



Coronary Microvascular Dysfunction and Microvascular Angina

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Abstract

Many patients present with myocardial ischemic symptoms, but fail to be diagnosed of obstructed coronary artery disease, since the normal coronary arteries or no any atherosclerosis stenosis $\geq 50\%$ at coronary angiography. Myocardial ischemia can be caused by either abnormalities of epicardial coronary arteries or coronary microvascular dysfunction (CMD). Patient with microvascular angina in the absence of coronary artery disease and myocardial diseases, CMD is suggested to be the unique cause of symptoms. The previous clinical and pathogenetic classification of CMD is based on presence or absence of coronary artery disease, myocardial diseases, or other traditional risk factors, which would obscure the importance of the disease primarily provoked by CMD. The role of atherosclerotic plaque rupture in epicardial coronary arteries and the abnormality of hemorheology (especially in perimenopausal women) should be more stressed in the pathogenetic mechanism of CMD. The pathogenetic mechanism of CMD will be classified according to microvascular structure (embolization and stenosis), microvascular function and blood risk factors in this paper. The CMD related diseases including cardiac X syndrome and coronary slow flow would be better uniformly named as microvascular angina. While little data supported therapies for CMD related diseases so far, the blood healthy therapy as a novel method is recommended to treat microvascular angina, especially in the patients with high hematocrit, increased blood viscosity and coronary slow flow.

INTRODUCTION

Myocardial ischemia can be caused by abnormalities of epicardial coronary arteries as well as coronary microvascular dysfunction (CMD) [1-6]. CMD is defined as impaired coronary flow reserve and myocardial ischemia owing to structural and/or functional abnormalities of the microcirculation. Diseases related to CMD include cardiac syndrome X (CSX), coronary slow flow (CSF) and microvascular angina (MVA), in which the patients present with myocardial ischemic symptoms, and have either normal coronary arteriogram or non-obstructive ($< 50\%$ stenosis) coronary artery disease (CAD) [1-6]. Diagnosis of MVA requires an extensive workup to rule out other potential causes of chest pain and can be

relatively expensive. Treatment with conventional anti-anginal medications is often not successful, which results in patients being limited in their daily activities, seeking emergency care for their chest pain, and needing to take time off or abandon their work because of persistent symptoms. Prolonged and recurrent chest pain also necessitates repeated coronary arteriographies as well as regular outpatient visits. The lifetime cost of healthcare for a woman with non-obstructive chest pain is estimated at approximately \$1 million [7, 8] which is often comparable with that caused by obstructive CAD. CMD can be classified into the following categories: in the absence of CAD and myocardial diseases, in the presence of myocardial diseases, in the presence of

obstructive epicardial CAD, iatrogenic dysfunction [1-5], and after cardiac transplantation [3]. The pathogenetic mechanisms of CMD can be structural, functional or extravascular [1, 3]. In MVA, patients with angina attacks in the absence of CAD and myocardial diseases, CMD has been suggested to be the unique cause of symptoms [2, 3, 6]. Given the CMD as the pathogenetic mechanism in MVA, the role of atherosclerotic plaque rupture in epicardial coronary arteries [9], as well as the abnormality of hemorheology [10], especially in perimenopausal women, should have been stressed in the development of CMD. This article will focus on CXS, CFS and MVA, discuss the pathogenesis of CMD from microvasculature to blood, and introduce the blood healthy therapy as a novel method for treatment and prevention of MVA.

Pathogenetic Mechanisms of CMD

The coronary arterial system is composed of different compartments which including large epicardial arteries (500 μ m to 2 to 5mm in diameter), pre-arterioles (< 500 μ m), arterioles (< 200 μ m, intramyocardial vessel) [1, 3] and capillaries (~7 μ m). The coronary microcirculation is the coronary arteries that are not be visualized at angiography (< 500 μ m), which are important in regulating blood flow to match oxygen demand, inflammation, coagulation, and permeability. The pathogenetic mechanisms of CMD will be reviewed and classified in microvascular structure (embolization and stenosis), microvascular spasm and blood risk factor, as shown in Table 1.

