Clin. Cardiol. 22, 85–90 (1999)

Lack of Association between Prior Infection with *Chlamydia Pneumoniae* and Acute or Chronic Coronary Artery Disease

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Summary

Background: Higher than normal serologic titers and the detection of bacteria within atheroma have suggested an association between *Chlamydia pneumoniae* (*C. pneumoniae*) infection and coronary heart disease (CHD), but the relationship has not been well established.

Hypothesis: The study was designed to establish a lack of relationship between chronic *C. pneumoniae* infection and CHD.

Methods: Chlamydia-specific IgG-antibody was assayed using an indirect immunofluorescence test in the serum of 159 patients with severe arterial disease and 203 patients with a heart valve prostheses and no demonstrable CHD. Fatal and nonfatal vascular events and systemic thromboembolism were recorded over a 2-year period.

Results: In the arterial group 107 patients (67.3%) and in the valvular group 120/203 (59.1%) were positive for *C. pneumoniae* antibody. The number of patients with fatal or nonfatal vascular events (double end point) in the arterial and valvular groups was 23 and 2, respectively ($p < .0001$). Triple end points (fatal plus nonfatal vascular events plus thromboembolism) were also more frequent in the arterial group ($p < 0.002$). The prevalence of chlamydia antibody positivity was the same in the arterial and valvular groups, and the occurrence of clinical events was also the same for chlamydia-positive (227 patients) as for chlamydia-negative (135 patients). After adjustment for confounding variables, only arterial disease was a predictive factor for double (OR 17.0; 95% CI 3.94–73.3) or triple (OR 3.12; 95% CI 1.56–6.25) end points.

Conclusion: We find *C. pneumoniae* chronic infection not to be an independent risk factor for acute or chronic arterial disease.

Key words: *Chlamydia pneumoniae*, coronary disease, atherosclerosis

Introduction

The known risk factors for coronary heart disease (CHD) such as hypertension, serum lipids, diabetes, age, gender, smoking, and familiar history, are not sufficient to explain all the epidemiologic variations of the disease. Recently, several studies have proposed chronic infection to be an additional risk factor[1–7] and a predictor of adverse cardiovascular events after myocardial infarction.[6] The elevated serologic titers[2] as well as the presence of *Chlamydia pneumoniae* (*C. pneumoniae*) within atherosclerotic plaques[8–13] provided grounds for the hypothesis that *C. pneumoniae* infection is associated with CHD.

Whether *C. pneumoniae* causes CHD or atherosclerotic lesions are subsequently infected by chlamydia remains to be shown.[8] Most of the studies assayed chlamydia-specific circulating immune complex in patients with chronic CHD and in a population with no evidence of CHD. In these studies, the controls had not undergone the invasive procedures as did most of the coronary patients. In vitro studies showed that endothelial cells, smooth muscle cells, and macrophages derived from peripheral blood monocytes were susceptible to infection with *C. pneumoniae*.[14] We hypothesized that *C. pneumoniae* might have been activated during the invasive procedures. For this reason the control group in our study consisted of patients in whom a heart valve had been replaced and who had had an invasive procedure not dissimilar to those undergone by the patients of the arterial group. We compared the serologic titers of *C. pneumoniae* in patients with severe chronic coronary or peripheral artery diseases with those in patients with prosthetic cardiac valves and subsequently determined whether the titers have any relationship to the incidence of acute arterial and arterial thromboembolic events during the study period of just over 2 years.

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Received: June 2, 1998
Accepted with revision: September 11, 1998

Materials and Methods

Subjects

The trial was a single-center, open-label, nonrandomized study. From February 1, 1995, to April 30, 1997, patients receiving oral anticoagulant therapy at our Center were divided in two groups.

Group 1, with a clinical history of arterial disease indicated by angiography, included 142 patients with severe CHD: documented myocardial infarction in 28 patients, coronary artery bypass grafting (CABG) in 77 patients (57 had also a cardiac valve replacement), ischemic dilated cardiomyopathy in 24 patients, unstable angina in 4 patients, percutaneous transluminal coronary angioplasty (PTCA) in 12 patients, and obstructive peripheral vascular disease in 17 patients. Group 2 comprised 203 patients with mechanical heart valve prostheses, without significant demonstrable coronary disease, who had undergone invasive procedures similar to Group 1 patients. Of the patients referred to our Center for anticoagulant treatment, 83% came from the Department of Cardiovascular Surgery or the Coronary Unit, Güemes Hospital, Buenos Aires.

