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HELICOBACTER PYLORI INFECTION IN CORONARY ARTERY DISEASE

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The role of inflammation in the pathogenesis and progression of coronary artery disease (CAD) has been increasingly discussed, but still remains unclear. Inflammatory changes in the vessel wall play an important role in the pathogenesis of atherosclerosis. Systemic inflammatory reaction can be detected by showing increased plasma levels of different proinflammatory cytokines and acute-phase proteins. Infectious agents have been linked to coronary heart disease on epidemiological and pathogenetic grounds. The prevalent condition and the exact mechanism of initiation of atherosclerotic vascular disease remain unclear. Nevertheless, many similarities exist between the processes of inflammation and atherogenesis, and the evidence is growing for the role of an active inflammation in the atherosclerosis in the coronary circulation and elsewhere. Although the seroepidemiological and eradication studies have suggested a causal relationship between *Helicobacter pylori* (Hp) infection and coronary heart disease; the issue is still controversial. The detection of Hp specific DNA in atheromatous plaque material from coronary arteries, but more important, the reduction in restenosis of coronary vessels after Hp eradication could be interpreted as an evidence for the involvement of a Hp infection in the progression of CAD induced by a local inflammatory process.

Key words: *Helicobacter pylori, coronary artery disease, restenosis, atherosclerosis, cytokines*

INTRODUCTION

Atherosclerosis is a very complex disease entity. The lesions of atherosclerosis take different forms, depending upon their anatomic site (coronary artery disease, cerebral arteries, lower extremity arteries); the age,

genetic and physiological *status* of the affected individual; and, presumably, upon the risk factors to which each individual may have been exposed. Despite of declining mortality from cardiovascular disease, these disorders still remain the leading cause of death in the Western industrial countries. Understanding the pathophysiology of atherosclerosis is useful in treating its consequences. The prevalent condition and the exact mechanism of initiation of atherosclerotic vascular disease remain unclear. Nevertheless, many similarities exist between the processes of inflammation and atherogenesis, and the evidence is growing for the role of an active inflammatory process in the pathogenesis of atherosclerosis in the coronary circulation and elsewhere. In particular, monocytes and macrophages have long been recognized as components of atheromatous plaques. Elevated levels of the acute phase proteins, fibrinogen and C-reactive protein (CRP) and pro-inflammatory cytokines are known to be associated with an increased risk of cardiovascular events (1). The possibility that an undetected chronic infection may be behind these changes in inflammatory markers is an attractive hypothesis, and has led to the spotlight falling on microorganisms, which is known to be commonly detectable in asymptomatic individuals. The aim of this review is the analysis of relationship between *Helicobacter pylori* (Hp) infection and coronary artery disease (CAD) by overviewing of reported studies and own experience.

Seroprevalence of Hp infection in coronary artery disease (CAD)

The role of inflammation mechanisms in the pathogenesis and progression of CAD has been increasingly discussed, but still remains unclear. Epidemiological studies have suggested an association between atherosclerosis and chronic Hp infection. The association of Hp to atherosclerosis, particularly to CAD, is based on serological findings, but this is a controversial issue. Mendall *et al.* (2), Danesh *et al.* (3) and Glynn *et al.* (4) showed a close association betweens Hp seropositivity and CAD. Pellicano *et al.* (6) reported significantly higher prevalence of Hp infection in patients with CAD than in controls (77% vs 59%). Danesh *et al.* (7) found, however, only moderate association between Hp infection and CAD. Other studies such as performed by Singh *et al.* (8) and Pasceri *et al*. (9) evaluated the prevalence of Hp positive CagA-strains in patients with CAD. Their studies have demonstrated a higher prevalence of Hp CagA-positive strains in patients with CAD compared with control group (52% vs 43% or 43% vs 17%).

Bacterial infection with Hp has been suggested to influence the development of atherosclerotic changes in coronary arteries postulating a damaging influence of these microorganisms or their products (cytokines, endotoxins, cytotoxins and other virulence factors) on coronary endothelium. Niemela *et al*. (10) and de Luis *et al.* (11) have demonstrated, that infection with Hp leads to various lipid, thrombotic protein changes. Hoffmeister *et al.* (12) shoved a good correlation

between Hp infection and decreased HDL cholesterol. The association between Hp infection and plasma levels of CRP, cholesterol, lipid profile and fibrinogen has been investigated by Pieniążek *et al.* (13). These authors demonstrated higher levels of investigated parameters in CAD-patients than in age- and sex-matched controls. Hp infection was reported by Pellicano *et al.* (14) to induce also platelet activation and aggregation as well as an increase of plasma levels of triglycerides and various proatherogenic factors including homocysteine. Recently, the Hp infection has been associated with an increased risk of CAD, possibly through the activation of acute phase responses and procoagulant hemostatic factors.

