

Inflammation and Pre-atherosclerotic Changes in the Coronary Arteries of Children

a report by

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Mounting evidence suggests that atherosclerosis begins in early childhood,^{1,2} possibly already during foetal life.³ This underscores the importance of primary prevention in early life. As many people suffering from atherosclerotic disease lack conventional risk factors (e.g. heredity, dyslipidaemia, smoking, obesity, diabetes and hypertension), interest has gradually increased in research on 'non-traditional' conditions that could contribute to atherosclerosis. Inflammation is a central feature of the atherosclerotic process. Infection is the most common aetiological factor for inflammation. Evidence accumulated during the last few decades has reinforced an old hypothesis that infectious pathogens could play a role in the development of atherosclerosis.

The possibility that infectious organisms contribute to the development of atherosclerosis was first raised in 1908 by Sir William Osler, who speculated that the "experimental production of arteriosclerosis by various bacterial toxins afford an explanation of this gradual production of sclerosis in the chronic infections". This hypothesis received consistent support in the late 1970s when Fabricant et al. induced changes resembling atherosclerosis in coronary arteries and aortas from young chickens infected with an avian herpes virus.⁴ Importantly, they observed greater lesions in the infected animals receiving a hypercholesterolaemic diet than in those placed on an ordinary diet. Prominent intimal thickening has been observed in the coronary arteries of children with signs of infection at their death.⁵ Further support to the infection hypothesis was provided by Saikku et al., who found a greater prevalence of *Chlamydia pneumoniae* antibodies among patients with myocardial infarction (MI) than in controls.⁶

There is some evidence suggesting that children with viral infections might be more susceptible to developing atherogenic changes in their coronary arteries.^{5,7} This observation is corroborated by an ultrasound study on children with acute systemic infections (upper respiratory, gastrointestinal and urinary tract infections) requiring hospitalisation.

The intima-media thickness of the carotid artery was significantly increased three months after recovery from the infectious disease as compared with values taken on the day of admission and to those from controls, suggesting residual vascular changes following an acute infection.⁷

In adults, acute respiratory infections have been shown to associate with an increased risk of acute MI. The risk was highest during the first three days after the clinical onset of the acute respiratory tract infection, the odds ratio being 4.958. Common cold was reported to be associated with an increased incidence of acute MI in middle-aged people who did not have a history of conventional coronary risk factors.⁹ Multiple infections acting simultaneously or in succession might have a cumulative pathogenic effect on the coronary arteries as suggested by the 'infection burden' hypothesis.^{10,11}

Arterial endothelial cell damage is an important contributor to the pathogenesis of arteriosclerosis. It is now apparent that the damage is most often of functional type. Endothelial dysfunction can be identified in many conditions with cardiovascular risk, such as hyperlipidaemia, diabetes and tobacco smoking. The magnitude of endothelial dysfunction seems to predict the risk of developing a major vascular event in later life. A variety of infectious pathogens have been causally linked to endothelial dysfunction. Whether the pathogens as such or rather the immune responses to infection could be determinant in developing this early atherogenic process is not yet clarified. Of interest, even vaccines enclosing inactive pathogens cause alteration in endothelial function.¹²

The damage to the endothelial cells during acute infections is commonly characterised by a decreased availability of nitric oxide (NO), with subsequent decreased ability of the coronary arteries to dilate. In young apoE-knockout mice, repeated intranasal administration of *Chlamydia pneumoniae* caused a progressive impairment of aortic endothelial vasomotor function.¹³ Detrimental vascular effects of *Chlamydia pneumoniae* infection were also

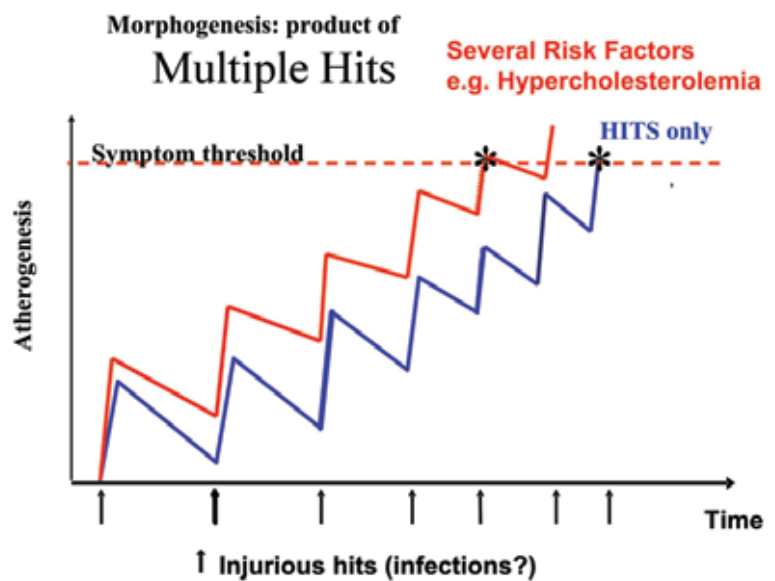
demonstrated to occur *in vivo* in the coronary circulation of young piglets.¹⁴ Although the symptoms caused by infection were hardly noticeable, the endothelial function was altered in both the epicardial and resistance coronary circulation. None of the sampled coronary segments displayed signs of inflammation, suggesting that the endothelial changes were probably mediated by immunological humoral factors such as interleukin (IL)-1, IL-6¹² and tumor necrosis factor (TNF)- α , which are induced by infection.