Patients with a history of repeated respiratory infectious disease or with malignancies were excluded. There were no geographic or genetic differences between groups.

All patients were receiving oral anticoagulant therapy with acenocoumarol (Sintrom®, Ciba-Geigy, Buenos Aires, Argentina) and 338 patients were also taking aspirin 100 mg daily. In all cases, patients continued with the treatment indicated by their own physicians. All patients were examined for clinical events at intervals of 2 to 3 months during the study period (just over 2 years) and were instructed to report any events to study personnel immediately.

Methods

Blood samples were drawn from an antecubital vein between 8 and 11 A.M. after an overnight fast, collected in glass tubes, and left to clot for 2 h at room temperature. After centrifugation, the serum fraction was removed and frozen in aliquots at -30° C until assayed. The samples were coded so that the investigators performing laboratory assays were blinded to diagnosis. The presence of specific IgG antibody to *C. pneumoniae* was assayed using the indirect immunofluorescence test commercially available from Bion, Park Ridge, Illinois, USA, with the following specifications: Source: ATCC N*VR-1310 (American type culture collection); Strain TWAR (CCDC/CWL-029) Cell-line HEp-2. A threshold titer $\geq$ 1:32 was chosen to indicate antibody positivity. *Chlamydia trachomatis* was assayed with IgG TMB ELISA from Clark Laboratories, Inc., Jamestown, N.Y., USA. Samples cross reacting with IgG antibody to *Chlamydia trachomatis* were coded as "probably positive" for *C. pneumoniae*.

The expert observer (RSA) was blinded to the purpose of the study and to the group allocation of patients.

Total serum cholesterol was assayed with the reagent from Biosystem S.A., Barcelona, Spain.

End Points

Acute coronary artery events during the study (documented myocardial infarction or unstable angina), PTCA, CABG, acute peripheral arterial events or progression of arterial disease indicated by angiography, and death due to vascular disease were chosen as primary end points, systemic thromboembolic complications and nonvascular death as secondary end points. Criteria for embolism of cerebral arteries were as previously described.[15] Double end point was defined as the sum of fatal and nonfatal vascular events, and the triple end points was the sum of fatal and nonfatal vascular events and arterial thromboembolism.

Statistical Analysis

Statistical analysis of dichotomous variables was by the chi-square test (Yates corrected) or Fisher's exact test. Student's *t*-test was used to assess differences between groups for two continuous variables. To estimate the multivariate predictive value of several independent covariates (with single, double, and triple end points as dependent variables), three stepwise multiple logistic regression models were used. Degree of fit of the data to each model was estimated by the Hosmer/Lemeshow test, and the percentage of the variance was obtained. The predictive value for each significant covariant was expressed as the odds ratio (OR), obtained from the beta coefficient of each model. A 95% confidence interval (CI) was derived as the standard error of these beta coefficients. Statistical significance was taken as $p < 0.05$. The software used was CSS/Statistica, 3.1 (Statsoft Corp., Tulsa, Okla., USA).

Results

The baseline characteristics of patients in the two groups are shown in Table I.

A systolic pressure > 150 mmHg or diastolic pressure > 90 mmHg were the criteria for defining arterial hypertension. Serum cholesterol > 220 mg/dl was the criterion for hyperlipidemia, and fasting blood sugar $\geq$ 120 was the criterion for diabetes. Both previous and current users of antihypertensive, antilipidemic, or antidiabetic medication were coded as hypertensive, hyperlipidemic, or diabetic.

Follow-up time was similar in Group 1 and 2 patients, that is, 329.3 and 438.2 patient/years, respectively. More patients in Group 1 (87.4%) than in Group 2 (53.7%) were male and had a higher statistical significant incidence of dyslipidemia ($p < 0.018$) and diabetes ($p = 0.012$). Atrial fibrillation was more frequent in Group 2 patients ($p < 0.001$).

