EDITORIAL

Helicobacter Pylori Infection and Long Term Prognosis in Patients with Acute Coronary Syndrome

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SILDENAFIL IN HEART FAILURE

In recent years, numerous studies have confirmed the role of inflammatory mechanisms in the genesis of atherosclerosis and coronary artery disease. Inflammatory mechanisms trigger endothelial cell activation, which, in turn, facilitates the infiltration and accumulation of inflammatory cells in the arterial intima. (1, 2) Upon activation, endothelial cells express leucocyte adhesion molecules, i.e. vascular cell adhesion molecule-1 (VCAM-1) and monocyte chemoattractant protein-1 (MCP-1), among many other molecules that mediate the interaction between the endothelium and circulating inflammatory cells. Atherosclerotic vessels show an increased production of reactive oxygen species, which further contribute to the inflammatory process. (2) Oxidised LDL-cholesterol, a major contributor in the pathogenesis of atherosclerosis, increases the expression of VCAM-1 and MCP-1. (2) The exact mechanisms that trigger the inflammatory process underlying CAD are not known, but it has been proposed that chronic infections by viruses and bacteria may play a substantial role. A revival of the old "infectious hypothesis" proposed by Osler (4) took place some years ago as a result of findings in sero-epidemiological studies and pilot antibiotic trials. (5, 6)

CHRONIC INFECTION AND CORONARY ARTERY DISEASE

Infectious agents involved in atherogenesis include bacteria such as Chlamydia Pneumoniae (CPn), Helicobacter Pylori (HP) and porphyromonus gingivalis, among others. Viruses such as cytomegalovirus (CMV) and herpes simplex virus have been also postulated as pathogenic candidates. (3) The relationship between HP and CAD has been postulated in several studies (7-10) but some of these have been criticized due to important limitations, including controversial results regarding serological findings and cardiovascular disease, **a small sample size, and a poor assessment of confounding variables.**

CPn in particular attracted the attention of several groups on both sides of the Atlantic as a likely candidate to contribute to both atherogenesis and rapid CAD progression. Sero-epidemiological studies showed a correlation between antibody titres and CAD, and other studies demonstrated the presence of active forms of CPn in atheromatous tissue, whilst experimental studies in animals revealed that CPn inoculation induces or accelerates the atherogenic process. (11) However, the results of large antibiotic studies in patients showed categorically a lack of effect of CPn eradication on CAD progression. (12-14)

In this issue of the Revista Argentina de Cardiología, Macin et al present interesting data regarding the prevalence and prognostic value of positive serology for helicobacter pylori (HP) in patients admitted to hospital with a diagnosis of acute coronary syndrome (ACS). (15) The authors aimed at establishing the prevalence of a positive serology for HP in patients admitted to hospital with an ACS, and the potential role of a positive serology as a biomarker of further cardiovascular risk in these patients. In 67 patients admitted with ACS (unstable angina [UA]/acute myocardial infarction [AMI]) within 24 hours from the onset of symptoms who underwent serological assessment for HP-IgG using a commercial enzyme immunoassay (Meridian Diagnostics, USA), Macin et al found that a cut-off point of 185 IU was a predictor of impaired clinical outcome during one-year follow up (hazard ratio, 5.588). Of interest, over 25% of patients in the study showed Hp-IgG levels above the cut-off point. In their study, Macin et al (15) revive the debate about the role of chronic infections as triggers of CAD, and raise the issue of whether a positive serology for HP can be considered to represent a clinical marker of risk in patients with a diagnosis of ACS.

Athough the report is interesting and generates important research questions, the impact of its findings is seriously hampered by several important limitations that include a small single center-based patient population, a broad study endpoint encompassing both

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hard and soft variables, and an observational study design. A definitive study able to answer the question as to whether HP infection can be a pathogenic factor in atherosclerosis requires a large study population, a proper power calculation based on the relevant variables, and a painstaking characterisation and handling of confounding variables. Moreover, variables known to affect prognosis after an acute coronary event such as left ventricular function, heart failure, residual myocardial ischemia, among others, need to be meticulously recorded and included in the analysis. In addition to the search for an association between serological and clinical variables, a mechanistic study would be desirable.

With regards to the potential role of positive HP serology as a biomarker of cardiovascular risk –the second point raised by Macin et al (15)–, similar concepts apply.