Table 1. Classification of Pathogenetic Mechanisms of Coronary Microvascular Dysfunction

	Microvascular angina		Macrovascular angina
	CSX	CSF	CAD
Severity of epicardial coronary stenosis	1-49%	1-49%	\geq 50%
Microvascular embolization	+	++	+
Plaque rupture	+	+	+
Microvascular stenosis	++	+	\pm
Atherosclerotic disease burden		+	++
Diabetes	+	+	+
Hypertension	+	+	+
Micro-vasculitis	+		
Microvascular spasm			
Endothelial dysfunction	+	+	\pm
Abnormal autonomic nervous system	+		
Blood risk factors			
Blood viscosity \uparrow	++	+	\pm
Hematocrit \uparrow	+	\pm	\pm
Dyslipidemia	\pm	\pm	\pm
Homocysteine \uparrow	\pm	\pm	\pm
Lipoprotein (a) \uparrow	\pm	\pm	\pm
Inflammatory cytokines \uparrow	+	+	+
Other factors			
Female/male	++/ \pm	\pm /++	
Perimenopause	+		+
Current smoking		++	+
Emotional stress	+		\pm
Cold outside	+	+	\pm
Oxygen-poor/enclosed environment	+		

\pm indicates may /or may not have effect; + indicates having effect; ++ indicates having more effect.

CSX : cardiac syndrome X, CSF: coronary slow flow, CAD: coronary artery disease.

Microvascular Embolization

Microvascular embolization is one microvascular structure abnormality mainly caused by either plaque rupture or erosion in epicardial coronary arteries. After atherosclerosis plaque rupture or erosion, three harmful consequences could be followed: (1) acute large thrombotic occlusion of a coronary artery presents with acute coronary syndrome; (2) debris released from necrotic core leads to distal microvascular embolization causing CMD; (3) microvascular embolization and large thrombosis forms simultaneously or successively. Many times after plaque rupture there is no large thrombosis without typical acute coronary syndrome, but some microvascular embolization or microvascular

obstruction forms as the debris obstructs blood flow in pre-arterioles, arterioles and capillaries [11, 12]. A sparse distribution of myocardial ischemia or necrosis leads to small area or foci of myocardial infarction. It is sufficient to produce ECG changes and myocardial perfusion scintigraphic defects, but may not result in detectable contractile abnormalities, because of the normal function of the surrounding myocardial tissue. Similarly, the release of ischemic metabolites by the sparse myocardial ischemic foci into the coronary sinus can go undetected because of their dilution in the larger flow normal myocardial areas [2, 4]. Actually, in lesions with advanced lumen narrowing (>50% stenosis), histopathology almost invariably reveals 1 or more healed subclinical plaque ruptures. Plaque rupture is not only found in the narrowest coronary artery [13]. Plaque

rupture and its healing lead to progressive lumen obstruction. Plaque rupture and its healing can also lead to CMD and small area of new or old myocardial infarction. Repeat hospitalization for chest pain might associate with plaque rupture or erosion [9], if some coronary arteries were stenotic at angiography.

Numerous studies have provided the evidence that the particular matter and vasoactive molecules releasing into the microcirculation at the time of percutaneous coronary intervention (PCI) and can cause CMD [1, 4, 14].