In Group 1, a history of myocardial infarction was more frequent among patients with *C. pneumoniae* negative titers ($p = 0.031$) (data not shown). In Group 2, dyslipidemia and former smoking were more frequent among patients with a *C. pneumoniae* negative test ($p = 0.013$). Other characteristics were similar among patients with a positive or negative test.

TABLE I Baseline clinical characteristics of patients

	Arterial group (Group 1) (n=159)	Valvular group (Group 2) (n=203)	p Value (Chi^2)
Follow-up (years)	329.3 2.07 per patient	438.2 2.16 per patient	
Sex			
Male (%)	139 (87.4)	109 (53.7)	<0.0001
Female (%)	20 (12.6)	94 (46.3)	
Age (years)			
Mean	65.5 ± 8.4	60 ± 10.9	<0.0001[a]
Range	38–84	28–81	
Risk factors			
Atrial fibrillation (%)	14 (8.8)	45 (22.2)	<0.001
Smoking			
Current (%)	10 (6.3)	12 (5.9)	0.881
Former (%)[b]	39 (24.5)	34 (16.7)	0.067
Never (%)	108 (67.9)	155 (76.4)	0.079
Body mass index	27.3 ± 5.0	26.98 ± 4.38	0.116[a]
Dyslipidemia (%)	89 (56.0)	87 (42.9)	<0.018
Diabetes (%)	24 (15.1)	13 (6.4)	<0.012
Hypertension (%)	64 (40.2)	71 (35.0)	0.357
Diagnosis at entry			
Myocardial infarction (%)	28 (17.6)	—	
Dilated cardiomyopathy (%)	24 (15.1)	—	
TIA or *Amaurosis fugax* (%)	6 (3.8)	15 (7.4)	0.217
Peripheral artery disease (%)	17 (10.7)	—	
Valve replacement (%)	57 (35.8)	203 (100)	<0.001
Mitral	9	63	
Aortic	48	130	
Mitral + aortic		10	
PTCA (%)	12 (7.5)	—	
CABG (%)	77 (48.4)	—	
Unstable angina (%)	4 (2.5)	—	

[a] Student's t-test.

[b] Stopped smoking for more than 12 months.

Abbreviations: TIA = transient ischemic attack, CABG = coronary artery bypass graft, PTCA = percutaneous transluminal coronary angioplasty.

The prevalence of IgG titers ≥ 1:32 for *C. pneumoniae* antibody was similar in both groups. In Group 1, 96 patients (60.4%) were positive, 52 patients (32.7%) were negative, and 11 patients were "probably positive," with the result that 67.3% of samples showed evidence of circulating antibody for *C. pneumoniae* (titers ≥ 1:32) and were coded as positive. In Group 2, 102 patients (50.2%) were positive, 83 patients (40.9%) were negative, and 18 patients (8.9%) were "probably positive," resulting in 59.1% of patients with evidence of circulating antibody for *C. pneumoniae* who were coded as positive. These results did not reach statistical significance.

In healthy persons tested by our group, (mean age 66.5 years, range 48–82), considering a similar cutoff (≥ 1/32), the prevalence of positive tests was 47.6%. The difference between Groups 1 and 2 is statistically significant ($p < 0.001$ by chi-square test).

Current smokers were significantly more likely than nonsmokers to have high serological titers of antibody to *C. pneumoniae*.[16] In the present study, only a few patients in each group were current smokers (6.3 and 5.9% in Groups 1 and 2, respectively) at the beginning of the study.

