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Relationship between Coronary Slow Flow and Endothelial Dysfunction

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Coronary slow flow (CSF) is a vascular phenomenon which is detected by angiography images, created using a contrast dye, that are characterized by delayed distal vessel opacification without any significant epicardial coronary artery stenosis. This phenomenon, in clinical practice, is observed with a respectively high incidence, a rate of 7% in patients who have diagnostic coronary angiography [1]. CSF is seen in higher rates with patients who are young male smokers. Patients who have CSF might have a variety of symptoms from being asymptomatic to typical angina or unstable angina with a diagnosis of acute coronary syndrome [2].

Since this phenomenon was first identified, multiple hypotheses have been proposed to enlighten the pathophysiology of CSF, including small vessel disease, microvascular vasomotor dysfunction, diffuse atherosclerosis and endothelial dysfunction. But these pathophysiological mechanisms remained as hypotheses and the exact mechanism for this angiographic phenomenon had never been fully understood. Mosseri et al. [3] hypothesized that local small vessel dysfunction was the reason behind CSF and this hypothesis was supported by myocardial biopsies in research which revealed a loss of luminal size due to thickening of vessel walls during coronary microcirculation. But further research, in 1996, by Beltrame et al. [4] indicated a decreased response to endothelial stimuli in CSF patients. After these studies, intravascular ultrasound (IVUS) was used to observe the vessel thickening. Researchers showed that CSF patients had diffuse intimal thickening together with calcification which did not cause any luminal irregularities in the coronary angiography. Similarly in 2004, Pekdemir et al. [5] demonstrated that CSF patients had extended and widespread calcification in the epicardial coronary arteries and suggested that these calcifications may be a preliminary sign or cause of atherosclerotic disease in the coronary arteries; furthermore, CSF could be a form of early detection for atherosclerosis, a condition which affects the microvascular circulation [5]. Another finding revealed the relationship between ectasia in the coronary arteries and slow flow [6]. It is known that the velocity of fluids in pipes can be altered when the pipe is suddenly enlarged or curved. Accordingly, abrupt changes in the vessels, like ectasia, can create a flow that might be slower compared to a vessel with ideal conditions. Based on the research, pathophysiology behind the CSF might be suggested not only as a structural problem but also as a microcirculatory dysfunction in the coronary arteries.

On the other hand, the assessment of flow-mediated dilatation (FMD) of the brachial artery has been widely used to investigate the endothelial function of the arteries. One of the studies showed that there was a concomitant relationship between CSF and FMD of the brachial artery. Patients who had CSF also showed reduced endothelial-dependent FMD of the brachial artery in an ultrasound [7]. Another finding indicated the concentrations of nitric oxide (NO) and endothelin-1 (ET-1) were lower in the CSF patients [8]. Kurtoglu et al. [9] investigated the effect of dipyridamole treatment which showed beneficial progress in restoring the flow in these patients. In another study, Tanriverdi et al. [10] showed impairment of endothelial function due to homocysteine induced oxidative stress in CSF patients. These findings suggest that CSF might be associated not only with local disease but with systemically affected endothelial dysfunction.

Both this systematical involvement and the microcirculation abnormality of coronary arteries may be associated with impaired choroidal microcirculation. It has been shown in animal models that atherosclerotic changes occurred in choroidal arteries [11]. Studies showed that subfoveal

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choroidal thickness (SFCT) decreased in the patients who had retinitis pigmentosa due to a microcirculation abnormality [12,13]. These findings revealed the obvious relationship between vascular beds. In 2014, Ahmad et al. [14] showed that patients with coronary artery diseases had a thinner macular choroid than controls. In 2014, Altinkaynak et al. [15] showed that patients with congestive heart failure presented lower SFCT compared to age- and gender-matched controls. Another study indicated a close relationship between CSF and SFCT; additionally, the study demonstrated improvement of SFCT with the treatment of statin therapy [16].

Patients with CSF may also present with other clinical features. Yilmaz et al. [17] studied the clinical and laboratory relationships of CSF patients and found a close relationship between CSF and the following clinical problems: insulin resistance, impaired glucose tolerance, metabolic syndrome with the presence of higher total cholesterol, low-density lipoprotein cholesterol, fasting glucose and body mass index. Therefore, anti-inflammatory statin therapies are studied for patients who have CSF and mentioned clinical problems.

Statins work in a variety of ways to effect CSF patients **(Figure 1)**. Statins can effectively lower cholesterol levels by inhibiting endogenous cholesterol synthesis. This lowering effect might restore the endothelial function; however, trials showed that endothelial function was restored in patients before the levels of lipids were lowered, suggesting the cholesterol-independent effect of statins [18]. Taken together, endothelium dependent vasodilation was triggered by statin therapy which was associated with lowering cholesterol; statins also reduced the endothelin-1 release in endothelial cells [19,20]. Another effect of statin treatment was the modulation of the inflammatory process in the coronary arteries. Commonly, statin treatment significantly lowered the high-sensitive C-reactive protein (CRP) [21]. A statin lowered not only high-sensitive CRP, but it also decreased the interleukin-6 (cultured mononuclear cell) levels as well as inflammatory cytokine levels in *in vitro* studies of human cells [22,23].

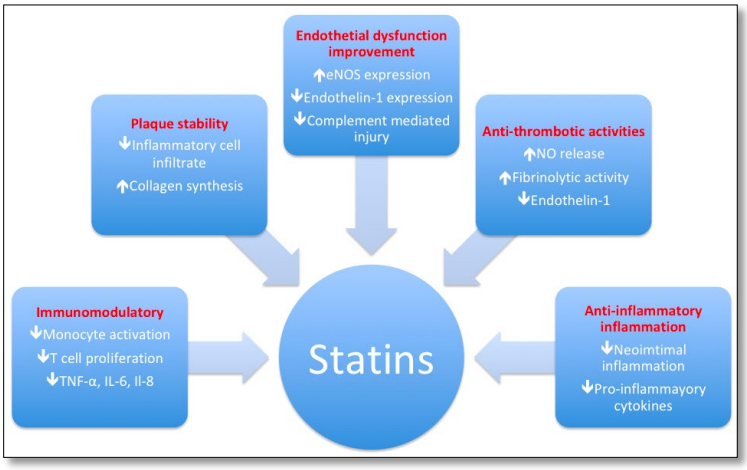

Figure 1. Pleiotropic effects of statins in atherosclerotic disease: Focus on the endothelial dysfunction.

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