Abdelmouttaleb *et al.* (15), Gasbarrini *et al.* (16) and Stone *et al*. (17) reported that the host immune response to the bacteria colonizing the stomach may play an important role in the pathogenesis of vascular disorders, probably through the action of various vasoactive substances, such as cytokines, eicosanoids and others.

Gastric infection with Hp may also induce the synthesis of acute phase reactants (18, 19) and activate immune mechanisms due to cross-reacting antibodies to Hp and heat shock protein (HSP 60/65) with endothelial-derived HSP 60/65 (20). Birnie *et al.* (20) reported strong association between anti-HSP-65 titers and coronary atherosclerosis; moreover the eradication therapy led to fall of anti-HSP-65 titers. Franceschi *et al.* (21) have demonstrated, that anti-Cag A antibodies reacted with the cytoplasm and the nuclei of myocytes in atherosclerotic vessel wall and cytoplasm of fibroblast-like cells in atherosclerotic plaques. The authors have suggested, that the cross-reaction leads to progression of atherosclerosis. Mendall *et al.* (22) revealed a strict correlation between the increment in serum levels of some proinflammatory cytokines (IL-1β, IL-8, TNFα) and cardiovascular risk factors.

Our preliminary studies (23, 24) showed that frequency of the Hp infection in patients with coronariographically confirmed CAD (one- to three-vessel-disease and PTCA or CABG in the past) was significantly higher than in the healthy population of similar age and gender (*Fig. 1)*. These and other case-controlled studies did not confirm, however, the causality but merely suggested an association, which requires adjustment for many confounding factors before solid conclusions could be drawn. Among these confounding factors, the socio-economic class, age, family history of CAD, hypertension and smoking habit should be considered.

We reported, that in homogenous group of patients, those with CAD had significantly higher Hp IgG and CagA seroprevalence (69,79% *vs* 58,20%) as compared to non-CAD controls (40,62% *vs* 35,89%). We found that there is a significant link between CAD and infection with Hp, especially expressing CagA proteins (25).

The prospective studies may be of help but their results are controversial. Wald *at al*. (26) found no association between Hp seropositivity and ischemic heart disease in a population of 21.531 professional men attending routine medical examination and the bias due to socio-economic class was considered not

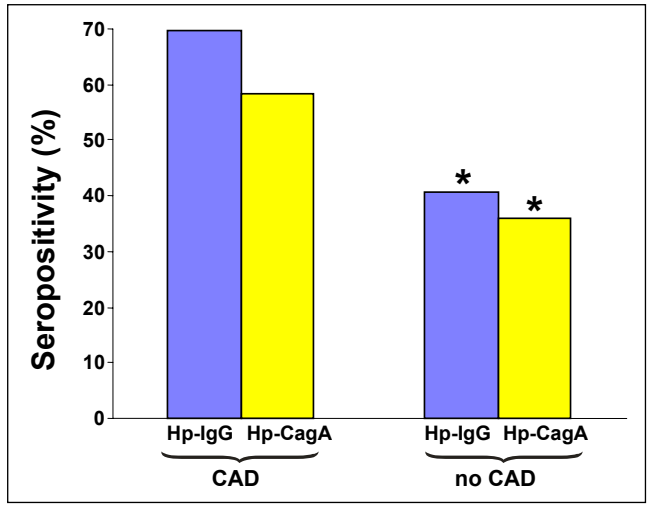

Fig. 1. Serum IgG anti-Hp and anti-CagA in patients with CAD and controls. Mean ± S.E.M. in 96 CAD patients and 96 controls. Asterisk indicates significant ($P < 0.05$) change as compared to the values recorded in CAD patients (adapted from 25).

to be the major factor in that study. Strachan *et al.* (27) reported results of prospective investigations on 1800 men with nearly 300 cases. Cause of death and occurrence of CAD were assessed over a 13 yr period from a population in South Wales. Hp seropositivity was significantly associated with fatal CAD, although not with non-fatal CAD. Furthermore, the effect was significantly greater in men of non-manual occupation and the risk of death in those that developed CAD was increased by a factor of three in those with Hp infection. The main conclusion of this study was that Hp infected patients show a 10-30% increased risk of developing of CAD and this could be clinically important in the society with high Hp prevalence, partially if this risk were entirely reversible. In another recent study (28) based on 165 patients with at least one coronary lesion occupying about 50% of the luminal diameter on coronary angiography and 127 controls with normal coronary angiography, no significant difference in Hp seropositivity was found between patients (69.1 %) and controls (77.2 %). After adjustment for age, gender, socio-economic status and cardiovascular risk factors, the Hp seropositivity was not found to be significantly elevated in patients with CAD. Polish epidemiological studies (29) based on Hp detection using urea breath test (UBT) performed in larger population (N = 1225) of patients with CAD also failed to confirm significant association of the Hp infection with CAD (OR = 0.93; 95% CI: 0.72 - 1.20).