Outcomes Events

In Group 1, 17.6% (28/159) of patients and in Group 2, 6.4% (13/203) of patients reported events during the study period ($p < 0.0016$). The percentage of fatal plus nonfatal events was 14.5% (23/159) and 1.0% (2/203), respectively, a highly significant difference ($p < 0.0002$) (Table II). The difference between groups for arterial thromboembolism was not statistically significant (5 in Group 1, 11 in Group 2, $p = 0.431$). Atrial fibrillation was not an additional risk factor for

TABLE II Outcomes in the two groups

Outcomes	Arterial group (Group 1) n = 159	Valvular group (Group 2) n = 203	p Value (Chi^2)
No events (%)	131 (82.4)	189 (93.1)	<0.002
Vascular deaths (%)	4 (2.5)	0	0.036[c]
Arterial thromboembolism (%)	5 (3.1)	11 (5.4)	0.431
Nonfatal vascular events (%)	19 (11.9)	2 (1.0)	<0.0001
Fatal nonvascular events (%)	0	1 (0.49)	
Double end points (%)[a]	23 (14.5)	2 (1.0)	<0.0001
Triple end points (%)[b]	28 (17.6)	13 (6.4)	<0.002

[a] Double end points: Fatal plus nonfatal vascular events.
[b] Triple end points: Fatal plus nonfatal vascular events plus arterial thromboembolism.
[c] p Value from Fisher's exact test.

arterial embolism: 1/5 in Group 1 with arterial embolism and 2/11 in the Group 2 had atrial fibrillation.

Correlation between *C. pneumoniae* and Events

Table III shows the presence of *C. pneumoniae* antibody at ≥ 1:32 dilution together with the percentage of patients with events in each group. Only arterial thromboembolism was significantly higher in chlamydia-negative patients in Group 1 (p = 0.04, Fisher's exact test).

Although the incidence of chlamydia-positive patients was similar in both groups, 107 and 120 patients, respectively, (Table IIIA, B) double and triple end point events were significantly higher in Group 1: 17 versus 0 for double (p < 0.001), 18 versus 7 patients (p < 0.015) for triple end points. The relationship was similar, though not statistically significant, for chlamydia-negative patients (6 vs.2; 10 vs. 6 patients).

When all chlamydia-positive (227) and chlamydia-negative (135) patients were compared (Table IV), no differences in clinical outcomes were statistically significant.

After adjustment for confounding variables (age, gender, lipid profile, diabetes, arterial hypertension, body mass index, smoking, or presence of *C. pneumoniae*) only the presence of arterial disease proved to be a predictive factor for outcome (double end point OR 17.0, 95% CI 3.94–73.3, triple end point OR 3.1, 95% CI 1.56–6.25).

Discussion

Several recent studies have found an association between *C. pneumoniae* infection and CHD[1–6] or atherosclerotic lesions of coronary and carotid arteries,[8–13] myocarditis,[17] myocardial infarction,[5] plaque instability,[18] and sudden death.[19] These studies used asymptomatic persons as controls and compared them with patients with chronic CHD who had

TABLE IIIA Presence of *C. pneumonia* antibody versus clinical events in the arterial group (Group 1)

Outcomes	Chlamydia-positive subgroup (n = 107)[d]	Chlamydia-negative subgroup (n = 52)	p Value (Chi^2)
No events (%)	89 (83.2)	42 (80.8)	0.879
Vascular deaths (%)	3 (2.8)	1 (1.9)	0.999
Arterial thromboembolism (%)	1 (0.9)	4 (7.7)	0.04[c]
Nonfatal vascular events (%)	14 (13.1)	5 (9.6)	0.71
Double end points (%)[a]	17 (15.9)	6 (11.5)	0.623
Triple end points (%)[b]	18 (16.8)	10 (19.2)	0.879

TABLE IIIB Presence of *C. pneumonia* antibody versus clinical events in the valvular group (Group 2)

Outcomes	Chlamydia-positive subgroup (n = 120)[d]	Chlamydia-negative subgroup (n = 83)	p Value (Chi^2)
No events (%)	112 (93.3)	76 (91.6)	0.899
Vascular deaths (%)	0	0	
Arterial thromboembolism (%)	7 (5.8)	4 (4.8)	0.999[c]
Nonfatal vascular events (%)	0	2 (2.4)	
Fatal nonvascular events (%)	1 (0.8)	0	
Double end points (%)[a]	0	2 (2.4)	0.166[c]
Triple end points (%)[b]	7 (5.8)	6 (7.2)	0.914

[a] Double end points: Fatal plus nonfatal vascular events.
[b] Triple end points: Fatal plus nonfatal vascular events plus arterial thromboembolism.
[c] p Value from Fisher's exact test.
[d] Chlamydia-positive includes positive and "probably positive" test.

