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Evaluation of the Role of Chlamydia pneumoniae in the Pathogenesis of Atherosclerosis – a Review

B. Scheller, T. Markwirth, H. Schieffer, B. Hennen

In recent years inflammatory changes attributable to auto-immune processes or infection have been discussed, in addition to the classic risk factors, as possible causes of atherosclerosis. An association between atherosclerosis and Chlamydia pneumoniae (CP) has been reported by several epidemiological studies. It is hypothesized that infection with CP can promote the progression of coronary heart disease by triggering either a local vascular or systemic inflammatory process.

The studies conducted to date have reached contradictory conclusions about the pathogenic relevance of Chlamydia pneumoniae in coronary heart disease. The serological studies are hampered by the difficulty in controlling the impact of other risk factors and the frequent absence of angiographic validation. Moreover, no correlation has been found between positive serum antibodies and the direct isolation of Chlamydia pneumoniae from coronary plaque. Chlamydia pneumoniae was directly demonstrated in coronary plaque at rates ranging from 0 % to 100 %. The results of studies performed with macrolide antibiotics are conflicting and do not necessarily prove that Chlamydia pneumoniae plays a key role in causing atherosclerosis or triggering acute coronary syndromes. *J Clin Basic Cardiol 2000; 3: 155–8.*

Key words: coronary heart disease, Chlamydia pneumoniae, pathogenesis

Atherosclerotic disease is still the most common cause of death in the western industrial nations. The response-to-injury theory postulates that injury of the vascular endothelia facilitates the adhesion of platelets promoting the proliferation of smooth muscle cells via the release of growth factors. Simultaneously, infiltration by macrophages and lipid accumulation takes place [1]. In recent years inflammatory changes resulting from auto-immune processes or infection have been discussed as possible causes of atherosclerosis in addition to the classic risk factors [2, 3]. Measurement of C-reactive proteins in the serum of patients known to have coronary heart disease or to have suffered a recent myocardial infarction, for example, reveals levels two to four times above normal values [4]. An association between atherosclerosis and microorganisms such as cytomegalovirus, Helicobacter pylori and Chlamydia pneumoniae has been reported in several epidemiological studies [5]. At present Chlamydia pneumoniae is the microorganism attracting the greatest interest in this context.

Chlamydia pneumoniae

Chlamydia pneumoniae was first described as an agent causing atypical pneumonia in 1986 [6]. Morphologically, it resembles the gram-negative bacteria, but is characterized by obligate intracellular parasitism. The prevalence in the general population is above 50 % [7]. It has been postulated that infection with Chlamydia pneumoniae can promote the progression of coronary heart disease by triggering either a local vascular or a systemic inflammatory process [8]. Several mechanisms have been discussed in this context; the resulting pathology is either acute (eg, plaque rupture, thrombosis) or chronic (eg, atherogenesis) (Table 1) [5, 9, 10].

The majority of acute coronary syndromes is associated with plaque rupture [11]. Activated monocytes may, by releasing proteinases, promote plaque rupture [12]. Bacterial lipopolysaccharides lead to the expression of surface tissue factor on monocytes [13]. This can trigger thrombus formation. Furthermore, infection with Chlamydia pneumoniae results in increased production of acute phase proteins such as fibrinogen [14]. This promotes platelet aggregation and thrombus formation [15, 16].

Another interesting aspect was found in a mouse model where the injection of Chlamydia outer membrane proteins induced perivascular inflammation, fibrotic changes, and blood vessel occlusion in the heart due to an antigenic mimicry of a heart muscle-specific protein [17].

In vitro studies have shown that Chlamydia pneumoniae is capable of infecting three cellular components of the human vascular wall – namely endothelial cells, smooth muscle cells and macrophages – and can proliferate in these components [18]. Respiratory endothelium is the initial target of Chlamydia pneumoniae. The macrophages represent potential vectors for the dissemination of the organism [19]. The macrophages may adhere to coronary vessels, for example, where they can cause chronic cytokine-mediated inflammatory reactions inflicting direct endothelial damage.

