

Helicobacter Pylori Infection: A Hypothetical Balance between Improvement of Coronary Blood Flow and Permissive Pathophysiologic Promotion of Chronic Inflammatory Process of Atherosclerotic Plaque: A Case Report

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Abstract

Helicobacter pylori infection, in patients with classic risk factors of coronary heart disease, can present with typical clinical manifestations of ischemic heart disease without characteristic electrocardiographic changes or elevation of serum cardiac biomarkers. H. pylori does not participate in the initiation of inflammatory process of coronary atherosclerotic plaque. Instead, a commensal bacterium increases the coronary blood flow even in presence of classic risk factors of coronary heart disease. Under certain circumstances, Helicobacter pylori may aggravate an already existing inflammatory atherosclerotic process of coronary vasculature with consequent rupture and development of ischemic heart disease. This is in analogy with the physiologic role of platelet in primary haemostatic plug versus its undesired role in formation of vascular thrombosis. The factors that lead to shifting of Helicobacter pylori from a commensal promoter of coronary blood flow to a pathogenic organism activating the inflammatory response of atherosclerotic plaque remain to be elucidated.

Keywords: H. pylori, coronary heart disease, inflammatory process, atherosclerotic plaque, heart work, oxygen extraction.

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INTRODUCTION

Marshall and Warren [1], two Australian researchers who discovered the bacterium Helicobacter pylori (H. pylori) and deciphered its role in gastritis and peptic ulcer disease. H. pylori is a microphilic gram negative bacteria belonging to the family helicobacter, is found mainly in the gastrointestinal tract of human beings. It infects about 50% of world population, out of which 10% develop peptic ulcer and around 10% develop gastric cancer [2]. H. pylori plays an important role in chronic inflammatory process of the pathogenesis of gastrointestinal diseases [3]. H. pylori can form a biofilm on gastric epithelial cells which contribute in adapting to the changing environment in gastric mucosa, helping in longer survival and fight against immune system [4]. Numerous diagnostic methods exist to detect infection that include endoscopic and non-endoscopic methods, technique used may be direct (culture, microscopic demonstration) or indirect methods (urease test, stool culture, PCR) [5]. Different treatment regimens are

used which include the first line therapy (concomitant therapy and hybrid therapy), second line therapy (bismuth-containing quadruple therapy or levofloxacin-containing therapy) and third line therapy (culture-guide therapy) [6]. Because of its proinflammatory nature, H. pylori infection has been associated with wide range of extra gastrointestinal diseases [7]. These include cardiovascular diseases, respiratory tract disorders like laryngeal and lung cancer, dermatological disorder like chronic urticaria, hematological disorders like immune thrombocytopenic purpura, Henoch-Schonlein purpura, iron deficiency anemia and cobalamin deficiency anemia [8]. Coronary heart disease (CHD) is the term given to heart problems caused by narrowed coronary arteries that supply blood to the heart muscle. Although the narrowing can be caused by a blood clot or by constriction of the blood vessel, most often it is caused by buildup of atherosclerotic plaque [9]. It is the most common of the cardiovascular diseases [10]. Types of CHD include stable angina, unstable angina, myocardial infarction,

and sudden cardiac death [11]. A common symptom is chest pain or discomfort which may radiate into the shoulder, arm, back, neck, or jaw. Occasionally pain may be felt like heart burn. Shortness of breath may occur and sometimes no symptoms are present [12].

CASE PRESENTATION

A 55-year-old man who is significantly overweight, diabetic, and hypertensive for the last five years. He is on oral hypoglycemic and angiotensin converting enzyme inhibitor agents. He had a 30-year-history of smoking 2 packs of cigarettes per day.

On the day of his presentation, he wasn't feeling well and had a sensation of about to faint on assumption of standing position and complained of chest pains and heart burns. He awakened at 3:00 A.M. with shortness of breath, crushing pressure at his chest, and pain radiating down his left arm. He was nauseated and sweating profusely. He had no history of similar attacks. He had positive family history of cardiovascular disease and hyperlipidemia).

