The light of inflammation in the darkness of the coronary slow flow phenomenon

Koroner yavaş akım fenomeninin karanlığında enflamasyon ışığı

Patients with the syndrome of angina and normal coronary arteries, the so called cardiac syndrome X, often exhibit the coronary slow flow phenomenon, described for the first time forty years ago by Tambe et al. (1) and defined as an angiographic pattern characterized by delayed distal vessel opacification despite the absence of obstructive coronary artery disease. The main pathophysiological hypothesis to justify the occurrence of this phenomenon is an impairment of microvascular function. Prognosis of patients with microvascular angina is generally good (2). However, it has been recently outlined that in presence of the slow flow phenomenon prognosis is worse (3). In fact, the slow flow phenomenon has been associated to increased risk of cardiac dysfunction (4), fatal arrhythmias (5), diffuse atherosclerosis (6) and acute coronary syndromes (7). Several studies have in the past addressed the potential pathophysiological mechanisms of angina in patients with cardiac syndrome X (8). In particular, it has been suggested that increased sympathetic outflow to the cardiovascular system may be responsible for both symptoms and inducible ischemia (9-13). Since the autonomic nervous system plays a central role in the regulation of coronary blood flow, increased sympathetic activity could be responsible for both primary reduction of coronary blood flow and reduced vasodilator reserve, which is observed in some patients with syndrome X (14, 15). Previous studies have also shown that endothelial dysfunction (16-18) and inflammation (19) might play important roles in the pathogenesis of microvascular angina. Furthermore, histopathological studies have demonstrated structural abnormalities of the cardiac microvasculature (20). However, the mechanisms responsible for the dysfunction of coronary microcirculation in patients with slow flow require further investigation.

In the present issue of the Anatolian Journal of Cardiology, Durakoğlugil et al. (21) report the results of a study aimed at evaluating the relationship between the coronary slow flow phenomenon and the levels of soluble CD40, a marker of inflammation and prothrombotic state, in a group of patients with angina and normal coronary arteries. The authors analyzed data from 50 patients with coronary slow flow and 20 matched controls with normal flow. The clinical characteristics were not different between the two groups and also serum C-reactive protein levels were similar. Conversely, serum CD40 was shown to be higher in the slow flow group and in multivariate analysis was also shown to be a predictor of coronary slow flow.

This is an interesting study since it tries to better define the relationship between two important, but not yet completely understood, pathophysiological elements in cardiac syndrome X, namely slow coronary flow and inflammation. In the recent years the latter has increasingly become a mainstay, to an extent that atherosclerosis is today considered as an inflammatory disease involving multiple components of the immune system (22), even though many points still need to be addressed and, furthermore, translated in everyday clinical practice (23). As stated above, inflammation has been considered as one of the possible underlying mechanisms also in patients with slow flow (19, 24). In fact, increased platelet activation (25) and elevated plasma markers such as endothelin-1 (17, 18, 26) and adhesion molecules ICAM-1, VCAM-1 and E-selectin (27) have been shown to be present in this context. Inflammation appears to be also present in most patients with acute (28) and chronic coronary disease (29) as well as in patients with metabolic syndrome (30) who, on the other hand, share several characteristics with patients with microvascular angina (16-18). The study by Durakoğlugil et al. (21), in particular, has focused on the potential role of the soluble CD40. The CD40/CD40 ligand system has a widely accepted role in atherothrombosis (31). Elevated levels of soluble CD40 have already been shown to be associated with severe ischemic burden in cardiac syndrome X (32). In view of the prognostic role of slow flow in cardiac syndrome X and the evidence that elevated soluble serum CD40 can be a predictor of ischemia magnitude, the results of the study published in the present issue of the Anatolian Journal of Cardiology appear particularly stimulating (21). Taken together with previous studies, they offer another piece of the way that can conduct towards new therapies for the case of slow coronary flow. Furthermore, the paper by Durakoğlugil et al. (21) can help in understanding some of the effects observed administering well-

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known drugs. Statins, for example, have been shown to be beneficial in patients with coronary slow flow and it has been suggested that this can be due to their pleiotropic and anti-inflammatory properties (33): recently, in particular, simvastatin and atorvastatin have been demonstrated to reduce the expression of CD40 ligand on platelet surface (34).

The results of Durakoğlugil et al. (21) open a new path in the understanding of microvascular angina pathophysiology. Certainly further studies will be necessary to evaluate the long-term prognostic implications of coronary slow flow, the role of inflammation in the pathogenesis of this phenomenon and the potential role of specific anti-inflammatory pharmacological interventions.

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