Table 1. Possible mechanisms triggering atherosclerosis (modified as proposed by Danesh [5])

Classic risk factors
• HDL cholesterol –
• Fibrinogen +
• Triglyceride +
Systemic inflammatory reactions
• C-reactive protein +
• Leukocytes +
• Cytokines +
Auto-immune reactions
• Heat shock protein 60-cross-reactivity with bacterial antigens
Infection of the arterial wall
• Proliferation of smooth muscle cells with p53 activation
• Local inflammation
Systemic infection
• Endothelial damage or endothelial dysfunction caused by circulating endotoxins

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Seroepidemiological studies

The classic coronary risk factors do not completely explain the time-related and geographical differences that can be observed in the incidence of coronary heart disease. An association between coronary heart disease and persistent bacterial or viral infections has been reported in many studies carried out during the last decade. Several seroepidemiological studies discovered a positive correlation between Chlamydia pneumoniae seropositivity and coronary heart disease [20–24] (Table 2). Moreover, Chlamydia pneumoniae seropositivity seems to be associated with restenosis after percutaneous transluminal coronary angioplasty [25].

It has been shown that Chlamydia pneumoniae antibody prevalence increases significantly with age [7] and there is evidence of an association between smoking and Chlamydia pneumoniae seropositivity in the general population [26, 27]. However, many of the seroepidemiological studies failed to control these risk factors and they generally lacked angiographic validation.

Recently, in a large-scale series of socio-economically homogeneous males controlled for age, smoking, as well as other cardiovascular risk factors, there was no evidence of a relation between Chlamydia pneumoniae IgG seropositivity and risk of myocardial infarction [27]. In an elderly study cohort (1503 Framingham heart study cohort participants, mean age: 70 years), Chlamydia pneumoniae seropositivity was not associated with increased risk of cardiovascular disease [28]. In the two angiographically controlled studies, no reliable relationship was established between coronary heart disease and seropositivity [4, 29] (Table 2). The study carried out by Anderson et al. [4] found no correlation between Chlamydia pneumoniae seropositivity and coronary heart disease or acute myocardial infarction (Table 2). In the paper published by Thom et al. [29] in 1992, an elevated risk for coronary heart disease was found only among smokers. Non-smokers seropositive for Chlamydia pneumoniae displayed in fact a lower incidence of coronary heart disease (Table 2).

Furthermore, most studies found no correlation between serum antibodies and the direct isolation of bacteria in plaque specimens [30, 31].

Direct detection

If Chlamydia pneumoniae plays a causative role in atherogenesis, it should be possible to isolate it in material from significant coronary plaques. The methods available for this purpose include direct bacterial culture, morphological identification by electron microscopy, tagging of surface antibodies with immunohistochemical methods and direct demonstration of DNA by the polymerase chain reaction (PCR).

The studies performed to directly detect Chlamydia pneumoniae in atherosclerotic coronary vessels have yielded highly discordant results. Depending on the detection method used (eg, immunohistochemical tests, electron microscopy, *in-situ* hybridization, PCR), the prevalence of Chlamydia pneumoniae in specimens of human plaque material ranges from 0 % to 100 % [30, 32–43] (Table 3).

So far, few researchers have succeeded in directly isolating the organism from coronary material [31, 33, 36]. The results of the electron microscopy studies are also discordant. Weiss et al. [36], for example, found no traces of Chlamydia pneumoniae in 22 samples they examined, whereas Bauriedel and co-workers frequently detected elementary bodies of Chlamydia pneumoniae in large phagocytizing macrophages by electron microscopy [39]. The largest numbers of positive findings were achieved with immunohistochemical methods [35, 40]. A problem associated with this detection method is its limited specificity [44]. For example, there is possibly cross-reactivity with cardiolipin, a substance commonly found in atherosclerotic plaques.

