Chronic Infections and Atherosclerosis

WATTANA LEOWATTANA, M.D.*

Abstract

The established risk factors for atherosclerosis such as hypertension, smoking, diabetes mellitus, hyperlipidemia, and hyperhomocysteinemia do not explain clinical and epidemiological features of coronary heart disease (CHD). The role of infectious disease as a CHD risk factor may partly explain these features. Chronic infection with various microorganisms, particularly, *Chlamydia pneumoniae*, Cytomegalovirus (CMV) and *Helicobactor pylori* may play a role in etiological factors, linking inflammation and atherogenesis. Results from epidemiological studies, pathology of atherosclerotic plaques, animal studies, molecular biology and clinical antibiotic trials indicated a positive association between *C. pneumoniae* infection and CHD. Chronic infection might also influence preexisting plaque by enhancing T cell activation, which participate in destabilization of intimal cap. However, the exact nature of pathophysiological link between the organisms and CHD remains to be elucidated. Future antibiotic interventional studies may help to further clarify the role of chronic infection and inflammation in CHD.

Key word : Chronic Infection, Atherosclerosis, Coronary Heart Disease, *Chlamydia pneumoniae*, CMV, *Helicobactor pylori*

LEOWATTANA W
J Med Assoc Thai 2001; 84 (Suppl 3): S650-S657

Atherosclerosis is the principal underlying cause of coronary heart disease (CHD), which is the commonest cause of death in the industrialized world. It is also the cause of stroke and peripheral vascular disease, which are significant causes of morbidity and mortality. The atherosclerotic process starts as a protective response to injuries to the endothelium and smooth muscle cells of the wall of the artery, and progresses to the formation of atherosclerotic plaques, which narrow and may totally obstruct the lumen of the affected artery. The earliest atherosclerotic lesions are fatty streaks, which are

* Department of Clinical Pathology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand.

found even in young asymptomatic subjects[1]. Over the years, these develop into fibrous plaques, which consist of a fibrous cap overlying a lipid-rich core. It is well established that numerous factors may contribute to the progression of atherosclerosis, including hypertension, increased blood lipids, cigarette smoking and diabetes[2]. However, known risk factors do not account for the entire incidence of cardiovascular disease and investigators continue to investigate other possible risk factors[3-7].

Sir William Osler introduced the association between infections and atherosclerosis nearly 100 years ago. In 1978, experimental infection of germ-free chickens with an avian herpes virus was found to produce arterial diseases that resemble human atherosclerosis. Subsequently, various infections have been reported as being associated with the development of cerebral and myocardial infarctions[1,8-10]. These include *Helicobactor pylori* (*H. pyroli*), Cytomegalovirus (CMV) and *Chlamydia pneumoniae* (*C. pneumoniae*)[11-19]. As reviewed by Danesh et al, *H. pylori*, CMV and *C. pneumoniae* share some common characteristics[20]. The proportion of adults in developed countries who have antibodies to these infections is about one half. The probable mode of spread is through the aerodigestive tract. Infections may be acquired at an early age with most being asymptomatic and reinfection being very common. The organisms develop a persistent or silent state and may become reactivated by appropriate stimuli.

Cytomegalovirus (CMV)

Several epidemiological studies reported odds ratios of at least two for an association between anti-CMV antibodies and cardiovascular disease[21, 22]. However, many of the studies were small and the results were not adjusted for confounding factors. In addition, only a minority of the studies was undertaken in the setting of classical coronary artery disease (CAD). DNA from both herpes simplex virus (HSV) and CMV have been detected in atherosclerotic lesions, but the evidence for a causative role is weak[15,23]. In the 18 studies of CMV in pathological samples there were only small differences in the proportion of atheromatous and non-atheromatous blood vessels positive for CMV (47% *vs* 39%, with an odds ratio of about 1.4)[16,24-25]. Some features of atherosclerosis resemble benign neoplasia, and herpes viruses can help induce genomic transformation. CMV has been studied in relation to p53, a protein that is indirectly involved in DNA repair[26]. In patients who have just undergone coronary angioplasty, infection of smooth-muscle cells by CMV is associated with cellular proliferation that can lead to coronary restenosis. This finding raises the possibility that a similar mechanism might underlie primary atherogenesis. Moreover, the finding that neointimal proliferation in CMV-infected rats is increased after vascular injury also supports the relevance of CMV to arterial lesions[27].

