DOI: 10.15806/j.issn.2311-8571.2015.0027 World J Tradit Chin Med 2015; 1(4): 38–41

Pathophysiological Characteristics of Phlegm-stasis Cementation Syndrome in Coronary Heart Disease: a Review and Update

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ABSTRACT

The pathophysiological characteristics of Phlegm-stasis Cementation Syndrome in Coronary Heart Disease (CHD) has been summarized in this article. According to epidemiological investigations, phlegm-stasis cementation syndrome has become a dominant syndrome in CHD along with the improvement in living and dietary condition. The interaction between blood stasis and phlegm turbidity that is called Phlegm-stasis Cementation Syndrome exists in CHD and other diseases. The bridge linked blood stasis and phlegm turbidity lies in the adversely effects of lipid metabolism disorder on platelet activation, vascular function and hemorheology indexes. Lipid metabolism disorder also can induce persistent inflammation including monocyte/macrophage activation and oxidative stress. Inflammation also is an important stimulating factor for atherosclerosis and the biology that underlies the complications of CHD, which belonged to the concept of "toxin" in Traditional Chinese medicines (TCM). On the other hand, the important function of inflammatory process on abnormal hemorheology, platelet activation and vascular dysfunction can be used to elucidate the basic pathogenetic condition of the toxin inducing blood stasis in TCM. Therefore, it is this pathological process that can be used to address the basic pathogenetic theory of phlegm turbidity inducing the symptom of toxin and blood stasis, and subsequently phlegm-stasis cementation in TCM. We deduced that lipid metabolic disturbance, inflammation activation, vascular dyfunction and hemorheological disorders could be as pathophysiological characteristics of Phlegm-stasis cementation syndrome.

Key words: pathophysiological characteristics, phlegm-stasis cementation syndrome, coronary heart disease, review
Received 5 August 2015; Accept 29 October 2015

INTRODUCTION

Coronary heart disease (CHD) continues to be the leading cause of morbidity and mortality among adults in the developing countries[1]. Over the last decades, the quest to develop systematic therapies to cure the CHD has been fraught with frustration and failure. Despite the success in coronary stent implantation, nearly all efforts in the development of pharmaceutical options to limit the progression of CHD have led to disappointment. Traditional Chinese medicine (TCM) has been used in the treatment of CHD over centuries. TCM is gaining popularity among hyperlipidemic patients in China due to its low cost and minimal adverse effects[2]. TCM has a unique theoretical system incorporating its ancient wisdom, philosophy and culture over more than two thousand years. TCM syndrome or pattern ("Zheng" in Chinese Mandarin) is an integral part of TCM theory and is a characteristic profile of clinical presentations identified by TCM practitioners. Zheng differentiation is a critical part of TCM diagnosis that will guide the clinical treatment. There are usually several syndromes, such as syndrome of qi deficient with blood stasis and syndrome of cold-coagulation with blood stasis existing in the process of CHD[3,4]. But following the improvement in living condition and dietary structure in China, the main syndrome in CHD has also changed[5]. Accumulated evidence indicates that phlegm-stasis cementation syndrome is now a dominant syndrome which yields predictive and prognostic information of considerable clinical utility[6]. The current review is design to provide an overview of pathophysiological characteristics and basis of the phlegm-stasis cementation syndrome in CHD.

THE CHARACTERISTICS SYNDROME IN CHD

1. The characteristics of phlegm turbidity (phlegm) syndrome in CHD

Phlegm turbidity is one of the important syndromes in TCM and is a specific risk factor for a range of diseases[7]. Phlegm turbidity is associated with metabolic disorders caused by fat and sugar rich food and/or addiction to alcohol and cigarette smoking. According to TCM theory, phlegm turbidity may block blood circulation, interfere with the normal function of important body systems, and cause a variety of complex pathological changes characterized by diverse clinical manifestations. Specifically when phlegm turbidity blocks the coronary arterial system, ischemic impairments will occur as a result of inadequate blood supply to meet the need of cardiac contractions leading to symptoms of

angina pectoris such as feeling of squeezing, pressure, heaviness, tightness, or pain across the chest.

Thus phlegm turbidity syndrome refers to symptoms caused by the retention of phlegm in the body although the consensus on the standards for diagnosing Phlegm turbidity has not been acquired. Due to the fact that phlegm turbidity derives from metabolic disturbance of nutrients including lipid metabolism, we deduced that phlegm turbidity could correlate with hyperlipidemia. Kong et al[4] have demonstrated that the plasma levels of triglycerides (TG), total cholesterol (TC) and LDL cholesterol (LDL-C) were higher in phlegm turbidity syndrome when compared with other TCM syndromes with asthenia nature. Patients with both early and late-stage hyperlipidemia exhibit pathological changes similar to the characteristic features of phlegm turbidity[8]. Moreover, there is accumulating evidence that TCM interventions aiming to improve phlegm turbidity demonstrate beneficial effects in the treatment of hyperlipidemia[9].