In the emergency room, his pulse rate was, 130 beats per minute; respiratory rate, 30 breaths per minute; core body temperature 37.3 degree celsius; arterial blood pressure, 150/100 mm Hg. He had chest wheezing. His percentage saturation of hemoglobin with oxygen was 97%. His ejection fraction, measured with two-dimensional electrocardiography was 0.60.

Sequential electrocardiograms did not show evidence of ischemic heart disease and serum levels of cardiac enzymes were not elevated.

13C-urea breath test was positive for *H. pylori* infection. The patient was treated with proton pump inhibitor simultaneously with two antibiotics; amoxicillin and clarithromycin.

DISCUSSION

Mendall and co-workers [13] showed for the first time that CHD patients have elevated levels of serum anti-*H. pylori* antibodies. Following this finding, some authors confirm and some exclude the existence of this connection. Still there is no universal agreement on the role of *H. pylori* in either causation or progression of CHD [14, 15].

On basis of extra gastro-intestinal involvement of *H. pylori* [16, 17], we propose that *H. pylori* produces some mediators, the nature of which is unknown, that reach the cardiopulmonary system. Among organs that acted upon by these mediators, the specialized conducting system of the heart; ventricular muscle proper; coronary vasculature; and pulmonary stretch receptors. The chronic long-term inflammatory process in the gastric epithelium [18, 19] disseminate to these cardiopulmonary organs. The mediators induce reduction in the threshold potential of cardiac

nociceptive receptors [20] or potentiation of nociceptive pathways that will elicit pain typical to that of ischemic heart disease. The pain is often described as a discomfort that is neither sharp nor stabbing, and it doesn't vary significantly with inspiration [21]. *H. pylori* mediators interact with the endothelium of pulmonary microcirculation [22]. We propose that, this interaction induces changes in pulmonary capillary hemodynamics, which result into increased pulmonary capillary hydrostatic pressure, pulmonary congestion, and pulmonary interstitial edema. Juxtacapillary receptors are pulmonary stretch receptors located in alveolar walls close to pulmonary capillaries. These receptors are endings of non-myelinated C fibers, which carry afferent signals to medullary respiratory neurons.

Laboratory chemical stimulation of these receptors results in shallow, rapid breathing or apnea if stimulation is intense. There is evidence that pulmonary congestion and interstitial edema stimulate these receptors [23]. This may explain the sensation of shortness of breath in this case. *H. pylori* has been isolated from tracheal secretions of intubated patients [24] and produce inflammatory cytokines [25]. These cytokines stimulate irritant receptors located between epithelial cells in the large airways. Impulses are carried by myelinated vagal fibers and reflex effects include coughing, bronchoconstriction, mucus secretion and hyperapnea [23]. This explains the sensation of chest tightness and wheezes in our case.

H. pylori mediators increase work of the heart through stimulation of sympathetic nervous system. This, probably, is achieved by two mechanisms; decreased sensitivity of baroreceptors [20] and increased activity of excitatory sympathetic afferents [26]. We propose that, *H. pylori* mediators stimulate both of these two mechanisms. This results in increased heart rate (positive chronotropic effect), increased stroke volume (positive inotropic effect), and consequently increased cardiac output [27]. Sympathetic stimulation of systemic veins will lead to increased central venous pressure (venous return) with further increase in force of myocardial contraction in accordance with Frank-Starling law of the heart [28]. Atrial stretch receptors stimulated, also, by increased central venous pressure to send impulses through vagus nerve to excite the medullary inspiratory neurons. This helps to oxygenate the extra-amount of blood reaching the lungs from the right ventricle (Harrison's reflex) [29].