Biagi *et al.* (30) investigated the relationship between Hp infection and CAD in a group over 75-year-old patients. This study did not show any positive association between prevalence of Hp infection and CAD. Pasceri *et al.* (9) and Gunn *et al.* (31) reported a correlation between CagA-positive Hp - families and CAD with respect to acute myocardial infarction. Pellicano *et al.* (32) reported, that the prevalence of antibodies against Hp in patients with CAD was not related

to CagA-positivity. Similar results have been shown a prospective study by Stone *et al.* (33). Whincup *et al.* (34) have performed prospective study aimed at determining any possible correlation between Hp infection with CagA-positive strain and CAD (34). This study did not show any relationship between CagA-positive strain infection and CAD. Similar results have been obtained by König *et al*. (35) in another study. The authors reported, that Hp infection is not a major independent risk factor for CAD. Additionally, a prevalence of CagA-strains was not different in patients with CAD and controls (27,9% *vs* 21,7%; p = 0,076). Even the suggested correlation between CAD, antibodies against Hp-HSP 60 and inflammatory markers in plasma has been reported controversial (36). Actually there is only a small number of data regarding the influence of Hp-infection on PTCA-results. In particular, studies on higher re-stenosis rate after PTCA in Hp-positive patients, as compared to non-infected patients, were reported, but this trend is not uniform (37, 38). The reason for that might be attributed to difference in virulence of particular Hp strains. Although new data, reported by König *et al.* (35) and Whincup *et al.* (34), did not show any correlation between Hp CagA-positive infection and CAD, the influence of a high-virulent Hp-infection on re-stenosis rate after PTCA with stent implantation remains unclear. The influence of a local or systemic inflammatory process, triggered by Hp, on intravasal reactions against a foreign body has to be investigated.

We (25) found, that the mean lumen loss after PTCA with stent in Hp-IgG positive patients was higher compared to the Hp-IgG negative patients (p= 0,0196) (*Figs 2 and 3*). Patients infected with CagA - positive Hp show significantly greater coronary artery lumen loss after PTCA with stent (44,32+17,94% vs 30,44+14,05%; p=0,0035), arterial re-stenosis, CAD manifestations and recurrence coronary interventions after PTCA with stent

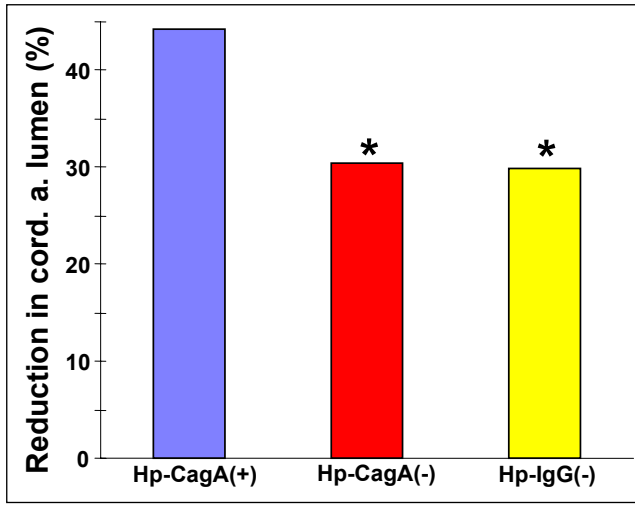

Fig. 2. Mean ± S.E.M. coronary artery lumen reduction in per cent, six months after PTCA with stent in Hp - Cag A positive (subgroup a), negative (subgroup b) and Hp IgG - negative patients (subgroup c) (adapted from 25).

