

Infectious Agents in Coronary Atherosclerosis

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In 1908, Sir William Osler was the first to suggest that infection might play a role in the pathogenesis of atherosclerosis¹. Even though this view was not widely accepted originally, a renewed interest currently abounds regarding the contribution of infection to the pathogenesis and progression of ischemic heart disease. The current concept of atherosclerosis is based on the model “response to injury” proposed by Ross in 1986². This model suggests that infection may contribute to the formation of atherosclerosis through injury to the vascular endothelium along with inflammatory, metabolic and hemostatic mechanisms². In the ‘70s, formation of atherosclerotic lesions in the arteries of chickens infected with herpes virus was demonstrated experimentally³. The recent discovery of *Helicobacter pylori*, as an etiological agent of another chronic disease, peptic ulcer, suggests that an infectious etiology for atherosclerosis should be considered⁴. Since then, associations between ischemic heart disease and some Gram-negative bacteria, such as *Helicobacter pylori* and *Chlamydia pneumoniae*, and certain herpes viruses, especially cytomegalovirus⁵, have been reported. Most of the published material consists of epidemiological studies based on associations between the serology of the respective antibodies and ischemic heart disease or on immunohistochemical evidence of the presence of bacteria or viruses in atherosclerotic lesions. Recently, new evidence originating from controlled clinical trials has emphasized this new paradigm for managing ischemic heart disease⁶. This study aims to provide an updated review of the evidence available relating infection to coronary atherosclerosis.

Serum-epidemiological studies

Chlamydia pneumoniae – In 1988, a Finnish case control study showed that, after an acute myocardial infarction, most patients (68%) developed significant seroconversion against a specific epitope of *Chlamydia pneumoniae*, while this happened only in 3% of the control patients and in none of those patients with chronic coronary heart disease⁷. In addition, anti-*Chlamydia* IgG and

IgA anti-bodies were increased in patients with heart disease as compared with control patients.

In 1992, Thom et al⁸ showed that patients with high levels of anti-*Chlamydia pneumoniae* IgG had twice the chance of having angiographically detectable coronary heart disease. In a study about prevalence⁹, carried out in a British community, a strong association between the anti-*Chlamydia pneumoniae* titers and the anti-*H. pylori* levels (IgG >1/64) with ischemic heart disease diagnosed by electrocardiographic evidence of ischemia or infarction was demonstrated. This association remained significant after correction by a large range of potential confounding factors. This study also demonstrated that fibrinogen levels were higher in patients with elevated serology for both *Chlamydia pneumoniae* and for *H. pylori*, pointing to the possible mechanism involved.

Stronger evidence of the role that *Chlamydia* plays in ischemic heart disease has been provided by a study nested on the Helsinki Heart Study¹⁰, a randomized double blind clinical trial, primarily designed to check the efficacy of gemfibrozil in reducing the risk of ischemic heart disease. Analysis of serum collected from study participants 3 and 6 months prior to a coronary event showed that high serum levels of anti-*Chlamydia pneumoniae* antibodies constituted an independent risk factor for the development of a fatal or nonfatal coronary event, as compared with the control group who received the same treatment at the same time and place but had no infarcts¹⁰. The degree of association between the anti-*Chlamydia pneumoniae* antibodies and the risk for ischemic heart disease increased according to the serum levels of IgA and IgG; this degree of association was statistically significant, even after correction for the traditional risk factors for ischemic heart disease. This study documented not only the association between the two variables but also the temporal relation between elevation of antibodies and coronary events.

In addition to these 3 population-based observational studies and the Helsinki Heart Study, a clinical trial, most of the published studies on serology of *Chlamydia pneumoniae* and atherosclerosis have found an odds ratio of at least 2; some studies have even reported that the higher the level of antibodies, the higher the risk. These studies were carried out in different populations, following different criteria, with different degrees of adjustments for confounding factors being, therefore, prone to bias. Consistency and directionality of the findings in a total of 2,700 patients

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studied suggest that a true association between *Chlamydia pneumoniae* and ischemic heart disease does exist¹¹.