Helicobactor pylori

Since the first report in 1994, there have been numerous sero-epidemiological studies of about 2,600 cases, reporting an association between the presences of antibodies to *H. pylori* and CAD, or stroke[11,28,29]. Most of the studies reported strong associations, but there was little adjustment for possible confounders in many of these studies. A meta-analysis of 18 epidemiological studies, over 10,000 patients, found no correlations between evidence of *H. pylori* infection and blood pressure, leucocytes count, serum total cholesterol, triglycerides, fibrinogen and C-reactive protein (CRP)[30]. The earlier claims of correlations between *H. pylori* seropositivity and cardiovascular risk factors may be explained by chance or preferential publication of positive results.

Chlamydia pneumoniae

The evidence for a link between *C. pneumoniae* and CAD is much stronger than any other infectious organism. In 1988, Saikku et al reported the first evidence suggesting a role of *C. pneumoniae* infection in CAD patients. Since then, the possible etiological link has been widely investigated in both seroepidemiological studies and by demonstration of the organism in atherosclerotic plaques using various techniques for example ELISA, PCR, electron microscopy and isolation in tissue culture [31-37]. Moreover, the presence of circulating *C. pneumoniae*-specific immune complexes in a high proportion of CAD patients suggests the persistence of chronic infection[38]. Recently, Danesh et al reviewed published seroepidemiological studies and showed that a raised anti-*C. pneumoniae* antibody titer was associated with a 2 - 4 fold increased prevalence of CAD[39]. More convincing evidence for a causative role of *C. pneumoniae* infection and atherosclerosis comes from studies that demonstrated

C. pneumoniae DNA, protein and elementary bodies in human arterial tissue and peripheral blood mononuclear cell (PBMC) using molecular techniques. Nearly 20 published pathological studies revealed *C. pneumoniae* was present in arterial tissue in 52 per cent of atheromatous lesions but in only 5 per cent of control samples giving a weighted odds ratio of approximately 10 (95%CI = 5 – 22)[12,35,40-42]. In addition, *C. pneumoniae* has been cultured from coronary atheroma, further indicating that the organism is viable within atheromatous plaque[43]. The demonstration of the living organism within atheromatous plaque does not, however, establish a causal relationship between *C. pneumoniae* and atherosclerosis. The possibility that *C. pneumoniae* is an "innocent bystander" must also be considered.

While there is increasing evidence of an association between *C. pneumoniae* and CAD, a clear mechanism of action of *C. pneumoniae*-induced atherosclerosis has not yet been established. It is likely that macrophages become infected with *C. pneumoniae* in the lungs and reach the atheromatous lesion *via* the blood stream. The organism may persist in the macrophages making any association between the presences of *C. pneumoniae* and atherosclerosis purely coincidental. Conversely, evidence that *C. pneumoniae* is associated with atherosclerosis by inducing foam cell development has been reported by Kalayoglu et al[44]. A variety of mechanisms have been proposed to explain the link between infection and atherosclerosis. These include the role of infection in initiating and perpetuating initial damage. Infection with *C. pneumoniae* may induce a chronic immune response orchestrated by cytokines that may result in direct damage to the endothelium, increased synthesis of acute-phase proteins or alteration of plasma lipid profile[45-49]. Activation of monocytes may also lead to increased expression of procoagulant factors, which increase the risk of thrombus formation.

Attempts to establish whether *C. pneumoniae* has a causal role in atherosclerosis and CAD have been hampered by diagnostic difficulties. At present, the identification of persons with *C. pneumoniae* infection of atherosclerotic arteries depends entirely on the examination of vascular tissues removed during surgical procedures. A better assay to identify vascular infection is needed. Directed detection methods based on peripheral blood components might be more useful markers of infection. In 1997, Naidu et al demonstrated *C. pneumoniae* DNA in sera of a large proportion of subjects with either MI or chronic CHD, much more frequently than in sera from age- and gender-matched controls without CHD[50]. This finding suggests that DNA might be liberated continuously or intermittently from *C. pneumoniae* organisms in vessels or elsewhere. Subsequently, many investigators tried to detect *C. pneumoniae* in peripheral blood mononuclear cells (PBMC) by using a nested PCR method. Maass et al in Germany, Boman et al in Sweden, Wong et al in the United Kingdom and Mahony et al in Canada independently confirmed positive identification of *C. pneumoniae* within PBMC of patients with CAD[51-54]. In the future, blood-based PCR assays may become valuable for identifying patients persistently infected with *C. pneumoniae*.