This explains the normal percentage saturation of hemoglobin with oxygen in our case. Atrial stretch receptors, in addition, send impulses to medullary cardiac centers, which result in a positive chronotropic effect. This will help to increase cardiac output and prevent accumulation of blood in the right side of circulation (Bainbridge reflex) [30, 31]. Cardiac muscle has a high oxygen extraction ratio under resting

condition (75%), and remains stable over a wide range of myocardial workload [32]. Thus, during stress conditions, exercise for example; the only way for the cardiac muscle to increase its oxygen supply is to increase its coronary blood flow (CBF). The increased cardiac work will be associated with accumulation of metabolites. Metabolites have been suggested as mediators of coronary vasodilatation; with consequent decrease in oxygen demand to oxygen supply ratio [33]. This is an appropriate physiologic response of normal coronary vasculature to accumulation of cardiac metabolites. More than 90% of persons with myocardial ischemia have advanced coronary atherosclerosis [34]. Atherosclerotic plaque with exposure to circulating elements of blood as well as endothelial dysfunction is the major trigger of coronary thrombosis [35, 36].

Multiple studies demonstrated the involvement of *H. pylori* infection in inflammatory process of atherosclerotic plaque [37]. CHD occurs due to endothelial dysfunction within the vessels, accompanied remodeling of vascular wall, local inflammation, platelet aggregation, and blood clotting. These disorders promote formation of atheromatous plaque, which is often unstable and subsequently ruptures. This might impair the blood flow leading to vascular blockage or myocardial infarction [37, 38].

The ensuing deficiency of myocardial oxygen supply is translated into clinical ischemic manifestations of ischemic heart disease, typical electrocardiographic changes, and elevation of serum cardiac biomarkers [39, 40]. Typical electrocardiographic changes include (prolongation of the Q wave (necrosis), elevation of ST segment (injury), and T wave inversion (ischemia) [39]. Serum cardiac biomarkers include cardiac myocyte troponins, myoglobin, and intracellular enzymes that can be released into the blood as a result of myocardial death [40]. CBF will be increased and oxygen supply will be enough to meet the metabolic demands of the heart despite such increase in the work of the heart; as long as the coronary vasculature is intact, nonsclerotic for example. Studies of the effect of eradication of *H. pylori* infection on atherosclerotic plaque process in patients with CHD revealed conflicting results. Some authors reported that eradication of *H. pylori* infection is associated with an attenuation of inflammatory response of atherosclerotic plaque [41, 42] while others did not [43, 44].

We propose that *H. pylori* does not participate in initiation of inflammatory process of atherosclerotic plaque, it has a permissive effect on this process. That is why neither the electrocardiographic changes nor the cardiac biochemical markers can be demonstrated in this case. *H. pylori* may promote the persistence or the progression of atherosclerotic plaque.

We propose that *H. pylori* increases CBF. This can be achieved by direct effect, of mediators produced by *H. pylori*, on coronary vasculature or the vasodilator effect of metabolites produced as a result of increased cardiac work. However, under certain circumstances, *H. pylori* may promote the inflammatory process of atherosclerotic plaque with consequent clinical manifestations of ischemia, characteristic ECG changes, and elevation of serum cardiac biomarkers. These circumstances that lead to shifting of *H. pylori* from a commensal promoter of CBF to a pathogenic organism activating the inflammatory response of atherosclerotic plaque process remain to be elucidated. From the physiologic point of view, this proposal is analogous to the haemostatic role of platelets to provide a procoagulant function versus its undesired role in induction of thrombosis.

When a normal blood vessel is injured, the endothelial surface becomes disrupted and the thrombogenic connective tissue is exposed. Formation of primary haemostatic plug is the first line of defense against bleeding. It is the function of circulating platelets. While primary haemostatic plug forms, the exposure of subendothelial tissue factors triggers the plasma coagulation cascade, initiating the process of secondary haemostasis which ultimately forms a thrombus (fibrin clot) by the action of thrombin. This clot stabilizes and strengthens the primary platelet plug. The normal haemostatic system minimizes blood loss from injured vessels, but there is little difference between this physiologic response and the pathologic process of coronary thrombosis triggered by disruption of atherosclerotic plaques [45].

In conclusion, *H. pylori* promotes CBF even in the presence of classic risk factors of CHD. Under certain circumstances, *H. pylori* may aggravate an already existing inflammatory atherosclerotic process of coronary vasculature with consequent rupture and development of ischemic heart disease. Further studies are needed to address the role of *H. pylori* in pathogenesis of haematological and cardiovascular diseases.

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