Helicobacter pylori – For *Helicobacter pylori*, available evidence suggests a milder relation to coronary atherosclerosis. A brief analysis of the controlled and prospective studies published so far suggests an odds ratio of approximately 1.5, but without statistical significance. These data are derived from case control trials from large prospective studies, therefore reducing the selection bias, and assessing infection prior to the appearance of clinical manifestations. The sample size, however, is not large enough to detect, in a reliable manner, the association between *Helicobacter pylori* and coronary atherosclerosis¹¹. None of the studies with more than 100 patients and 100 controls has revealed a significant association between *Helicobacter pylori* and ischemic heart disease¹¹. Smaller and cross sectional studies, which detect stronger associations between *Helicobacter pylori* and coronary heart disease, are subject to innumerable not completely controlled variables, such as socioeconomic status, a factor known to be associated with infection by *Helicobacter pylori* and with ischemic heart disease.

Based on current evidence from the analysis of case control studies, one may say that a trend toward a positive association between *Helicobacter pylori* and ischemic heart disease exists; the results, however, may be due to biases not completely controlled and be, therefore, overestimated. In addition, independently from the degree of association occasionally found in these studies, they are, by definition, insufficient for assessing any causal association between infection by *Helicobacter pylori* and ischemic heart disease.

Cytomegalovirus – A series of case control studies on the relationship between cytomegalovirus and some forms of cardiovascular disease has already been published. Most of the studies report that patients with positive serology for cytomegalovirus have at least twice the chance of developing cardiovascular disease as compared with the controls whose serologies are negative, showing concordance and directionality in the findings. A major limitation of these studies, however, is that only two of them approach ischemic heart disease in its classical form¹¹. The study that found the strongest association examined the relation between cytomegalovirus and restenosis after atherectomy¹². In this study, 75 patients with symptomatic coronary heart disease, who had undergone atherectomy, were tested for the presence of anti-cytomegalovirus IgG to determine whether this constituted a risk factor for restenosis in 6 months, which was assessed through a new coronary angiography. Other studies examined different contexts, such as atherosclerosis after heart transplantation, or different anatomical regions with small samples and with little control for known confounding factors¹¹. In the case of cytomegalovirus, even if this strong association is confirmed, it will not be possible to assure its role in the coronary atherosclerosis of native arteries.

Evidence of the analysis of atherosclerotic plaques

Chlamydia pneumoniae – This agent has already been identified through immunohistochemical analysis and polymerase chain reaction in coronary atheromas in autopsies of South African men^{13,14}. More recently, the same team of researchers demonstrated *Chlamydia pneumoniae* in specimens of directional coronary atherectomy in 20 out of 38 specimens studied¹⁵. These studies were restricted to descriptions of the findings and did not report any association between the patients' serology for *Chlamydia pneumoniae* and the presence of the microorganism in the atheromatous plaques. The hypothesis that *Chlamydia pneumoniae* was more frequently found in patients with symptomatic ischemic heart disease than in those with other heart diseases was prospectively tested by Muhlestein et al¹⁶. They found evidence of *Chlamydia pneumoniae* in 79% of the atherosclerotic specimens studied and in 4% of the controls, which included individuals with healthy coronary arteries and posttransplantation coronary heart disease. According to a recently published meta-analysis that compiled results from 13 studies in this context, the chance (confidence interval of 95%, 5-22) of finding local infection by *Chlamydia pneumoniae* in an atherosclerotic plaque is 10 times higher than in control specimens¹¹. It should be noted, however, that even if a real and significant association occurs, it does not differentiate by itself whether the infection by *Chlamydia pneumoniae* causes the atheroma or whether the presence of the atheroma creates a favorable environment for the microorganism.

Helicobacter pylori – Studies are currently being carried out investigating whether *Helicobacter pylori* can be found in atherosclerotic lesions. In the only study that has been published so far, no DNA of *Helicobacter pylori* was found in abdominal aortic aneurysms in the 50 patients studied¹⁷.

Cytomegalovirus – Recent evidence from experimental studies has shown that some herpes viruses can alter the metabolism of cholesterol in smooth muscle cells, activate coagulation factors, and increase the expression of cytokines and adhesion molecules of the vascular wall^{18,19}. In addition, some characteristics of atherosclerosis are similar to those of a benign neoplasia²⁰, and herpes viruses may induce genomic transformation¹⁸. When atheromatous arteries were analyzed in regard to the presence of cytomegalovirus and compared with normal arteries, an analysis of 16 studies published found a slight positive association with atherosclerosis (odds ratio = 1.4; confidence interval of 95% = 1.0 – 1.9)¹¹. One difficulty in this context is that, even if the infectious agent starts the atherosclerotic process, it may not remain detectable. Therefore, the more sensitive the method employed, the greater the odds ratio found between cytomegalovirus and atherosclerosis. When the analysis of the plaques was performed through polymerase chain reaction, cytomegalovirus was detected in 75% of the atheromatous

vessels and in 36% of the control specimens, generating an odds ratio of 2.5 (confidence interval of 95% = 1.6 - 3.8)¹¹. Even though the relation between cytomegalovirus and coronary heart disease is conventionally significant, it is not expressive, and does not provide convincing evidence regarding the relevance of the role of cytomegalovirus in atherosclerosis¹¹.

