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Possible role of *Helicobacter pylori* infection via microvascular dysfunction in cardiac syndrome X

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Abstract

Recently, some investigators have reported seeing microvascular dysfunction in patients with cardiac syndrome X (CSX). In addition, Helicobacter pylori *(*H. pylori*), a bacterium causing chronic gastritis and peptic ulcers, has recently been associated with CSX. Yet the mechanism(s) by which* H. pylori *infection leads to CSX is poorly understood. We propose a link between* H. pylori *and microvascular dysfunction infection in the development of CSX.* (Cardiol J 2009; 16, 6: 585–587)

Key words: cardiac syndrome X, *Helicobacter pylori*, inflammation, endothelial, microvascular dysfunction

Introduction

Cardiac syndrome X (CSX) is a condition characterized by the presence of angina pectoris and a positive response to stress or radionuclide tests (thallium scan) with a normal coronary arteriogram [1]. It is found in up to 20% of angina patients undergoing angiography [2]. The varied pathogenic mechanisms responsible for the condition, and the varying diagnostic criteria used by different investigators, have helped complicate the diagnosis and management of CSX patients [3].

H. pylori and inflammation

Previous studies have shown an association between viral and bacterial infections (such as *Helicobacter pylori* [*H. pylori*] infection) with vascular diseases such as ischemic heart disease and CSX [4]. *H. pylori* is a gram-negative bacterium which infects the human stomach [5], may cause extra-intestinal manifestations some of which are functional ischemic heart disease andrespiratory system disease [6, 7], and has recently been associated with CSX [2]. Infection with *H. pylori* may be associated with systemic and vascular inflammation. Prevalence of seropositivity to *H. pylori* significantly increases in subjects with high sensitive C reactive protein (CRP), a sensitive marker of systemic inflammation. Furthermore, serum CRP levels positively correlate with anti-*H. pylori* antibody titer levels.

Therefore, chronic infection with *H. pylori* may account for, at least in part, the elevated serum CRP level [7]. Chronic infection of *H. pylori* is most probably the cause of increased production of various inflammatory metabolites, such as interlukin-1, interleukin-6 and tumor necrosis factor-alpha which also affect blood vessel motility and induce endothelial dysfunction [8]. It has been shown that *H. pylori* induces gastric mucosal injury and inflammation that might be caused by the oxidant-mediated expression of inflammatory cytokines, and inflammatory enzymes [9, 10]. Systemic inflammatory reaction can be detected by showing increased plasma levels of different pro-inflammatory cytokines and acute-phase proteins which then may lead to several diseasessuch as CSX [11]. A circulating soluble form of intercellular adhesion molecule-1

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(ICAM-1), which is expressed on the activated endothelium in response to inflammatory cytokines, also was elevated in subjects positive to anti-*H. pylori*. Moreover, a previous study showed that *H. pylori* eradication was associated with a significant reduction in serum CRP levels and a significant rise in serum HDL-cholesterol [12].

Inflammation and endothelial dysfunction

On the other hand, many observational studies have indicated that an elevated level of CRP is independently associated with future risk of coronary heart disease and stroke [13], supporting the hypothesis that inflammation plays an important role in the pathogenesis of atherosclerosis [14].

Recent observations suggest a role of inflammation in the pathogenesis of endothelial dysfunction [15] and correlation of CRP-concentration with severity of symptoms in patients with CSX [16]. The potential importance of inflammation in the pathogenesis of CSX is highlighted by the beneficial effects observed with the use of statins and angiotensin- converting- enzyme inhibitors in patients with CSX [17]. Chronic inflammation leads to an increase in the generation of pro-inflammatory cytokines, cell adhesion molecules, and growth factors that can elicit inflammatory and proliferative changes in the vessel walls, resulting in endothelial dysfunction [18]. Leukocyte binding to cellular adhesion molecules on the surface of vascular endothelium in response to many inflammatory cytokines and CRP may be the earliest event in a vascular inflammatory process [14].