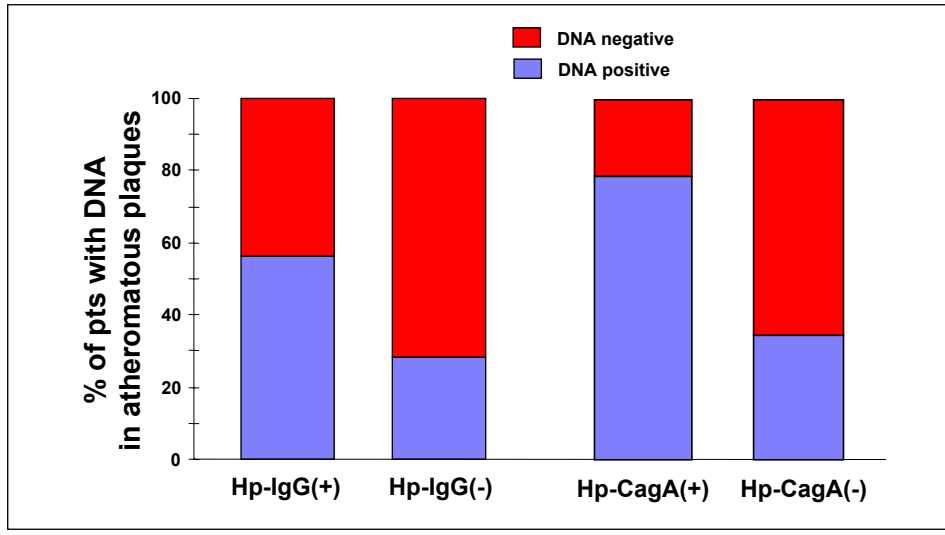

Fig. 3. Detection of Hp specific DNA in human atheromatous coronary artery plaques of patients with and without Hp infection. 4 DNA positive patients in Hp IgG-Ab negative group - after Hp eradication therapy in the past (adapted from 25).

implantation than CagA negative Hp pts, possibly due to higher virulence and more intense proinflammatory effects of CagA positive strains. It seems possible, that cellular processes (marked intimal proliferation), leading to an "in-stent re-stenosis", may be aggravated under the influence of local inflammatory Hp toxins (39 - 41). The quantitative and qualitative reactions of an inflammated vessel wall on incorporated foreign bodies (stent material) may be intensified.

Detection of Hp specific DNA in human coronary artery plaques

The direct proof of bacteria in arteries of affected organs seems to be more convincing, as the previous failure to demonstrate the presence of Hp in atherosclerotic plaque material (42) was one of the main arguments against the implication of the inflammation hypothesis with this bacterium in coronary atherogenesis. Blasi *et al.* (42) examined material from surgical specimens of patients with aortic abdominal aneurysm but found no evidence of Hp infection.

We found that Hp DNA was detected in considerable number of atherosclerotic plaques of Hp-positive patients undergoing coronary artery bypass grapht (CABG) (*Fig. 4),* supporting the idea of direct involvement of this *bacterium* in the development of atherosclerosis (25). The significant association of DNA detection and clinical symptoms ("unstable angina") may support the hypothesis of an important role of Hp infection in the development of unstable angina due to plaque instability and rupture. The significantly higher detection of Hp DNA in CagA-positive patients may be due to higher virulent factors to