In both rabbit and mouse models, several studies have reported that *C. pneumoniae* contributes to the progression of atherosclerosis[55-58], and in conjunction with hyperlipidemia, it results in the exacerbation of lesion progression. In New Zealand white rabbits fed a high fat and high cholesterol diet, *C. pneumoniae* infection has been shown to increase maximal intimal wall thickening. This effect was reversed by treatment with antichlamydial antibiotics such as azithromycin[59,60]. In the ApoE-deficient mouse model, repeated *C. pneumoniae* infection has been shown to accelerate lesion progression[61]. In low-density lipoprotein (LDL)-receptor knock out mice, which were more susceptible to atherosclerosis when fed atherogenic diet, *C. pneumoniae* infection has also been shown to accelerate lesion progression[62]. A somewhat more controversial issue is whether *C. pneumoniae* infection alone can induce atherosclerosis and, if so, whether single or repeated infections are required. Cumulative evidence from animal models supports a pathogenic role for *C. pneumoniae* in atherosclerosis, with it being at the site of lesion formation. In the mouse model, infected macrophages disseminate the infection and establish persistent infection of the aorta in foam cells within atherosclerotic lesions[63,64]. This simulates human infection, in which the organism has also been found in foam cells. Finally, there is evidence that *C. pneumoniae* infection can accelerate the progression of atherosclerosis in conjunction with hyperlipidemia and initiate histopathological changes in the aorta in the

mouse and rabbit models. Whether infection alone can induce definitive atherosclerosis is a question worthy of further investigation.

Gupta et al reported the first application of antichlamydial therapy in human atherosclerotic disease in 1997(65). In this study, 220 men with stable symptoms after myocardial infarction were stratified into three groups on the basis of serum IgG antibodies against *C. pneumoniae*: 1) no detectable antibodies, 2) seropositive with titers of 1:8 to 1:32, and 3) seropositive with titers of 1:64 or more. The 60 subjects in the high-titer group were randomized to receive placebo or azithromycin. After 18 months' follow-up, the results showed that there was a 4-fold greater risk of experiencing adverse cardiovascular events if baseline anti- *C. pneumoniae* antibody titers were elevated (odds ratio 4.2 (95% CI 1.2-15.5, $p = 0.03$)). For the high-titer group receiving antibiotic therapy, the adjusted odds ratio was 0.9 (95% CI.0.2-4.6, $p > 0.5$), the same as that for the seronegative group. Furthermore, treatment with azithromycin was associated with a fall in antichlamydial IgG titer. In the same year, Gurfinkel et al compared a different macrolide, roxithromycin, with placebo in more than 200 patients with acute coronary syndromes(66). The study was plagued by a low rate of coronary events and a high dropout rate; approximately 30 per cent of treated and placebo patients failed to complete the 30-day study. There was no significant difference between subjects and controls in the occurrence of the single endpoints. However, when these three were combined into a triple endpoint, the treatment group showed a statistically significant reduction. The number of events decreased in both patients who completed the 30-day course of therapy and those who completed only 72 hours of therapy. In contradiction to Gupta' s study, antibiotic therapy had no effect on antichamydial IgG titers. The recently reported ACADEMIC (Azithromycin in Coronary Artery Disease: Elimination of Myocardial Infection with Chlamydia) study examined the effects of azithromycin and placebo in three-month's treatment of CAD patients(67). This study was similar to that performed by Gupta et al, although the sample size was much larger (300 *vs* 60 subjects) and the treatment regimen was more intensive. Markers of inflammation such as CRP and interleukin-6 were decreased at six months in the group that received azithromycin, but there was no significant change in antichlamydial IgG titers and no difference in the incidence of clinical cardiovascular events, compared with the placebo group.

At least three large-scale secondary prevention trials are now under way. WIZARD (Weekly Intervention with Zithromax against Atherosclerotic-Related Disorders) will examine the effects of three months of once-weekly azithromycin therapy in 3,500 patients who have had myocardial infarctions and who have antichlamydial antibodies. Follow-up is planned for 2.5 years. The second trial, ACES (Azithromycin and Coronary Events Study), will enroll 4,000 patients with documented CAD irrespective of antibody status. The treatment group will receive once-weekly azithromycin, and all subjects will be followed for four years. The third trial, MARBLE (Might Azithromycin Reduce Bypass-List Events?), aims to randomize around 1,300 CABG-waiting list patients to an azithromycin regimen identical to that in the WIZARD trial, or to placebo, and to assess whether the antibiotic reduces the incidence of cardiovascular events occurring before the surgery.