Although hyperlipidemia has been suggested to be associated with phlegm syndrome of CHD and biomarkers such as TG, TC and LDL-C were found to significantly increase the risk of phlegm syndrome of CHD in some studies, the phlegm syndrome of CHD is also associated with other pathological factors[10], such as insulin resistance, which can induce metabolic disorder in humans associated with disease from the perspective of the whole organism[11]. More future studies are needed to further investigate the relationship of the phlegm syndrome of CHD and metabolic disturbance of glucose and lipid.

2. The characteristics of blood stasis syndrome in CHD

Blood stasis syndrome (BSS) refers to slowing or stagnation of blood and is a complex pathophysiological state characterised by decreased or impeded blood circulation in the body. BSS has many symptoms and signs. In October 1988[12], "International Conference on Blood Stasis Syndrome" was held in Beijing, China. In the meeting, a consensus was reached by a group of academics from China, Japan, Korea, Singapore etc., on the following standards for diagnosing BSS: 1) Purple tongue or blood stasis spots on tongue; 2) Typical choppy pulse or no pulse; 3) Pain occurs in a fixed, local point (or chronic pain, stabbing pain, aversion to pressure); 4) Blood stasis in abdomen; 5) Accumulation of blood stasis; 6) Bleeding out of vessels (hemorrhage, bruises due to trauma); 7) Mucosal blood stasis, abnormality in blood vessels and collecterals; 8) Dysmenorrhea with dark blood clots, amenorrhea; 9) Abnormality on skin and nails; 10) Numbness in hemiplegia; 11) Mania due to blood stasis; and (12) Laboratory work-up shows stasis in blood circulation.

A recent epidemiological investigation has demonstrated that BSS is a major syndrome type of CHD. The BSS score was positively correlated with the number of coronary arteries involved, the more severe the BSS, the higher the thrombolysis in myocardial infarction (TIMI) risk score[13]. Similarly, the severity of BSS is significantly correlated with the complexity of coronary lesions and the degree of stenosis, and is an important factor affecting the occurrence of restenosis after percutaneous coronary intervention.

Previous studies have investigated the biomedical mechanisms underpinning BSS of CHD from the modern medicine's viewpoints in a variety of diseases ranging from hemorheological disorders, to inflammatory and immunological diseases[14]. Blood stasis is related to the obstruction in micro-circulation, irregularity in hemorheology, abnormality in hemodynamics, platelet and endothelial dysfunction, and unbalance of anti-coagulation and fibrinolysis.

Hemorheology is the study of flow properties of blood and its elements, including plasma, red blood cells, white blood cells, and platelets. The common hemorheological parameters include whole blood viscosity, plasma viscosity, hematocrit, fibrinogen, and red cell aggregation. The number and function of blood cells and other components affect blood viscosity. For example, an elevated concentration of fibrinogen and other high-molecular weight plasma proteins leads to increased blood viscosity, which can reduce organ perfusion under the condition of decreased pressure gradients and exhausted vascular reserve[15]. Changes in hemorheological parameters can eventually affect blood flow and coagulation process. Clinical studies showed that abnormality in hemorheological parameters is common in patients with BSS of CHD compared to their healthy counterparts. Chen et al[16] investigated the changes in hemorheology in 167 patients with BSS of CHD and found increased whole blood viscosity and fibrinogen, prolonged erythrocyte electrophoresis time, and faster erythrocyte sedimentation rate in patients with BSS of CHD compared with the healthy controls. The results from a study by Li[17] showed that the whole blood viscosity in patients with BSS of CHD was significantly higher than that in healthy controls. In a study of 34 patients with BSS of CHD and 40 with qi-deficiency of CHD, Yi[18] also found that the BSS group was associated with a significant increase in hematocrit, whole blood viscosity, and plasma viscosity when compared to the qi-deficiency group. Whilst these above studies demonstrate increased whole blood viscosity in BSS of CHD, further studies are required to determine whether BSS of CHD affect other hemorheological mechanisms.

Microcirculation refers to micro or small vessels in the vascular system and can be as the site where the earliest manifestations of cardiovascular disease occur.[19] Qiu et al[20] found that BSS was associated with blurred vascular loops, slowed blood flow, increased erythrocyte aggregation index and decreased diameter and length of vascular loops indicating that microcirculation disturbance may be one of the important pathological mechanisms underpinning BSS of CHD. The balance of coagulation and fibrinolysis processes plays an important role in the formation of thrombosis. Hypercoagulation commonly occur in patients with BSS of CHD. Liang et al[21] had demonstrated that antithrombin III: antibody and ATIII: antigen levels in the BSS of CHD were significantly less than those in the normal control group. This may be due to the activation of the coagulation system and the binding of ATIII to clotting factors suggesting that the coagulation function may be augmented in BSS of CHD.