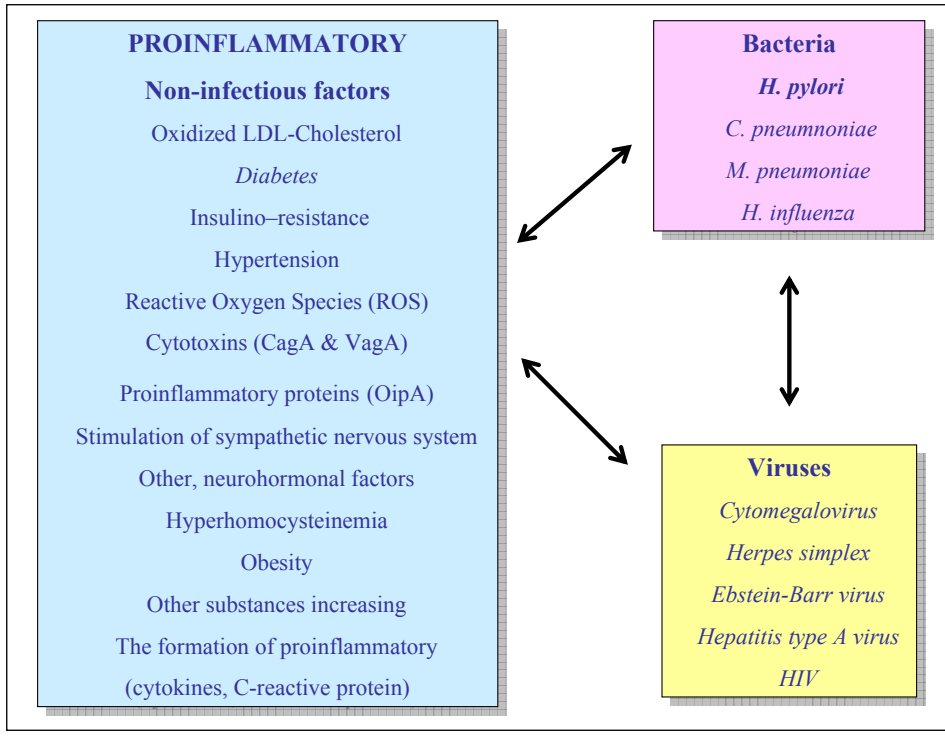

Fig. 4. Interaction of proinflammatory non-infectious factors, Bacteria and viruses on the formation of atheromatic plaques.

atherosclerotic plaques, which may result in an increased risk of premature myocardial infarction (31) and, possible, in an increased risk of re-stenosis after PTCA. The detection of Hp influences DNA in peripheral arteries was reported by Farsak *et al.* (43). Ameriso *et al.* (44), using polymerase chain reaction with UreCgen Hp DNA, found Hp DNA in 20 of 38 atherosclerotic plaques. Ten of the Hp DNA positive plaques showed immunohistochemical Hp infection (44).

Eradication study in CAD-patients with Hp infection

The major weakness of previous studies concerning the relationship between the Hp infection and CAD was the lack of direct evidence of whether or not the eradication of the Hp affects the course of CAD, particularly in patients undergoing coronary angiography and subjected to PTCA. If the Hp infection contributes to the development of CAD, it is expected that the therapy should attenuate the progress of CAD and to reduce the coronary artery re-stenosis in patients after PTCA. We found that the diameter of the coronary artery lumen six months after PTCA was significantly different between the patients after the Hp eradication therapy and those without such therapy (25). The mean reduction in

arterial lumen in Hp-eradicated patients was about 22%, whereas in those non-eradicated this reduction reached about 41% and this difference was statistically significant. The fact that the plasma proinflammatory cytokines, such as TNFα, IL-1β and IL-8, were significantly attenuated after Hp eradication in patients with PTCA suggests that the elimination of the inflammation could contribute to the decline in restenosis mechanism (45). Other study reported the effect of eradication therapy on the plasma levels of IL-8, fibrinogen and LDL-cholesterol. All those parameters was significantly declined after eradication (46).

Another study has also evaluated the effect of eradication of fibrinogen levels in patients infected by Hp with CAD. The levels of fibrinogen was significantly reduced after eradication ($p<0,01$) (47). Many studies did not confirm beneficial effects of the eradication therapy on risk factors for CAD. Stone *et al*. found not correlation between Hp eradication and risk factors for CAD (48). Schweeger *et al*. reported no significantly change in levels of fibrinogen and acuta phase proteine (49) after eradication therapy of Hp. Similar results found Lu *et al.* (50), who reported that after eradication of Hp the risk factors of CAD (lipid, sugar, fibrinolitic parameters) ware not significantly altered.

CONCLUDING REMARKS

1. Inflammatory changes in the vessel wall play an important role in the pathogenesis of atherosclerosis. A systemic inflammatory reaction can be shown by increased plasma levels of different proinflammatory cytokines and acute-phase proteins (for instance C-reactive protein) (51). 2. Infectious agents have been linked to coronary heart disease on epidemiological and pathogenetic grounds. 3. The mechanism of the action of Hp present in the stomach on coronary arterial wall is unknown but it could resemble the gastric endothelial damage by this germ involving toxic substances including proinflammatory cytokines, CagA cytotoxins, endotoxins, and others. This would support the hypothesis that the infection with Hp (especially CagA positive) influences the development of atherosclerosis. From the beginning of last decade, Hp infection was reported to be one of them. Since then, a number of studies have been published with controversial results. 4. Studies performed thus far show a high degree of heterogeneity in the selection of patients and also in the type of disease studied: chronic or acute coronary heart disease. The seroepidemiological and eradication study have suggested a causal relationship between Hp infection and coronary heart disease; the issue is still controversial. 5. The detection of Hp specific DNA in atheromatous plaque material from coronary arteries and its association to the CagA positivity and clinical symptoms could be interpreted as an evidence for the involvement of a Hp infection in the progression of pre-existent (development of “unstable angina” due to plaque instability and rupture) or concurrent CAD induced by a local inflammatory process. 6. In general,

because of relatively small number of studies a tendency of association between Hp infection and CAD and other organs can only be suggested and this requires confirmation on larger patients group in further studies.

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