

## Invited Editorial / Davetli Editöryal Yorum

### Cardiac syndrome X: An important cause of microvascular angina

#### Kardiyak sendrom X: Mikrovasküler anginanın önemli bir nedeni

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The definition of cardiac syndrome X (CSX) is angina-like pain on effort, ST-segment depression on an exercise stress test, and totally normal coronary arteries observed on an angiography in the absence of any other cardiac or systemic diseases known to influence vascular function (for example, hypertension or diabetes). Although the origin of the syndrome is still debated, several studies have suggested that CSX is mainly caused by coronary microvascular dysfunction, and indeed the term is often used as a synonym for microvascular angina.<sup>[1]</sup> In an attempt to provide more pathophysiological insight, and to reflect technological developments, the definition of this clinical entity evolved over time to include evidence of impaired coronary flow reserve and, more recently, newer techniques that increase the diagnostic capacities of angiography (Table 1).<sup>[2]</sup>

Despite agreement on the clinical characteristics and the favorable long-term outcome of CSX, there are multiple inconsistencies regarding the etiology of chest discomfort in these patients. Three decades of conflicting research have culminated in 2 major hypotheses. The traditional “ischemic hypothesis” proposes that chest discomfort in these patients is the clinical manifestation of myocardial ischemia, most likely secondary to abnormal coronary microvascular function. However, the inability to reliably and consistently demonstrate microvascular dysfunction/myocardial ischemia in all patients with CSX, in conjunction with major technical advances in imaging modalities, have led to the proposal of an alternative “nonischemic

hypothesis,” which proposes that alterations in pain perception and/or myocardial hypersensitivity may be the basis of chest discomfort in this group of patients.<sup>[3]</sup> Abnormalities in coronary microvascular function resulting from a combination of impaired relaxation and/or increased sensitivity to vasoconstriction in vessels of less than 500 µm in diameter form the cornerstone of the ischemic hypothesis. It is now generally accepted that in a proportion of patients with syndrome X, a cascade of events starting with transient episodes of microvascular dysfunction leads to impaired myocardial perfusion, with resistant myocardial ischemia causing episodes of chest discomfort.<sup>[4]</sup>

A wide variety of invasive studies (using coronary sinus thermodilution and intracoronary Doppler) and noninvasive studies (using a radionuclide scan, echocardiography, positron emission tomography [PET], magnetic resonance imaging [MRI], brachial artery ultrasonographic flow, and glyceryl-trinitrate-mediated dilation) have been undertaken in an attempt to demonstrate microvascular abnormalities in CSX. The results have demonstrated that both endothelium-dependent (as investigated by coronary flow responses to pacing and/or acetylcholine) as well as endothelium-independent (as investigated by responses to adenosine, dipyridamole, and/or papaverine) microcirculatory dysfunction may be present in each patient. Furthermore, a proportion of patients may also

#### Abbreviation:

CSX Cardiac syndrome X

PET Positron emission tomography

MRI Magnetic resonance imaging

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**Table 1. Proposed definition of cardiac syndrome X**

Typical stable angina, exclusively or predominantly induced by effort
Findings compatible with myocardial ischemia/coronary microvascular dysfunction on diagnostic investigation*
Normal (or near normal**) coronary arteries on angiography
Absence of any other specific cardiac disease (for example, variant angina, cardiomyopathy, valvular disease)

\*Including one or more of (1) diagnostic ST-segment depression during spontaneous or stress-induced typical chest pain, (2) reversible perfusion defects on stress myocardial scintigraphy, (3) documentation of stress-related coronary blood flow abnormalities by more advanced diagnostic techniques (for example, cardiac magnetic resonance imaging [MRI], positron emission tomography [PET], or Doppler ultrasound), or (4) metabolic evidence of transient myocardial ischemia (cardiac PET or MRI, invasive assessment).

\*\*Vascular wall irregularities or discrete very mild stenosis (<20%) in epicardial vessels seen on angiography.

simultaneously exhibit a profoundly abnormal coronary microvascular vasoconstrictive response (as investigated by coronary responses to ergonevine, hand grip, and/or cold pressor test).<sup>[5]</sup>

The earliest body of convincing data indicating microvascular dysfunction in CSX was derived from work by Cannon et al.<sup>[6]</sup> They demonstrated the effect of the endothelium-dependent and -independent responses on microvascular resistance in patients with CSX. Metabolic markers of ischemia were also measured simultaneously to establish that the proposed abnormal microcirculatory responses resulted in a significant reduction in myocardial perfusion, and hence, less myocardial ischemia. Symptomatic patients had a significantly higher oxygen extraction capacity (derived from a widening of arterial–coronary sinus oxygen differential) and a decrease in myocardial lactate utilization, such a fall being an indicator of anaerobic metabolism.<sup>[7]</sup> Buffon et al.<sup>[8]</sup> have reported a decrease in coronary sinus pH and sustained increases in lipid hydroperoxides and conjugated diene levels, indicative of myocardial ischemia, in coronary sinus blood samples during symptomatic phases of patients with CSX. In a noninvasive <sup>31</sup>P-nuclear magnetic resonance spectroscopy study, where in response to handgrip testing, patients with CSX demonstrated a greater loss in the phosphocreatinine/adenosine triphosphate ratio in comparison with patients with established coronary artery disease.<sup>[9]</sup> Cetin et al.<sup>[10]</sup> reported in a study published in the Archives of the Turkish Society of Car-

diology that myocardial energy expenditure, which was calculated using transthoracic echocardiography-derived parameters: circumferential end-systolic stress, left ventricular ejection time and stroke volume, was increased in CSX patients compared with control groups. It was an important study that demonstrated increased energy expenditure in CSX using echocardiography, which is easily available, but their results might be supported by invasive (using coronary sinus thermodilution and intracoronary Doppler) and non-invasive (PET or MRI) methods in large-scale studies. Moreover, another study limitation was the inclusion of patients with diabetes mellitus, which is a secondary cause of microvascular dysfunction, in the study.

In conclusion, CSX constitutes a significant subset of patients undergoing coronary angiography. It is essential to identify and treat them specifically for microvascular angina.

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