SUMMARY

The mechanisms by which infection might induce atherogenesis may be direct or indirect. Atherosclerosis is now regarded as a chronic inflammatory disease and evidence is growing that infection may be a cardiovascular risk factor which plays a role in perpetuating the inflammation. While associations of various infections with atherosclerosis have been reported, the evidence is strongest for *C. pneumoniae*. As yet, there is no proof of the possible causative role of *C. pneumoniae* in atherosclerosis, but the potential for prevention or treatment has been sufficient to prompt the initiation of therapeutic clinical trials with antichlamydial antibiotics. If the results of the antibiotic intervention trials confirm this hypothesis, the implications for global health will be enormous.

(Received for publication on September 21, 2001)

REFERENCES

1. Ross R. The pathogenesis of atherosclerosis: A perspective for the 1990s. Nature 1993; 362: 801-9.
2. Ross R. Atherosclerosis--an inflammatory disease. N Engl J Med 1999; 340: 115-26.
3. Leinonen M. *Chlamydia pneumoniae* and other risk factors for atherosclerosis. J Infect Dis 2000; 181 (Suppl 3): S414-6.
4. Mehta JL, Saldeen TG, Rand K. Interactive role of infection, inflammation and traditional risk factors in atherosclerosis and coronary artery disease. J Am Coll Cardiol 1998; 31: 1217-25.
5. Memon RA, Staprans I, Noor M, et al. Infection and inflammation induce LDL oxidation *in vivo*. Arterioscler Thromb Vasc Biol 2000; 20: 1536-42.
6. Melnick JL, Adam E, DeBakey ME. Cytomegalovirus and atherosclerosis. Arch Immunol Ther Exp 1996; 44: 297-302.
7. Ameriso SF, Fridman EA, Leiguarda RC, Sevlever GE. Detection of *Helicobacter pylori* in Human Carotid Atherosclerotic Plaques. Stroke 2001; 32: 385-91.
8. Nieminen MS, Mattila K, Valtonen V. Infection and inflammation as risk factors for myocardial infarction. Eur Heart J 1993; 14 (Suppl K): 12-6.
9. Benitez RM. Atherosclerosis: An infectious disease? Hosp Pract (Off Ed) 1999; 34: 79-82.
10. Cassell GH. Infectious causes of chronic inflammatory diseases and cancer. Emerg Infect Dis 1998; 4: 475-87.
11. Folsom AR, Nieto FJ, Sorlie P, Chambless LE, Graham DY. *Helicobacter pylori* seropositivity and coronary heart disease incidence. Atherosclerosis Risk In Communities (ARIC) Study Investigators. Circulation 1998; 98: 845-50.
12. Farsak B, Yildirir A, Akyon Y, et al. Detection of *Chlamydia pneumoniae* and *helicobacter pylori* DNA in human atherosclerotic plaques by PCR. J Clin Microbiol 2000; 38: 4408-11.
13. Gasbarrini A, Cremonini F, Armuzzi A, et al. The role of *Helicobacter pylori* in cardiovascular and cerebrovascular diseases. J Physiol Pharmacol 1999; 50:735-42.
14. Bertrand ME, Bauters C. Cytomegalovirus infection and coronary restenosis. Circulation 1999; 99: 1278-9.