Cytokines induce hepatic synthesis of acute-phase proteins such as C-reactive protein (CRP), serum amyloid A and fibrinogen, which perpetuate vascular pathology. Particularly CRP appears to damage the endothelial cells directly. Plasma high-sensitivity CRP correlates with the degree of sub-clinical atherosclerosis, and may predict the risk of ischaemic events.¹⁵ Furthermore, CRP levels added to the predictive value of dyslipidaemia in determining the risk of MI in apparently healthy men.¹⁶

Diabetes is a known risk factor for atherosclerosis. Type 1 diabetes mellitus could rise during viral infections and the risk for childhood diabetes seems to increase in accordance with a higher number of infections during the year preceding diagnosis.¹⁷ Furthermore, diabetic patients are more vulnerable to viral infections due to defective lymphocyte-related immunity. In a recent cross-sectional study on 76 diabetic children aged six to eight years, it was found that recurrent viral infection in the upper airways ('common cold') during the previous year had cumulative adverse effects on the elastic properties (i.e. compliance) of carotid arteries.¹⁸ In a multivariate analysis, the number of viral infections, along with age and plasma levels of glycosylated haemoglobin, significantly and independently predicted the decrease in carotid artery compliance.

Ross and Glomset presented in 1976 their response-to-injury theory that a single damaging hit would initiate endothelial cell damage and consequently intimal thickening.¹⁹ This is followed by incomplete resolution and, hence, subsequent noxious hits could have a cumulative effect with a new thickening building up on the existing one (see *Figure 1*). This hypothesis is in keeping with data from serial angiographic studies suggesting a stepwise rather than a linear progression of atherosclerosis. The stepwise development of atherosclerosis also fits well into the mathematical model developed by Murphy, who speculated that coronary occlusion (due to atherosclerosis) could develop in response to independent insults taking place with a constant risk at the same that power would result (according to a pattern of gamma distribution) after 25 random hits

Figure 1: Hit Theory – Multiple Short-acting Noxious Hits Damage the Arterial Wall, Which Leads to Atherosclerosis



in coronary occlusion. The prevalence curve would resemble the existing age distribution of patients at that time.²⁰ Experimental evidence for the hit theory is missing.

Infections often cause an atherogenic lipid profile consisting of decreased plasma concentration of high-density lipoprotein (HDL)-cholesterol, which is known to have protective vascular effects. HDL-cholesterol functions as a reverse cholesterol transporter, binding to peripheral tissues by HDL receptors and transferring cholesterol from the tissues to the liver. It has also antioxidant properties. Decreased HDL cholesterol was documented in children with symptoms of infection and elevated acute phase protein concentrations during the preceding two weeks.²¹ Also, serum albumin concentration may be decreased during and shortly after infections. Low serum albumin has been shown in population studies to be a risk factor for coronary disease.²¹

Even if infections as generally taken seem to be risk factors for coronary disease, the early childhood infections such as varicella, scarlet fever and measles may have protective effects. One recent study on the dual role of infections as risk factors for coronary heart disease²² suggests a role of elevated viral and chlamydial infections in increased incidence of acute coronary syndromes in an additive manner. These findings are in keeping with previous studies suggesting increased risk of developing coronary artery disease with rising number of infectious pathogens (pathogen burden). The study suggests further that early childhood contagious diseases actually protect in a cumulative

way against later coronary disease. This inverse relationship between early childhood infections and coronary disease is similar to that found in the context of asthma and multiple sclerosis, being currently integrated in the so-called hygiene hypothesis. Infection early in childhood might be necessary for the development of a normal immune response, which is a precondition for prevention of the atherogenetic process.

Conclusions

The atherosclerotic process begins in early childhood. Since an individual's lifespan is a

continuum of microbial invasions with subsequent immunological responses, it is tenable to assume that infections could play a role in atherosclerosis, particularly in those individuals with other cardiovascular risk factors. It may well be that a process that eventually leads to CHD is initiated in early life by infections acquired in childhood.

Co-infection with multiple pathogens might increase the risk in an additive manner. Infections also increase the risk factor profile. Primary prevention for the development of atherosclerosis should be started in childhood. One important target could be prophylaxis of infections by vaccinations. ■

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