is closely related to structural and functional changes in brain regions involved in stress responses. When these brain regions respond to stress, they trigger a series of neurophysiological reactions, including the generation of fear emotions, the formation of memories, and the regulation of peripheral physiological functions. Therefore, changes in these brain regions are not only closely related to the pathogenesis of depression but may also increase the risk of comorbid coronary heart disease in depressed patients [22].

2.7. Others

In addition to the above possible mechanisms, the pathogenesis of coronary heart disease and depression is also related to bad habits, such as smoking history, reduced physical activity, unhealthy eating habits, and poor compliance. These factors increase the risk of developing the diseases and also contribute to poor disease prognosis [23]. Furthermore, relevant studies have reported [24] that genetic factors are also one of the etiologies of CHD-DD.

3. Clinical Treatment Methods

3.1. Behavioral Intervention Therapy

Studies have shown that the comprehensive approach combining psychological behavioral intervention therapy with physical exercise exhibits significant effects in alleviating depressive symptoms and also has a positive impact on a series of complications caused by depression [25]. In addition, social support intervention is also an important non-pharmacological treatment method. It not only plays an important role in directly improving patients' depressive behaviors but also has a positive effect in preventing the long-term risk of cardiovascular disease [26].

3.2. Pharmacological Treatment

3.2.1. Antidepressant Drugs

Traditional antidepressants are mainly classified into tricyclic antidepressants (TCAs), tetracyclic antidepressants, and monoamine oxidase inhibitors. Commonly used TCAs include imipramine and amitriptyline, which have certain efficacy in treating depression. However, long-term use may cause adverse reactions such as cardiotoxicity, anticholinergic effects, and autonomic nervous dysfunction, and may also induce severe arrhythmias and pose a risk of hypotension. Therefore, they should not be used long-term in the treatment of coronary heart disease patients [27]. The representative tetracyclic antidepressant is maprotiline, which has relatively selective effects on 5-hydroxytryptamine (5-HT) and norepi-

nephrine (NE) and fewer adverse reactions compared to TCAs [28].

In addition, new antidepressants have gradually come into use: ① Selective serotonin reuptake inhibitors (SSRIs). The representative drug of SSRIs is fluoxetine. Compared with traditional tricyclic antidepressants, SSRIs have less impact on the heart. The latest studies have found that SSRIs can significantly reduce the risk of myocardial infarction in patients with depression complicated by coronary heart disease [29]. ② Serotonin-norepinephrine reuptake inhibitors (SNRIs). SNRIs exert antidepressant effects by simultaneously inhibiting the reuptake of 5-HT and norepinephrine. Venlafaxine, as a representative drug of SNRIs (dual reuptake inhibitor of 5-HT and NE), has a significant therapeutic effect when combined with fluoxetine (an SSRI) and can reduce adverse reactions such as increased blood pressure and heart rate [30]. ③ Norepinephrine and specific serotonin antidepressants (NaSSAs), with mirtazapine as the representative drug. The mechanism of action of NaSSAs is to block presynaptic norepinephrine neuron receptors in the central nervous system, thereby enhancing the release and transmission of NE and 5-HT, and specifically blocking 5-HT2 and 5-HT3 receptors to exert their pharmacological effects [31]. The main side effect of such drugs is weight gain, but their impact on the cardiovascular system is minimal. Therefore, NaSSAs are the first-choice drugs for treating coronary heart disease patients with a history of PCI (percutaneous coronary intervention) and comorbid depressive symptoms. ④ Flupentixol and Melitracen Tablets (Deanxit). Deanxit is a composite drug composed of flupentixol hydrochloride and melitracen hydrochloride, which is commonly used in clinical practice for the treatment of anxiety and depression symptoms. This drug regulates nervous system function by increasing the levels of neurotransmitters such as dopamine (DA) in the body and inhibiting the secretion of adrenaline, thereby exerting anti-anxiety and antidepressant effects. Meanwhile, it can also enhance the therapeutic effect on angina pectoris [32]. Deanxit not only takes effect quickly but also has good safety. Its two components can restrict each other after combination, effectively reducing the occurrence of adverse reactions [33]. Therefore, it is often regarded as a preferred option in clinical treatment.