15. Horvath R, Cerny J, Benedik J, Hokl J, Jelinkova I. The possible role of human cytomegalovirus (HCMV) in the origin of atherosclerosis. J Clin Virol 2000; 16: 17-24.
16. Sorlie PD, Nieto FJ, Adam E, Folsom AR, Shahar E, Massing M. A prospective study of cytomegalovirus, herpes simplex virus 1, and coronary heart disease: The atherosclerosis risk in communities (ARIC) study. Arch Intern Med 2000; 160: 2027-32.
17. Gupta S, Camm AJ. Chronic infection in the etiology of atherosclerosis--the case for *Chlamydia pneumoniae*. Clin Cardiol 1997; 20: 829-36.
18. Saikku P. *Chlamydia pneumoniae* and atherosclerosis--an update. Scand J Infect Dis 1997; 104 (Suppl): 53-6.
19. Numazaki K, Chiba S. *Chlamydia pneumoniae* infection and coronary heart disease. Role of *C pneumoniae* in pathogenesis of atherosclerosis must be determined. BMJ 1997; 315: 1538.
20. Danesh J, Collins R, Peto R. Chronic infections and coronary heart disease: Is there a link? Lancet 1997; 350: 430-6.
21. Blum A, Giladi M, Weinberg M, et al. High anti-cytomegalovirus (CMV) IgG antibody titer is associated with coronary artery disease and may predict post-coronary balloon angioplasty restenosis. Am J Cardiol 1998; 81: 866-8.
22. Adam E, Melnick JL, Probtsfield JL, et al. High levels of cytomegalovirus antibody in patients requiring vascular surgery for atherosclerosis. Lancet 1987; 2: 291-3.
23. Melnick JL, Hu C, Burek J, Adam E, DeBakey ME. Cytomegalovirus DNA in arterial walls of patients with atherosclerosis. J Med Virol 1994; 42: 170-4.
24. Nieto FJ, Adam E, Sorlie P, et al. Cohort study of cytomegalovirus infection as a risk factor for carotid intimal-medial thickening, a measure of subclinical atherosclerosis. Circulation 1996; 94: 922-7.
25. Zhou YF, Leon MB, Waclawiw MA, et al. Association between prior cytomegalovirus infection and the risk of restenosis after coronary atherectomy. N Engl J Med 1996; 335: 624-30.
26. Tanaka K, Zou JP, Takeda K, et al. Effects of human cytomegalovirus immediate-early proteins on p53- mediated apoptosis in coronary artery smooth muscle cells. Circulation 1999; 99: 1656-9.
27. Zhou YF, Shou M, Guetta E, et al. Cytomegalovirus infection of rats increases the neointimal response to vascular injury without consistent evidence of direct infection of the vascular wall. Circulation 1999; 100: 1569-75.
28. Danesh J, Youngman L, Clark S, Parish S, Peto R, Collins R. *Helicobacter pylori* infection and early onset myocardial infarction: Case-control and sibling pairs study. BMJ 1999; 319: 1157-62.
29. Cammarota G, Pasceri V, Papa A, et al. *Helicobacter pylori* infection and ischaemic heart disease. Ital J Gastroenterol Hepatol 1998; 30 (Suppl 3): S304-6.
30. Danesh J. Is there a link between chronic *Helico-*