Another systematic review of the results obtained in 47 randomized trials with studies showed a significant improvement in walking, mainly in those which included more severe patients. The increase of distance walked varied according to target population, age, severity of the condition, and agent used. Most studies on the cited drugs demonstrated no improvement in functional capacity, but 5 out of the 7 which showed symptomatic improvement also demonstrated improvement in walking. (19) One study has shown that a substantial adjustment of the usual treatment may improve significantly the exercise capacity, with an overall increase of 80 meters in the distance walked after 2 weeks of optimal treatment. (20) Concerning the effect of sildenafil on VO2 max and walking at 12 weeks, an increase of 1.8 ml/kg/min and 29 meters respectively has been reported. (21)

BIOMARKERS OF INFLAMMATION AND RISK PREDICTION IN ACS

Inflammation occurs in the vasculature as a response to different forms of injury, including shear stress, lipid peroxidation, superoxide radical formation, infections, and immune reactions, among others. (16) Of interest, the atherogenic effects of conventional risk factors appear to be magnified in the presence of inflammation. Furthermore, the deleterious effects of diabetes, smoking and hypertension may be exerted, at least in part, via inflammatory mechanisms. Epidemiological and clinical studies have shown a relationship between markers of inflammation and risk of cardiovascular events, thus triggering interest in the potential role of inflammatory biomarkers. (16) Acute phase proteins, like C-reactive protein (CRP), fibrinogen, and serum amyloid A protein, produced in the liver upon stimulation by cytokines, are associated with the development of acute cardiovascular events in different populations. Of these inflammatory markers, the most extensively investigated and accessible one for clinical use is the CRP, and studies have suggested that high serum CRP concentration is a risk factor for cardiovascular disease and has prognostic implications in patients with ACS as well as in those with stable coronary disease. (16) Other inflammatory markers such as neopterin, pro-inflammatory cytokines, adhesion molecules, white blood cell count, CD40L, e-selectin, von Willebrand factor, pregnancy associated plasma protein A (PAPP-A), Lp associated phospholipase A2, neutrophil myeloperoxidase, etc., have been also proposed to represent cardiovascular risk markers in the ACS setting. However, little data exist regarding the true prognostic value of these molecules in patients with ACS.

Recently, the SIESTA (Systemic Inflammation Evaluation in Patients with Non-ST elevation Acute Coronary Syndrome) study (17) compared the predictive value of several inflammatory and non-inflammatory biomarkers in 610 consecutive NSTEMI ACS patients (73% male subjects). The study assessed hs-CRP, interleukins 6, 10 and 18, CD 40 ligand, P- and E- selectin, NT-proBNP, fibrinogen and cystatin C levels at hospital admission. Two composite end-points were considered: The first one, all-cause death, myocardial infarction, unstable angina, or artery bypass, and the second, all-cause death from any cause and myocardial infarction. The adjusted effect of biomarker levels on endpoints was analyzed by the Cox proportional hazards model, and its discrimination ability with the C statistic (AUC). At 1-year follow up, 206 (37.5%) and 54 (8.9%) reached the first and second composite endpoints, respectively. On univariate analysis, cystatin C, NT-proBNP, hs-CRP, and fibrinogen were significant predictors of outcome. AUC for prediction of the first composite endpoint using clinical variables only was 0.68 (95% CI 0.63-0.73) and 0.70 (95% CI 0.65-0.75, CHI2=2.71; p = 0.09) with the addition of cystatin C. NT pro BNP and fibrinogen combined increased AUC from 0.70 to 0.78 (p =0.03) for the prediction of second composite endpoint. Thus, in ACS patients, inflammatory biomarkers offer modest additional information to that of conventional risk markers. However, cystatin C, fibrinogen and NT proBNP improved prediction. (17)

The study by Macin et al (15) reported a good predictive value against HP raised antibodies as assessed by the area under the ROC curve, thus suggesting their role as markers of cardiac outcome. Therefore, it would be interesting to carry out a comparative study of HP serology versus other established biomarkers of risk to ascertain whether its assessment truly improves the predictive value of these markers, thus adding further clinically useful information.

While the inflammatory hypothesis of atherogenesis continues to be strongly endorsed by well designed studies, convincing data that chronic infections can play a pathogenic role in CAD are missing. The suggestion in the small observational study by Macin et al (15) that HP serology shows a potential pathogenic association with CAD and could represent a prognostic marker after ACS is intriguing, and may deserve further assessment in a definitive clinical trial. The demonstration that infections could have a causal role and/or a predictive role, may have important clinical implications.

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