3.2.2. Drugs for Treating Coronary Heart Disease

Drugs for relieving symptoms and improving ischemia include: ① Nitrate drugs. These drugs can rapidly dilate coronary arteries and peripheral blood vessels, reduce cardiac load, and relieve angina pectoris attacks, making them the first-choice drugs for treating coronary heart disease and angina pectoris. Representative drugs are nitroglycerin and isosorbide dinitrate. These drugs are currently recognized as effective in quickly relieving angina pectoris; however, they cannot fundamentally solve the problem of coronary artery stenosis. Patients still need to take other prognosis-improving drugs regularly and receive other treatments when necessary. ② β-receptor blockers. These drugs can slow down the heart rate, reduce myocardial oxygen consumption, and relieve angina pectoris. Representative drugs include metoprolol, bisoprolol, and atenolol. Li Yunliang *et al.* [34] ob-

served the efficacy of metoprolol combined with isosorbide dinitrate and aspirin in the treatment of elderly patients with unstable angina pectoris through a clinical controlled trial. They found that the effective rate was 96.67%, and the combined application could reduce the number of angina pectoris attacks, significantly improve cardiac function indicators, and have high safety. ③ Calcium channel blockers. Their mechanism of action is to block calcium ion influx, promote relaxation of vascular smooth muscle, and achieve dilation of coronary arteries and peripheral arterioles, thereby improving myocardial blood supply. Representative drugs include nifedipine and amlodipine. Chinese Expert Consensus on Clinical Application of Different Nifedipine Preparations [35] points out that nifedipine can significantly reduce the incidence of cardiovascular events in patients with coronary heart disease complicated with hypertension, with high safety, but long-term use may bring risks such as myocardial hypertrophy.

Drugs for preventing myocardial infarction and improving prognosis include: ① Antiplatelet drugs. These drugs can prevent platelet aggregation and reduce thrombus formation. Their representative drugs are aspirin and clopidogrel. Aspirin can irreversibly inhibit cyclooxygenase (COX-1), block the conversion of arachidonic acid to thromboxane A2 (TXA2), thereby inhibiting platelet aggregation and thrombus formation, and achieving the purpose of preventing myocardial infarction [36]. Although aspirin is beneficial to most patients with cardiovascular diseases, its use in specific populations such as those with diabetes or obesity requires caution. ② Statins. These drugs mainly stabilize atherosclerotic plaques by reducing the levels of cholesterol, triglycerides, and other components in the blood. Their representative drugs include atorvastatin and simvastatin. Zha Fei *et al.* [37] conducted a clinical comparative observation on 150 elderly patients with hypertension complicated with hyperlipidemia and found that individualized dose adjustment of simvastatin could effectively improve the patients' blood lipid levels. ③ ACEI/ARB drugs. These drugs can inhibit the renin-angiotensin system, reduce the production of angiotensin II, improve myocardial remodeling, and reduce the risk of cardiovascular events. Representative drugs include enalapril (ACEI) and valsartan (ARB).

3.3. Surgical Treatment and Others

Currently, the main surgical treatments for coronary heart disease with angina pectoris are percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG). Both treatment methods are used to restore blood supply to occluded coronary arteries using instruments (such as artificial stents or autologous/artificial blood vessels) when drugs fail to relieve the condition and surgical indications are met. They have significant efficacy and are widely promoted in clinical practice. In terms of surgical treatment for depression, some new studies and technologies in recent years have provided new ideas for the treatment of treatment-resistant depression (TRD). Yuki *et al.* [38] found through a series of retrospective studies that the use of electroconvulsive therapy (ECT) in TRD pa-

tients resulted in a symptom remission rate of 85.7% and an adverse event rate of 21.4%, with a significant reduction in suicide risk during long-term follow-up.

4. Integrated Traditional Chinese and Western Medicine Treatment

Integrated traditional Chinese and Western medicine treatment, which is characterized by complementary efficacy, reduced adverse reactions, decreased drug dosage, and shortened treatment course, represents a new trend in disease treatment in the future. Lin Zhiqiang *et al.* [39] conducted a clinical randomized controlled study on the treatment of CHD-DD using Ruangan Huaxian Decoction combined with Western medicine. The results showed that the clinical effective rates of angina pectoris and depression in the treatment group were higher than those in the control group ($P < 0.05$), with fewer adverse reactions. Cheng Mingwei [40] conducted a clinical intervention observation on 36 patients with coronary heart disease complicated with anxiety or depression (of the qi stagnation and blood stasis type) using Shugan Huxin Formula on the basis of conventional Western medicine treatment. The results showed that the total effective rate (97.22%) in the treatment group and safety indicators such as AST, SCr, and BUN were significantly better than those in the control group, demonstrating the superior effect of the synergistic treatment of this disease with integrated traditional Chinese and Western medicine.

5. Summary and Outlook

In recent years, the incidence of CHD-DD has been increasing year by year, and its pathogenesis and treatment methods have attracted extensive attention in academic circles. Western medicine treatment takes effect quickly, but problems such as adverse reactions, drug resistance, and dependence still exist; traditional Chinese medicine treatment has a long course, leading to poor patient compliance; while integrated traditional Chinese and Western medicine treatment, which adheres to the principles of holistic concept and syndrome differentiation and treatment and adapts to various stages of disease development, is favored by patients. However, its action targets and mechanisms are still under exploration. This article reviews the pathogenesis and treatment methods of CHD-DD, aiming to provide a reference for related mechanism research on this disease. However, the research on the literature in this paper may have deficiencies in terms of breadth and depth. In the future, efforts should be made to expand the literature database and the range of years to make up for these shortcomings.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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