bacter pylori infection and coronary heart disease? Eur J Surg Suppl 1998; 582: 27-31.

31. Saikku P. *Chlamydia pneumoniae* in atherosclerosis. J Intern Med 2000; 247: 391-6.
32. Ramirez JA. Isolation of *Chlamydia pneumoniae* from the coronary artery of a patient with coronary atherosclerosis. The *Chlamydia pneumoniae*/ Atherosclerosis Study Group. Ann Intern Med 1996; 125: 979-82.
33. Kuo C, Campbell LA. Detection of *Chlamydia pneumoniae* in arterial tissues. J Infect Dis 2000; 181 (Suppl 3): S432-6.
34. Leowattana W, Mahanonda N, Bhuripunyo K, Leelarasamee A, Pokum S, Suwimol B. The prevalence of *Chlamydia pneumoniae* antibodies in Thai patients with coronary artery disease. J Med Assoc Thai 1999; 82: 792-7.
35. Maass M, Bartels C, Kruger S, Krause E, Engel PM, Dalhoff K. Endovascular presence of *Chlamydia pneumoniae* DNA is a generalized phenomenon in atherosclerotic vascular disease. Atherosclerosis 1998; 140 (Suppl 1): S25-30.
36. Miyashita N, Toyota E, Sawayama T, et al. Association of chronic infection of *Chlamydia pneumoniae* and coronary heart disease in the Japanese. Intern Med 1998; 37: 913-6.
37. Muhlestein JB, Hammond EH, Carlquist JF, et al. Increased incidence of Chlamydia species within the coronary arteries of patients with symptomatic atherosclerotic *versus* other forms of cardiovascular disease. J Am Coll Cardiol 1996; 27: 1555-61.
38. Glader CA, Boman J, Saikku P, et al. The proatherogenic properties of lipoprotein(a) may be enhanced through the formation of circulating immune complexes containing *Chlamydia pneumoniae*-specific IgG antibodies. Eur Heart J 2000; 21: 639-46.
39. Danesh J, Whincup P, Walker M, et al. *Chlamydia pneumoniae* IgG titres and coronary heart disease: Prospective study and meta-analysis. BMJ 2000; 321: 208-13.
40. Matturri L, Cazzullo A, Turconi P, Roncoroni L, Grana D, Milei J. Inflammatory cells, apoptosis and *Chlamydia pneumoniae* infection in atherosclerosis. Int J Cardiol 2000; 75: 23-33.
41. Nadrchal R, Makristathis A, Apfalter P, et al. Detection of *Chlamydia pneumoniae* DNA in atheromatous tissues by polymerase chain reaction. Wien Klin Wochenschr 1999; 111: 153-6.
42. Wong Y, Thomas M, Tsang V, Gallagher PJ, Ward ME. The prevalence of *Chlamydia pneumoniae* in atherosclerotic and nonatherosclerotic blood vessels of patients attending for redo and first time coronary artery bypass graft surgery. J Am Coll Cardiol 1999; 33: 152-6.
43. Maass M, Bartels C, Engel PM, Mamat U, Sievers HH. Endovascular presence of viable *Chlamydia pneumoniae* is a common phenomenon in coronary artery disease. J Am Coll Cardiol 1998; 31: 827-32.
44. Kalayoglu MV, Byrne GI. A *Chlamydia pneumoniae* component that induces macrophage foam cell formation is chlamydial lipopolysaccharide. Infect Immun 1998; 66: 5067-72.
45. Summersgill JT, Molestina RE, Miller RD, Ramirez JA. Interactions of *Chlamydia pneumoniae* with human endothelial cells. J Infect Dis 2000; 181 (Suppl 3): S479-82.
46. Gaydos CA. Growth in vascular cells and cytokine production by *Chlamydia pneumoniae*. J Infect Dis 2000; 181 (Suppl 3): S473-8.
47. Rodel J, Woytas M, Groh A, et al. Production of basic fibroblast growth factor and interleukin 6 by human smooth muscle cells following infection with *Chlamydia pneumoniae*. Infect Immun 2000; 68: 3635-41.
48. Gaydos CA, Quinn TC. The role of *Chlamydia pneumoniae* in cardiovascular disease. Adv Intern Med 2000;45:139-73.
49. Quinn TC, Gaydos CA. *In vitro* infection and pathogenesis of *Chlamydia pneumoniae* in endovascular cells. Am Heart J 1999; 138 (5 Pt 2): S507-11.
50. Naidu BR, Ngeow YF, Kannan P, et al. Evidence of *Chlamydia pneumoniae* infection obtained by the polymerase chain reaction (PCR) in patients with acute myocardial infarction and coronary heart disease. J Infect 1997; 35: 199-200.
51. Boman J, Gaydos CA. Polymerase chain reaction detection of *Chlamydia pneumoniae* in circulating white blood cells. J Infect Dis 2000; 181 (Suppl 3): S452-4.
52. Maass M, Jahn J, Gieffers J, Dalhoff K, Katus HA, Solbach W. Detection of *Chlamydia pneumoniae* within peripheral blood monocytes of patients with unstable angina or myocardial infarction. J Infect Dis 2000; 181 (Suppl 3): S449-51.
53. Mahony JB, Chong S, Coombes BK, Smieja M, Petrich A. Analytical sensitivity, reproducibility of results, and clinical performance of five PCR assays for detecting *Chlamydia pneumoniae* DNA in peripheral blood mononuclear cells. J Clin Microbiol 2000; 38: 2622-7.
54. Wong YK, Dawkins KD, Ward ME. Circulating *Chlamydia pneumoniae* DNA as a predictor of coronary artery disease. J Am Coll Cardiol 1999; 34: 1435-9.
55. Campbell LA, Blessing E, Rosenfeld M, Lin T, Kuo C. Mouse models of *C. pneumoniae* infection and atherosclerosis. J Infect Dis 2000; 181 (Suppl 3): S508-13.