Endothelial dysfunction and microvascular dysfunction

CSX encompasses several possible causal mechanisms. Cardiac and non-cardiac mechanisms have been proposed, among which 'endothelial dysfunction' of the coronary microcirculation features prominently [19]. According to the response-to-injury hypothesis of atherosclerosis, endothelial dysfunction is the first step in atherosclerosis [14]. This hypothesis has been supported by many studies, indicating that endothelial dysfunction occurs in subjects with classic risk factors such as hypertension, diabetes mellitus, hypercholesterolemia, and smoking [20]. The mechanisms responsible for endothelial dysfunction in CSX patients are not well understood but risk factors such as obesity, hypertension, hypercholesterolemia, diabetes, hyperhomocysteinemia and smoking may play a role [11]. Moreover, plasma levels of circulating ICAM-1 and vascular adhesion molecule-1 are increased in patients with CSX, suggesting endothelial cell activation [11, 21]. Also, increased plasma concentration of the powerful vasoconstrictor endothelin-1 (ET-1) has been reported in peripheral blood of CSX patients and has been shown to correlate with endothelial dysfunction; moreover, ET-1 has been found to increase the coronary circulation of patients with CSX during arterial pacing [15].

On the other hand, CRP levels are known to be associated with endothelial cell activation and coronary endothelial dysfunction [22]. Reduced nitric oxide bioavailability due to endothelial dysfunction [23] and enhanced ET-1 expression, promoted by raised CRP levels [24], may be implicated in systematic endothelial vasoreactivity leading to microvascular angina [25, 26]. Several studies have shown that patients with CSX have coronary microvascular abnormalities [15]. Both vasodilator stimuli and vasoconstrictor stimuli have been used to assess coronary microvascular function in patients with CSX. The study of vasodilator function has further concerned the assessment of endothelium-dependent and endothelium-independent mechanisms. Thus, endothelial function has an important role in microvascular function [15]; and coronary endothelial dysfunction leading to microvascular angina has been proposed as a pathogenic mechanism in CSX [11, 25, 26]. Endothelium-dependent coronary microvascular function has mainly been studied by assessing the coronary blood flow response to acetylcholine, the vasodilator effect of which is mediated by nitric oxide release by endothelial cells [15, 23]. Some studies have shown reduced endothelium-dependent vasodilatation or increased vasoconstriction (or both) in response to various stimuli such as exercise in epicardial coronary artery vessels of patients with CSX [15].

Hypothesis

Due to the factors that occur secondary to *H. pylori* infection, we speculate that *H. pylori* may also cause endothelial dysfunction directly by affecting the structure and function of vascular endothelial cells via inflammation.

H. pylori may cause endothelial dysfunction. *H. pylori* infection causes chronic inflammation and increases the generation of pro-inflammatory cytokines, cell adhesion molecules, growth factors and acute-phase proteins. An increase in these factors may affect vessel motility and can elicit inflammatory and proliferative changes in the vessel walls

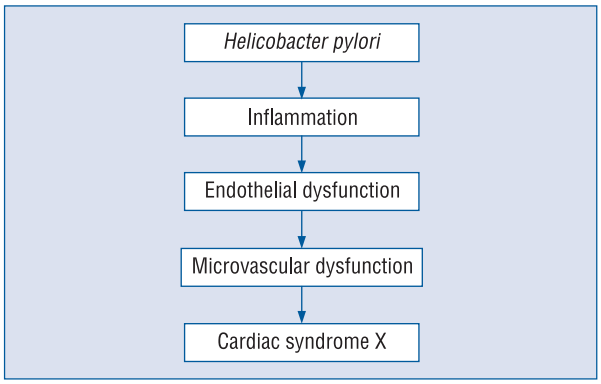

Figure 1. Scheme of the hypothesis based on the main pathogenic mechanisms and functional abnormalities that may contribute to microvascular dysfunction in patients with cardiac syndrome X.

(microvascular dysfunction) via endothelial dysfunction (Fig. 1).

In conclusion, we hypothesize that *H. pylori* infection can be a trigger for the probable mechanism of endothelial dysfunction via chronic inflammation in the pathogenesis of CSX.

Since endothelial dysfunction is the trigger point for many diseases, we must pay more attention to the diagnosis and treatment of *H. pylori*. *H. pylori* may be the cause of, or at least one of the leading factors in, many other diseases. To address this hypothesis, further prospective studies are warranted to evaluate the role of *H. pylori* eradication on endothelial function.

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