Tissue-type plasminogen activator (t-PA) and plasminogen activator inhibitor-1 (PAI-1) levels represent activity of the fibrinolysis system. Mao et al[22] showed that patients with BSS of CHD had a significantly higher plasma PAI-1 level and lower t-PA level. Furthermore, BSS of CHD group had the lowest ratio of t-PA to PAI-1 compared with the non-BSS of CHD and healthy control groups. These findings suggested that the abnormal fibrinolytic activity can expose patients with BSS of CHD to a prothrombotic state. These results also indicated that the dysfunction of the coagulation and fibrinolysis systems could be an important contributor to the pathogenesiss of BSS of CHD.

Endothelial dysfunction is a hallmark for vascular diseases and is often regarded as an important early event in the development of atherosclerosis[23]. Endothelial dysfunction and augmented constrictor sensitivity also can occur in patients with BSS of CHD. Ling et al[24] demonstrated that patients with BSS of CHD had higher Von Willebrand factor and sICAM-1 levels and lower soluble P-selection levels than those with non-BSS of CHD and healthy controls. Heightened platelet reactivity and activation also affect the occurrence of ischemic events in CHD patients[25]. Li et al[26] suggested that patients with BSS of CHD had abnormally higher levels of platelet activation sensitivity and thrombosis forming ability. In addition, CD41 and actin γ are possible marker proteins and play a crucial role in the occurrence and development of BSS in CHD.

3. The characteristics of interaction between blood stasis and phlegm turbidity in CHD

According to TCM theory, the interaction between blood stasis and phlegm turbidity exists in CHD and other diseases. The bridge linked blood stasis and phlegm turbidity not only lies in the adversely effects of lipid metabolism disorder on platelet activation, vascular function and hemorheology indexes, inflammation also be an important stimulating factor for atherosclerosis and the biology that underlies the complications of CHD, which belonged to the concept of "toxin" in the theory of Chinese medicine[27]. Blood lipids as the customary risk factors for CHD have been widely recognized. Previous studies showed there was an increased in platelet sensitivity to the aggregating agents, epinephrine and ADP in individuals with familial hypercholesterolemia[28]. Results from animal studies showed that short-term, diet-induced hypercholesterolemia increased the infarct size of the heart and this change results, at least in part, from a decrease in collateral blood flow to ischemic myocardium during coronary artery occlusion[29]. Moreover, hypercholesterolemia and advanced age selectively impair endothelium-mediated relaxation of the coronary microvasculature in response to acetylcholine[30].

On the other hand, in an animal model of obesity/metabolic syndrome induced by a diet high in saturated fat and refined carbohydrate with 0.15% cholesterol resulted in an increase of adipose tissue macrophage accumulation, local inflammation and chronic systemic inflammation compared to animals that received the same diet without added cholesterol[31, 32]. Low serum HDL cholesterol concentration is strongly correlated with enhanced status of inflammation, endothelial activation and oxidative stress. It is also an independent predictor for enhanced inflammation and endothelial activation, which are pivotal in the pathogenesis of atherosclerosis and atherosclerosis-related complications[33]. These results illustrated the link between lipid metabolism and inflammatory process, which underlies the interaction between phlegm turbidity and toxin in TCM. Further, clinical studies suggested that alterations of hemorheology in metabolic syndrome were probably due to the effect of chronic inflammation and oxidative stress[34]. Endothelin-1 (ET-1) is a potent vasoconstrictor and its plasma level correlates with systemic inflammation, but not with myocardial injury or left ventricular ejection fraction in patients undergoing percutaneous coronary intervention and on-pump coronary artery bypass grafting[35]. Therefore, the important influence of inflammation on hemorheology, platelet and vascular function can be used to elucidate the basic pathogenetic condition of toxin inducing blood stasis in TCM making inflammation a useful tool for risk assessment in clinical practice and a therapeutic target for treating CHD. The recent JUPITER trial supports the clinical utility of an assessment of inflammatory status in guiding interventions for cardiovascular events[36].

In summary, inflammatory process is the key linking lipid metabolism and hemorheology, platelet and vascular function in CHD although other unclear mechanisms may also play a role. This pathological process underpins the basic pathogenic theory of phlegm turbidity inducing toxin and blood stasis, and subsequently phlegm-stasis cementation in TCM.

CONCLUSION

Due to the improvement in living and dietary condition, phlegm-stasis cementation syndrome has become a dominant syndrome in CHD. Its pathophysiological process has involved lipid metabolic disturbance, inflammation activation, vascular dysfunction and hemorheological impairment, which represent the pathophysiological characteristics of phlegm turbidity and blood stasis in TCM respectively. Much more research is needed to establish the exact mechanisms underlying the tightly regulated phlegm-stasis cementation syndrome of CHD. One potential approach is to combine the laboratory tests with systems biology approaches, which include omics techniques, microRNA (miRNA) and mRNA expressions, etc, in the investigation of the potential presence of phlegm-stasis cementation syndrome of CHD. This hopefully would shed light on other potential mechanisms to better our understanding of phlegm-stasis cementation syndrome in the progression of atherosclerotic disease and its complications.

ACKNOWLEDGMENTS

This work is supported by a National 973 Project (No.2015CB554405).

DISCLOSURE

There are no conflicts of interest for any of the authors.

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