Microvascular Stenosis

Microvascular stenosis is another structural pathogenetic abnormality related to CMD. Studies reported that all patients with angina in the absence of obstructive CAD had some evidence of atherosclerosis [15]. Pathophysiological consequences of atherosclerosis may extend into coronary pre-arterioles or arterioles, where intimal atherosclerotic injury may relate to microvascular stenosis [4, 5], which might occur in hypertension, type 2 diabetes, micro-vasculitis (infection or rheumatoid disease), and coronary artery virus infection after cardiac transplantation. The structural abnormalities of the small intramural coronary arteries include medial hypertrophy, intimal hyperplasia, decreased luminal size and low resilience of arterioles, which are likely to induce CMD and myocardial ischemia. Additionally, the extramural compression of microvasculature by hypertrophic myocyte or myocardial edema makes arterioles luminal size to decrease, and affects myocardial blood flow, leading to CMD in hypertrophic cardiomyopathy, myocarditis, myocardial infarction, and no-reflow after PCI [15].

Microvascular Spasm

Microvascular spasm is considered as a functional abnormality of microvasculature, without stenosis or embolization in pre-arterioles and arterioles. When focal inflammation occurred in coronary microvasculature, the abnormal nitric oxide metabolism and the dysregulation of inflammatory cytokines would result in endothelial and/or medial smooth muscle dysfunction or injury. Impairment in endothelium-dependent dilation of the coronary microvasculature occurs in the early stages of epicardial atherosclerosis. Adrenergic receptors and alterations in the expression or production of local vasoactive substances such as angiotensin II and endothelin might take an important role for development of microvascular spasm [4]. The pathogenesis of CMD may variously involve a transient increase in neurohumoral vasoconstrictor activity and a background of increased susceptibility to vasoconstrictor agents by the coronary microcirculation [2]. An increased activity of the sympathetic autonomic nervous system coupled with parasympathetic

withdrawal leads to abnormal coronary microvascular tone. Declined protection of estrogen to endothelium thereby preferentially impacts peri- or postmenopausal women to be with microvascular spasm.

The endothelial and/or medial smooth muscle dysfunction, which can involve the whole coronary tree, can lead to severe coronary constriction that can be caused by a diversity of stimuli, e.g. exercise, anxiety, and yet unidentified triggers [16]. In one study, one hundred twenty-four patients with exertional angina and angiographically normal coronary arteries (0-20% diameter reduction) underwent intracoronary acetylcholine test. Coronary spasm was seen in 77 patients, 35 patients (45%) with epicardial spasm ($\geq 75\%$ diameter reduction with reproduction of the symptoms of the patient) and 42 patients (55%) had microvascular spasm (reproduction of symptoms, ischemic electrocardiographic changes, and no epicardial spasm) [16]. In another study, in 139 patients with angina in the absence of obstructive coronary artery disease, 32 patients (23%) had no coronary explanation for their angina, with normal endothelial function, normal coronary physiological assessment, and no myocardial bridging [17].

Blood Risk Factors

The risk factors of blood are conceivably associated with CMD. The risk factors include elevated hematocrit [18], erythrocyte ($\sim 7\mu\text{m}$ in diameter) with low deformability, hyperlipidemia, hyperglycemia, over-sensitive inflammatory cytokines, erythrocyte-immune complex after infection [19], increased plasma viscosity, and hypercoagulation. Specially, high level of fibrinogen, together with systemic or local suppression of fibrinolytic performance and platelet aggregation, leading to transient thrombosis or microvascular embolization that impairs the coronary blood flow or myocardial microcirculation, would be the risk for myocardial infarction [20], also play an important role in pathogenesis of CMD.

The changes of erythrocyte and the cholesterol in erythrocytes should be specially addressed in peri- or postmenopausal women. Free cholesterol content of the erythrocyte membranes exceeds that of all other cells in the body, with lipid constituting 40 percent of the weight. By contributing to the deposition of free cholesterol, and enlargement of the necrotic core, the accumulation of erythrocyte membrane within an atherosclerotic plaque may represent a potent atherogenic stimulus, and increase the risk of plaque destabilization [21]. As the estrogen level declining in postmenopausal women, forty years' regularity of menstruation (discharging about 60 ml blood each month) would cease abruptly. The natural way for releasing lipid in erythrocyte would close. That might affect the content and metabolism of cholesterol in erythrocyte, and lead to abnormality of hemorheology (elevated hematocrit, erythrocyte with low

deformability and increased blood viscosity), which would associate with the development of thrombosis or microvascular embolization, therefore, increase the risk of cardiovascular events as well as play the pathogenesis role of CMD.