TABLE IV Clinical events in all patients with *C. pneumoniae*-positive or -negative tests

Outcomes	All chlamydia-positive subgroup (n = 227)[d]	All chlamydia-negative subgroup (n = 135)	p Value (Chi^2)
No events (%)	201 (88.5)	119 (88.1)	0.776
Vascular deaths (%)	3 (1.3)	1 (0.7)	0.999[c]
Arterial thromboembolism (%)	8 (3.5)	8 (5.9)	0.417
Nonfatal vascular events (%)	14 (6.2)	7 (5.9)	0.877
Fatal nonvascular events	1 (0.4)	0	
Double end points (%)[a]	17 (7.5)	8 (5.9)	0.724
Triple end points (%)[b]	25 (11.0)	16 (11.8)	0.943

[a] Double end points: Fatal plus nonfatal vascular events.

[b] Triple end points: Fatal plus nonfatal vascular events plus arterial thromboembolism.

[c] p Value from Fisher's exact test.

[d] Chlamydia-positive includes positive and "probably positive" test.

undergone invasive procedures. We speculated that latent infection could be activated by invasive procedures (angiography, PTCA, CABG, cardiac surgery) since endothelial cells, smooth muscle cells, and macrophages derived from peripheral blood monocytes were susceptible to infection with *C. pneumoniae*,[14] and respiratory *C. pneumoniae* inoculation can induce vascular infection with dissemination via infected macrophages.[20]

All patients in the studies of Linnanmäki *et al.*[2] and Thom *et al.*[4] underwent coronary angiography, as did 42.9% of those in the trial of Saikku *et al.*[3] In none of these studies had controls undergone any invasive procedures. When controls were patients with no demonstrable coronary artery lesion on angiography, Thom *et al.*[5] found that, although the antibody titer was higher for cases than for controls, the statistical significance ($p = 0.04$) was weak.

Our study used as controls patients with cardiac valve replacement who had undergone almost the same invasive procedure (coronary angiography, cardiac surgery) as patients in Group 1, but had been found free of relevant coronary artery disease.

For antibody positivity, we chose a cutoff 1:32, close to the criterion of Patel *et al.* in which titer < 1:16 was negative.[21] Many different dilutions have been used,[2–7] and agents and methods vary from center to center,[22] so that there is no consensus on this matter at present. Our study showed that the presence in the serum of *C. pneumoniae* IgG antibody by these criteria was equally prevalent in patients in Groups 1 and 2, and that the number and percentage of patients suffering a clinical event was higher in Group 1 irrespective of chlamydia infection status. Moreover, when all patients in both groups, were divided according to positive (227 patients) or negative test (135 patients) for *C. pneumoniae*, the amount of outcomes was not statistically different (Table IV).

The differences between our results and those of others[2–4] can be explained by the difference in the choice of controls. Moreover, in the Helsinki Heart Study[6] the higher titer of IgG antibody for *C. pneumoniae* in patients who developed myocardial infarction did not reach statistical significance.

The confounding factors of gender, age, hyperlipidemia, hypertension, diabetes, atrial fibrillation, body mass index, and smoking did not significantly affect the lack of association between chronic chlamydia infection and the risk of CHD. All patients in both groups were receiving oral anticoagulant therapy and most of them (93.4%) aspirin as well, hence these therapies could not account for differences in outcome.

Libby *et al.*[22] and Danesh *et al.*[23] have reviewed the role of *C. pneumoniae* and other infectious agents in CHD and concluded that the link between *C. pneumoniae* infection and CHD remains plausible but unproven. Our study shows that patients with arterial disease are at higher risk of fatal and nonfatal vascular events than patients with heart valve prostheses without relevant arterial compromise, but the presence of IgG antibody in *C. pneumoniae* in the serum is not a predictive factor for acute arterial complications.

Acknowledgment

The authors wish to thank Ulises Questa, M.D. (Buenos Aires), for his critical review of the statistical analysis.

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