Evidence from randomized clinical trials – Based on the biological plausibility of the association between infection and coronary atherosclerosis and on the observational findings existing so far, 3 small secondary prevention clinical trials with pharmacological intervention have been performed. Gupta et al²¹ observed the relation between anti-*Chlamydia pneumoniae* antibody levels and clinical outcome in patients surviving a myocardial infarction and demonstrated a statistically significant reduction in cardiovascular events after treatment with an antibiotic in a group of patients with high anti-*Chlamydia pneumoniae* antibody levels. The ROXIS pilot study²² randomized 200 patients with unstable angina or non-Q-wave infarction to receive, in addition to all the conventional treatment, the antibiotic roxithromycin or placebo²². These patients received the drug for 30 days after the acute event, and the combined outcome of cardiovascular death, myocardial infarction and severe recurrent ischemia was assessed at the end of this period. At the end of 31 days, a statistically significant reduction in the rate of occurrence of the 3 cardiovascular events was found. To better interpret the results, one might say that for each 100 patients treated with roxithromycin and conventional therapy, 7 significant cardiovascular events can be avoided. Follow-up studies, however, demonstrate that the effect fades after 3 to 6 months. These two experimental works were the first to test a therapeutical possibility based on the paradigm of infectious agents in the genesis or progression, or both, of ischemic heart disease, and have opened a broad new line of research.

Currently, a third clinical trial is being carried out contributing to the scarce data available relating *Chlamydia pneumoniae* to human atherosclerosis. The ACADEMIC study²³ was designed with known stable ischemic patients, whose serology for *Chlamydia pneumoniae* was positive. Until now, an interim analysed with 1,800 patient-months did not show any difference in clinical outcomes between patients using azithromycin for a period of 3 months and patients receiving placebo. Even though studying different patients, with a lower risk but with positive serology, this trial provides data based on the largest number of patients already studied in this context. Until the study reaches its planned 2-year follow-up, we only have incomplete information that in some ways diverges from the information from other trials.

Conclusion

Knowing the data from the different available studies, one can say that evidence relating infectious agents to the etiology of atherosclerosis does exist. One cannot yet, however, define whether these agents have the capacity to cause atherosclerosis, to promote progression of the lesions, or simply to be innocuous commensals of atherosclerotic plaques²⁴. The first small trials addressing the role of *Chlamydia pneumoniae* in acute coronary syndromes provide incipient evidence that this bacterium may take part in the instability of the plaque and, therefore, in the genesis of myocardial infarction. On the other hand, other larger trials that are being carried out do not seem to provide positive results. Thus, it is not possible to choose a definitive management approach, either in regard to the role played by *Chlamydia pneumoniae* in ischemic heart disease or in regard to the role played by macrolide antibiotics in its treatment. In spite of all uncertainties, if antibiotics significantly reduce the incidence of coronary events, this will mark important progress in the treatment of ischemic heart disease.

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ERRATA

Em relação ao artigo “Ablação com Radiofrequência da Fibrilação Atrial Paroxística” publicado em *Arquivos Brasileiros de Cardiologia* 1999; 72: 693-700, no último parágrafo da discussão, onde é citado o artigo de Robbins e cols. (referência 24) devem ser suprimidas as palavras “...e colocação de *stent nas* ...”. Na realidade em ambos pacientes citados foi realizada apenas angioplastia das veias, sem colocação de *stent*. Portanto, a frase final deveria ser “...com necessidade de dilatação das quatro veias”.

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ERRATA

Regarding the paper “Radiofrequency Catheter Ablation in Patients with Atrial Fibrillation” published in *Arquivos Brasileiros de Cardiologia* 1999; 72: 693-700, in the last paragraph of the “Discussion”, where is mentioned the article of Robbins et al (n° 24) the words “...*stent positioning into the four veins* ...” must be eliminated. As a matter of fact, in both patients was performed angioplasty of the veins without stenting. So, the final proposition ought to be “...*requiring dilation of the four veins* ...”.

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