In the development of CMD, the vascular and blood factors can play the role independently, or interact with each other. Based on coronary microvascular stenosis, microvascular coronary spasm together with increased blood viscosity and slow blood flow would impair microcirculation more frequently. If so, recurrent focal myocardial ischemia and even microvascular embolization formation might occur, leading to cardiomyocyte apoptosis and necrosis, microvascular myocardial infarction and localizer of replacement fibrosis. Other factors contributing to CMD include female, positive family history as genetic background and lifestyle such as smoking, alcohol drinking, postprandial and even cold weather.

CMD related Diseases

Recurrent ischemic chest pain and the risk of myocardial infarction and heart failure were still very high even after successful PCI in many patients with CAD and CMD [2-4]. Some patients with diabetes hospitalized for heart failure as the onset symptoms, since the main pathogenesis of diabetes was CMD at the early stage of disease. Other diseases, such as hypertrophic cardiomyopathy, dilated cardiomyopathy, aortic stenosis, myocarditis, Anderson-Fabry's disease and amyloidosis, are associated with CMD in the pathogenesis. However, this review will focus on CSX, CSF and MVA, in which the patients present with myocardial ischemic symptoms, but fail to be diagnosed of obstructed CAD, since the normal coronary arteries or no any atherosclerosis stenosis $\geq 50\%$ at coronary angiography [3-5].

CSX

Harvey Kemp in 1973 named CSX, which could be defined broadly as angina-like chest discomfort with normal epicardial coronary arteries on angiography. A proposed more strict definition of CSX entails the following criteria: (1) exercise-induced, angina-like chest discomfort; (2) ST-segment depression during angina; (3) normal epicardial coronary arteries at angiography; (4) no spontaneous or inducible epicardial coronary artery spasm upon ergonovine or acetylcholine provocation; (5) absence of cardiac or systemic disease associated with microvascular dysfunction such as hypertrophic cardiomyopathy or diabetes.⁷ For many years, it was thought that CSX had a benign prognosis, however, recent evidence has challenged the assumption. Five-year annualized event rates for cardiovascular events (myocardial infarction, stroke, and hospitalization for heart failure) were 16.0%

in symptomatic women with nonobstructive CAD (stenosis 1% - 49%), 7.9% in symptomatic women with normal coronary arteries (0% stenosis), and 2.4% in asymptomatic women [22].

In patients with recurrent chest pain, the absence of any angiographic lesion greater than 50% in any coronary vessel is the primary exclusion criteria for the diagnosis of CSX. The large vessel coronary dysfunction (vasospastic angina) presents with angina at rest, reversible ischemic ECG changes (usually ST elevation rather than depression) and spontaneous/induced coronary spasm on angiography. Myocardial bridge is an anatomic variant created when the coronary artery (typically LAD) tunnels through a segment of myocardium [23]. Echocardiogram can be used to rule out structural and inflammatory disorders, such as hypertrophic cardiomyopathy and pericarditis. Chest pain of non-cardiac origin (e.g. gastrointestinal, musculoskeletal, pulmonary, or psychiatric) must be ruled out.

The pathogenesis of CSX is considered as the result of myocardial ischemia secondary to microvascular coronary spasm, microvascular stenosis and abnormal rheological variables. Chest pain in CSX may be hyperawareness of changes in right atrial pressure and volume during exertion. Psychologic and behavioral factors, such as hypochondriasis, anxiety, and panic disorders are common in CSX patients, whose chest pain could be usually provoked by stress. Repeated episodes of transient ischemia may functionally alter cardiac afferent nerve ending to a hypersensitive state [7]. Individuals with CSX often show the evidence of stress-induced ischemia, most in postmenopausal women.