The most specific detection method is the polymerase chain reaction, since this species can demonstrate specific genome sequences. Several PCR have been described for the demonstration of Chlamydia pneumoniae: a 436 bp fragment of the 16S rRNA gene [45, 46], 437 bp DNA [19], and the omp1 gene of the major outer membrane protein [47]. A

Table 2. Serum antibodies against Chlamydia pneumoniae and coronary heart disease

Author		n	Study design	End points	OR
Studies without angiographic control					
Saikku	[24]	111	Case control	History of CHD, MI	3.5
Saikku	[21]	206	Case control	Fatal or non-fatal MI, sudden cardiac death	IgA: 2.3 IgG: 1.8
Melnick	[22]	326	Case control	Carotid wall thickening	1.7
Patel	[23]	388	Case control	Abnormal ECG	3.1
Miettinen	[24]	1993	Prospective study, 7-year follow-up	Fatal or non-fatal MI	Non-diabetics: 2.6 diabetics: ns
Ridker	[27]	686	Prospective study, 12-year follow-up, controlled for age, smoking, and other risk factors	Future MI	IgG 1:16,1:32,1:64,1:128,1:256 all subjects: 1.1, 1.0, 1.1, 1.0, 0.8 non-smokers: 1.1, 1.1, 1.1, 1.0, 0.9 smokers: 1.1, 0.9, 1.1, 1.0, 0.7 CRP: no correlation
Studies with angiographic control					
Thom	[29]	291	Prospective	Coronary angiography	Smokers: 3.5 non-smokers: 0.8
Anderson	[4]	363	Prospective	Coronary angiography	CHD: 1.05 MI: 1.14

CHD = coronary heart disease; MI = myocardial infarction; ns = no significant difference; CRP = C-reactive protein; OR = odds ratio of seropositivity in cases vs. controls

potential problem associated with PCR is the use of non-specific primers; with these primers, false positive results can be expected after only 25 cycles [48]. When formalin is used as a fixative, faulty PCR results are to be expected [49]. It has been observed, furthermore, that fresh-frozen substrate yields more valid results than specimens treated with fixative [49].

In an attempt to clarify these contradictory findings, we examined plaque specimens obtained by directional coronary atherectomy (DCA) from 16 patients with significant coronary stenosis. In 9 of the 16 patients, it was possible to obtain material of more than 15 mg. The specimens were examined for unknown bacterial agents as well as specifically for Chlamydia pneumoniae with 4 different polymerase chain reactions (PCR; 2× 16S rRNA-DNA, 2× Chlamydia pneumoniae DNA). PCR was carried out under the conditions described by Campbell [19]. It has been shown that this PCR is 100 % specific and displays a very high sensitivity [19]. With one exception, all the specimens were negative for bacterial DNA. The sequential analysis of this one PCR product yielded acinetobacter, a result which can be interpreted as skin contamination. The sensitivity-optimized PCR conditions for Chlamydia pneumoniae DNA resulted in a sensitivity of 0.1 IFU for the HL-1-HR-1 primer pair or 1 IFU for the HM-1-HR primer pair. All the specimens were negative [38].

Our results are congruent with those of other studies performed to specifically detect Chlamydia pneumoniae in plaque material from human coronary arteries. Weiss et al. [36] succeeded in demonstrating Chlamydia pneumoniae by PCR in only one out of 56 atherectomy specimens. In the Haberbosch study [30], a positive PCR result was found in only one out of 80 atherectomy samples. In the study recently published by Paterson and colleagues, examination of 17 atherectomy specimens from carotid arteries, 16 autopsy samples of carotid arteries and 16 autopsy samples of coronary arteries produced no evidence of Chlamydia pneumoniae [41]. Moreover, Burke et al. [42] studied atherosclerotic plaques from patients with symptomatic coronary (n = 72) and carotid (n = 9) disease. No coronary or carotid plaque contained detectable Chlamydia pneumoniae DNA [42]. Kiss and co-workers [43] found no nucleic acid sequences specific for Chlamydia pneumoniae in tissue specimen obtained by atherectomy in patients with acute coronary syndromes.

