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Editorial

The Evolution of Diastolic Function may be a Marker of Myocardial Ischemia in Coronary Slow Flow Phenomenon

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The coronary slow flow phenomenon (CSFP) is characterized by delayed coronary vessel opacification in the absence of significant epicardial coronary artery stenosis. CSFP can lead to significant myocardial ischemia and even myocardial infarction, with elevation of cardiac enzymes.[1] CSFP has also been associated with life-threatening arrhythmias and sudden cardiac death.[2]

The pathophysiological mechanisms causing delayed coronary flow have not yet been fully elucidated. Coronary microvascular dysfunction is considered to be the main contributor to the pathogenesis of CSFP. The coronary circulation consists of the epicardial arteries and the microvasculature including the prearterioles and arterioles. The epicardial arteries act as conduit vessels and offer little resistance to coronary flow in the absence of stenosis; they start contributing to total coronary vascular resistance after the development of significant diameter stenosis of 50%, and may reduce basal flow only after more than 90% stenosis.[3] The prearterioles and arterioles (diameter <400 μm) are called resistance vessels and are the major component of coronary vascular resistance. The regulation of coronary blood flow is mainly controlled by the changes in the vasomotor tone of these resistance vessels.[3] Although obstructive coronary artery disease traditionally refers to stenoses of the epicardial coronary arteries, abnormalities in coronary microvasculature can also cause clinically significant myocardial ischemia.[4] Evidence of combined structural and functional abnormalities of the coronary microvasculature have been reported in CSFP. In patients with CSFP, histological changes were found in the coronary microvasculature, including fibromuscular hyperplasia, medial hypertrophy, myointimal proliferation, endothelial degeneration.[5] CSFP was also associated with chronically elevated resting coronary microvascular tone, with abnormal vasomotor responsiveness to cold pressor and acetylcholine stimuli in some patients.[6] Endothelial dysfunction, inflammation, subclinical atherosclerosis, increased tortuosity also contribute to the development of CSFP.[7]

The research by Zayat et al.[8] provide interesting observations on the changes of left ventricular (LV) diastolic function in patients with myocardial infarction caused by CSFP. This study included 92 patients with acute non-ST segment elevation myocardial infarction (NSTEMI) and CSFP confirmed by coronary angiography. NSTEMI was defined as symptoms

of acute myocardial ischemia along with rise in cardiac troponin levels, excluding ST segment elevation myocardial infarction. CSFP was diagnosed with coronary angiography using TIMI frame count greater than two standard deviations of the normal range for coronary flow. All patients had normal LV ejection fraction and there was a low prevalence of regional wall motion abnormalities with an average wall motion score index of 1.23; on the other hand, the prevalence of LV diastolic dysfunction was 75%. Three months after the NSTEMI, the prevalence of LV diastolic function decreased to 30.4%, and various echocardiographic indices of diastolic function such as isovolumic relaxation time, mitral E deceleration time, medial and lateral e′ as well as E/e′, and peak tricuspid regurgitation velocity showed significant improvement. Of the 69 patients with initial LV diastolic dysfunction, 41 patients showed improved diastolic function while 28 patients showed persistent diastolic dysfunction at 3 months follow-up. No significant differences in medications including angiotensin converting enzyme inhibitors, angiotensin receptor blockers, calcium channel blockers, statins, or dual antiplatelets were found between the patients with improved versus unimproved diastolic function. As expected, persistent LV diastolic dysfunction was associated with increased heart failure events. There were no significant predictors of improvement of LV diastolic dysfunction on multivariable analysis.

In myocardial ischemia, diastolic dysfunction precedes resting LV regional wall motion abnormalities, electrocardiographic changes, and angina, known as the ischemic cascade.[9] Impaired LV diastolic function has been consistently observed in patients with CSFP, with or without LV systolic dysfunction,[10-12] and can be attributed to myocardial ischemia related to slow coronary flow. The aggravation and improvement of LV diastolic function in patients with CSFP likely reflects the changes in coronary slow flow and subsequent ischemia, especially in the absence of regional wall motion abnormalities or systolic dysfunction. This implies that the LV diastolic function can be a sensitive parameter of myocardial ischemia in patients with CSFP. In parallel, revascularization and consequent resolution of myocardial ischemia have been associated with improved LV diastolic function in patients with obstructive coronary artery disease.[13]

In the study by Zayat et al,[8] the improvement of LV diastolic function suggests that myocardial ischemia and presumably coronary slow flow were improved during the follow-up after NSTEMI in these patients with CSFP. The improvement of LV diastolic function seemed to occur spontaneously, and no significant predictors of improvement of LV diastolic dysfunction were found. However, the use of beta-blockers was not checked in the study, which is a limitation. The use of beta-blockers was associated with improvement of LV diastolic function in patients with acute myocardial infarction due to obstructive coronary artery disease,[14] and may also improve LV diastolic function in patients with CSFP.[11] Also, dipyridamole was suggested to improve LV systolic and diastolic function in patients with CSFP.[15][16] Although insignificant (p=0.08), peak troponin levels tended to be higher in patients without improvement of diastolic dysfunction compared to those with improvement, which suggests that greater myocardial ischemia occurred in patients who later showed persistent diastolic dysfunction. In patients with ischemic cardiomyopathy, improvement of LV diastolic function was related to the amount of viable tissue at baseline.[13] In patients with CSFP, persistent diastolic dysfunction was associated with increased heart failure events, and implies that diastolic dysfunction can also act as a prognostic marker.

CSFP is yet a mysterious disease, it is yet unclear whether there is a fluctuation in the severity of delayed coronary flow in these patients, and what the contributing factors are that cause

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acute aggravation or improvement of coronary flow. The LV diastolic function also seems to fluctuate in CSFP, and presumably reflects myocardial ischemia related to aggravation of coronary slow flow. Diastolic function in CSFP may be useful as a non-invasive marker of the severity of myocardial ischemia and also a prognostic factor, especially in the absence of regional wall motion abnormalities or systolic dysfunction. Recently, LV longitudinal strain is being highlighted as a sensitive index of LV systolic function and also reflects diastolic function.[17] LV longitudinal strain is associated with the extent of myocardial ischemia[18] and may also be a useful parameter in patients with CSFP, which need future research. Further studies are warranted to elucidate the natural evolution of CSFP, and also to unearth the factors that are related to the aggravation or improvement of delayed coronary flow and may be potential therapeutic targets.

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