CSF

CSF was first described by Tambe et al. in 1972, as delayed opacification of coronary vessels during angiography without any evident obstructive disease. The presentation of CSF is extremely diverse ranging from stable or unstable angina, myocardial infarction, to ventricular tachycardia. The overall incidence of CSF is 1% patients who undergo coronary angiography [24, 25].

CSF without established pathogenesis could be affected by coronary microvascular stenosis, spasm and blood risk factors [24, 26] CSF, sometimes referred to as Syndrome Y, is given the proposed role of neuropeptide Y. Abnormal constrictor response to neuropeptide Y at the microcirculation level might be associated with the mechanism [27] Microvascular embolization, a result of activated platelets and vasoactive debris from plaque rupture in epicardial arteries, should play an important role in the development of CSF. The clinical features of CSF include a higher prevalence in current male smokers and rest or mixed-pattern angina rather than angina on exertion [2, 24, 25].

MVA

In 1998, Cannon and Epstein introduced the term of MVA for the patients who have chest pain, without fixed or dynamic obstruction in epicardial coronary arteries on arteriography [2, 5]. MVA can be defined as secondary and primary MVA, the latter was classified in stable and unstable MVA on the basis of clinical presentation [2, 4]. Stable MVA is characterized by angina episodes that are exclusively or predominantly related to effort and can be identified with the clinical entity usually referred as CSX [2]. Unstable primary MVA can be defined as a de novo or worsening pattern of angina, usually characterized by a prolonged attack or recurrent episodes at rest or with mild effort, caused by abnormalities in coronary microcirculation. Some of these patients also show mild elevation of serum markers of myocardial damage, particularly troponins. SCF may be a relatively frequent finding in patients with unstable MVA. The diagnosis of MVA requires ruling out CAD as a cause of the ischemic symptoms. Patients with epicardial spasm can be ruled out when their presentation is typical (i.e., angina at rest associated with ST-segment elevation) or when provocation tests of spasm are positive [2]. Stress-related cardiomyopathy, belonging to unstable MVA, also referred to as apical ballooning syndrome or takotsubo disease is usually triggered by sudden intense emotional or even physical stress. Patients are usually postmenopausal women and present with symptoms and signs compatible with acute coronary syndrome [2, 4].

From the concept and clinical setting, CSX and CSF seem to be included in MVA, of which the pathogenesis is mainly related with CMD. About half of individuals with angina or ischemic heart disease are fail to be diagnosed of CAD [6, 28]. The related diseases including CSX and CSF due to CMD would be better uniformly named as MVA for better communication and investigation. Additionally, if the elevations of troponins are detectable, coronary microvascular myocardial infarction could be diagnosed, given the pathophysiology of CMD. The category of microvascular myocardial infarction is better than subendocardial infarction or non-ST-segment elevation myocardial infarction.

Recently, the following standardized criteria were proposed for the investigative diagnosis of MVA due to CMD: (1) presence of symptoms suggestive of myocardial ischemia; (2) absence of obstructive CAD (<50% coronary diameter reduction and/or fractional flow reserve (FFR) >0.80); (3) objective evidence of myocardial ischemia as well as evidence of impaired coronary microvascular function. The latter may be documented by (a) an impaired coronary flow reserve (CFR) (cut-off values depending on methodology use between ≤ 2.0 and ≤ 2.5) or (b) coronary microvascular spasm, defined as reproduction of symptoms, ischemic ECG shifts, but no epicardial spasm during

acetylcholine testing or (c) abnormal coronary microvascular resistance indices (e.g. index of microcirculatory resistance, $IMR > 25$) or (d) CSF, defined as TIMI frame count > 25 [6].

Assessment of CMD

Diagnostic indices of CMD could be classified as invasive or noninvasive technique. Blood rheological variables and biochemical index can be assessed for the risk of CMD in the suspected patients with MVA.