Table 3. Detection of Chlamydia pneumoniae (CP) in human atherectomy specimens from coronary stenosis

Author	Material		Detection method of CP	Prevalence
Muhlestein	[35]	DCA, CHD	Immunohistochemistry	66/90 (73 %)
		Controls		1/24 (4 %)
Weiss	[36]	DCA, CHD	PCR	1/56 (2 %)
			Electron microscopy	0/22 (0 %)
Haberbosch	[30]	DCA, CHD	PCR	1/80 (1 %)
Maass	[37]	DCA, CHD	PCR	21/70 (30 %)
		Controls		0/17 (0 %)
Scheller	[38]	DCA, CHD	PCR	0/16 (0 %)
Paterson	[41]	DCA, CHD	PCR	0/16 (0 %)
Bauriedel	[40]	DCA, CHD	Immunohistochemistry heat-shock protein 60	27/42 (64 %)
Burke	[42]	Autopsy, CHD	PCR	0/72 (0 %)
Kiss	[43]	DCA, CHD	PCR	0/20 (0 %)

DCA = directional coronary atherectomy; CHD = coronary heart disease; PCR = polymerase chain reaction

Interventional studies

The results of antibiotic studies conducted with patients suffering from coronary heart disease or acute coronary syndromes may constitute indirect evidence of the pathogenic relevance of bacterial pathogens. To date three studies have been published on the use of antibiotics effective against Chlamydia, namely roxithromycin and azithromycin, to treat patients with acute coronary syndromes [50–52].

In the two smaller studies, a reduction of cardiac events was observed in the patient groups treated with antibiotics [50, 51]. On the basis of these findings, the authors concluded that Chlamydia pneumoniae plays an important role in acute coronary syndrome. However, in the ROXIS study, the beneficial effects of roxithromycin on the combined end points of death, myocardial infarction and severe recurrent ischaemia observed at 30 days were no longer statistically significant after 6 months [53] (Table 4). In the largest trial, the recently published ACADEMIC study, no differences in clinical events were observed at 3 and 6 months follow-up [52] (Table 4).

An alternative explanation for the short-term efficacy of the macrolides is that they lower the activity of the macrophages, which in the activated state facilitate plaque rupture [54]. The inhibition of macrophages is caused by the blockade of the large-conductance potassium channel by the macrolide antibiotics [55]. In contrast to this, in a retrospective case-control analysis by Meier et al. [56], there was no decrease of the risk of developing a first-time acute myocardial infarction in patients with previous use of macrolides. On the other hand, this study demonstrated an association between the use of tetracycline antibiotics or quinolones and the reduction (30 % and 55 %, respectively) of an acute myocardial infarction. It must be emphasized that this association does not prove the existence of a causal relationship and that these observational findings should not be interpreted as sug-

Table 4. Interventional studies

Author	n	Study design	Follow-up	Treatment	Placebo group	p
Gurfinkel [51, 53]	202	Patients with unstable angina or non-Q-wave myocardial infarction	30 days	2.0 %	9.0 %	0.032
		roxithromycin *vs* placebo	6 months	8.7 %	14.6 %	ns
I		combined endpoint[1]				
Anderson [52]	302	Patients with angiographic proven CAD and seropositive reaction to CP azithromycin vs placebo combined endpoint[2]	6 months	6.0 %	4.6 %	ns

CAD = coronary artery disease; CP = Chlamydia pneumoniae.
[1] Combined endpoint consisting of recurrent angina, acute myocardial infarction, and death
[2] Combined endpoint consisting of cardiovascular death, resuscitated cardiac arrest, non-fatal MI or stroke, unstable angina requiring hospitalization, and unplanned coronary interventions

gesting that antibiotics should be given to patients to prevent acute myocardial infarction. Further studies in a prospective, randomized, placebo-controlled design are needed, clarifying the role of antibiotics in this context.

Conclusion

The studies conducted to date have reached contradictory conclusions about the pathogenic relevance of Chlamydia pneumoniae in coronary heart disease. The serological studies are hampered by the difficulty in controlling the impact of other risk factors and the frequent absence of angiographic validation. Moreover, no correlation has been found between positive serum antibodies and the direct isolation of Chlamydia pneumoniae from coronary plaque.

Chlamydia pneumoniae was directly demonstrated in coronary plaque at rates ranging from 0 % to 100 %. The higher detection rate achieved by immunohistochemical methods in comparison with PCR is remarkable. The general problem presented by immunohistochemical methods is the possibility of cross-reactivity and false positives.

The results of the studies performed with macrolide antibiotics are conflicting and do not prove that Chlamydia pneumoniae plays a key role in causing atherosclerosis or triggering acute coronary syndromes.

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