After ruling out the patients with obstructive CAD by the conventional angiography, TIMI frame count can provide an approximate estimation of epicardial vs. microvascular abnormalities [4]. Classically, intracoronary acetylcholine has been used as a sensitive and safe test for the assessment of coronary vasomotor function in the catheterization laboratory. Its administration causes vasodilation under normal conditions but, in the absence of a functional endothelium, it leads to vasoconstriction by the unopposed stimulation of muscarinic receptors on vascular smooth muscle cells [3, 16].

The pressure-temperature sensor-tipped guidewire is another effective method of evaluation, allowing simultaneous measurement of FFR, CFR and calculation of IMR [3, 29]. Coronary blood flow measurements at baseline compared with maximal hyperemic stimuli are used to evaluate the function of the microcirculatory vessels. Adenosine is used as the gold standard to invoke an endothelium-independent hyperemic response in vessels less than $150\mu\text{m}$ by stimulating the adenosine A₂ receptors on smooth muscle cells. Same as adenosine, dipyridamole and papaverine are also used to trigger arteriolar vasodilation, increase coronary blood flow, mainly by a direct relaxing effect on vascular smooth muscle cells [3, 4].

IMR showed no correlation with FFR and angiographic lesion severity, and the predictors of high IMR value were different from those for ischemic FFR value [29]. Elevated IMR at the time of primary PCI predicts poor long-term outcomes [30]. Integration of FFR, CFR and IMR investigated the existence of differentiated patterns of ischemic heart disease that combine focal and diffuse coronary narrowing with variable degrees of CMD [31]. Transthoracic echocardiographic Doppler recording of coronary blood flow in the left anterior descending coronary artery could be used as a first routine method to identify CMD. Other non-invasive techniques for assessing CMD include the contrast stress echocardiography, cardiovascular magnetic resonance, and positron emission tomography [2, 3].

Treatment of MVA and Blood Healthy Therapy

Systematic reviews of treatment strategies for CMD in human subjects with angina, there was little data to

support therapies for CMD, and no specific treatment was sufficiently well-documented to be recommended [32, 33]. Developing strategies for the effective treatment of MVA is urgently needed.

Blood healthy therapy, as a new therapeutic apheresis based on isovolumic hemodilution and hemapheresis, was previously described [20] Briefly, withdrawing some vein blood in a certain ratio of blood/weight, separating plasma and blood cells, some plasma or erythrocyte would be discarded, if necessary, according to consider the rheological variables and blood biochemical index. Gradually improved the components in blood cells and plasma over a certain period of time, the risks factors in blood, such as elevated LDL-c, triglyceride, glucose, fibrinogen and large groups of macromolecules including inflammatory cytokines, could decrease. While discharged some erythrocyte with low deformability, the much younger red blood cells could carry more oxygen and penetrate into the microvasculature. Less erythrocyte aggregates and whole blood viscosity decreases. Blood flow velocity increases. As all tissue perfusion increased, more oxygen and nutrients will be delivered to cells. Spasticity in microvascular arteries might relieve. While the blood healthy therapy modulates the blood to be thrombosis resisting, it will be efficient to decline the rate of acute coronary events or stroke [20] and might be effective to treat the patients with MVA, including those with high hematocrit, increased blood viscosity and CSF, especially in the peri- or postmenopausal women.

CONCLUSIONS

Researches demonstrate that CMD can lead to myocardial ischemia and microvascular myocardial infarction. Many patients with chest pain owned to CMD. Their prolonged and recurrent chest pain necessitates repeated coronary arteriographies and regular outpatient visits. The lifetime cost of healthcare for this population is often comparable with that caused by obstructive CAD. The CMD induced diseases including CSX and CSF would be better uniformly named as MVA. Blood healthy therapy as a potential therapeutic approach in patients with MVA is recommended.

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