56. Fong IW. Antibiotics effects in a rabbit model of *Chlamydia pneumoniae*-induced atherosclerosis. J Infect Dis 2000; 181 (Suppl 3): S514-8.
57. Rothstein NM, Quinn TC, Madico G, Gaydos CA, Lowenstein CJ. Effect of Azithromycin on Murine Arteriosclerosis Exacerbated by *Chlamydia pneumoniae*. J Infect Dis 2001; 183: 232-8.
58. Burnett MS, Gaydos CA, Madico GE, et al. Atherosclerosis in apoE Knockout Mice Infected with Multiple Pathogens. J Infect Dis 2001; 183: 226-31.
59. Muhlestein JB. *Chlamydia pneumoniae*-induced atherosclerosis in a rabbit model. J Infect Dis 2000; 181 (Suppl 3): S505-7.
60. Fong IW, Chiu B, Viira E, et al. Can an antibiotic (macrolide) prevent *Chlamydia pneumoniae*-induced atherosclerosis in a rabbit model? Clin Diagn Lab Immunol 1999; 6: 891-4.
61. Liuba P, Karnani P, Pesonen E, et al. Endothelial dysfunction after repeated *Chlamydia pneumoniae* infection in apolipoprotein E-knockout mice. Circulation 2000; 102: 1039-44.
62. Moazed TC, Campbell LA, Rosenfeld ME, Grayston JT, Kuo C. *Chlamydia pneumoniae* infection accelerates the progression of atherosclerosis in apolipoprotein E-deficient mice. J Infect Dis 1999; 180: 238-41.
63. Campbell LA, Kuo C. Mouse models of *Chlamydia pneumoniae* infection and atherosclerosis. Am Heart J 1999; 138 (5 Pt 2): S516-8.
64. Kalayoglu MV, Indrawati I, Morrison RP, Morrison SG, Yuan Y, Byrne GI. Chlamydial virulence determinants in atherogenesis: The role of chlamydial lipopolysaccharide and heat shock protein 60 in macrophage- lipoprotein interactions. J Infect Dis 2000; 181 (Suppl 3): S483-9.
65. Gupta S, Leatham EW, Carrington D, Mendall MA, Kaski JC, Camm AJ. Elevated *Chlamydia pneumoniae* antibodies, cardiovascular events, and azithromycin in male survivors of myocardial infarction. Circulation 1997; 96: 404-7.
66. Gurfinkel E, Bozovich G, Daroca A, Beck E, Mautner B. Randomised trial of roxithromycin in non-Q-wave coronary syndromes: ROXIS Pilot Study. ROXIS Study Group. Lancet 1997; 350: 404-7.
67. Anderson JL, Muhlestein JB, Carlquist J, et al. Randomized secondary prevention trial of azithromycin in patients with coronary artery disease and serological evidence for *Chlamydia pneumoniae* infection: The Azithromycin in Coronary Artery Disease: Elimination of Myocardial Infection with Chlamydia (ACADEMIC) study. Circulation 1999; 99: 1540-7.

การติดเชื้อเรื้อรังกับการเกิดภาวะหลอดเลือดแข็งตัว

*วัฒนา เลี้ยววัฒนา, พ.บ.**

ปัจจัยเสี่ยงชนิดต่าง ๆ ที่เป็นที่ทราบดีกันอยู่แล้วอาทิ ความดันสูง การสูบบุหรี่ เบาหวาน ไขมันในเลือดสูงและโฮโมซีสทีนในเลือดสูง ไม่สามารถอธิบายเหตุแห่งการเกิดภาวะหลอดเลือดแข็งตัวได้อย่างครบถ้วน โดยเฉพาะอย่างยิ่งโรคหัวใจขาดเลือด สาเหตุส่วนหนึ่งน่าจะมาจากการติดเชื้อเรื้อรัง ซึ่งเกิดจากหลายสาเหตุเช่น การติดเชื้อ *คลามิเดีย นิวโมนิอี* ไซโต-เมกกาโลไวรัสและ*เฮลิโคแบคเตอร์ ไพลอรี* โดยเชื้อต่าง ๆ เหล่านี้อาจเป็นสาเหตุแห่งการเกิด หลอดเลือดแข็งตัวเองหรือเป็นตัวเชื่อมต่อระหว่างการเกิดการอักเสบของหลอดเลือดและภาวะแข็งตัวของหลอดเลือดแดง ยังไม่เป็นที่ทราบแน่ชัด จากการศึกษาทางด้านระบาดวิทยา พยาธิวิทยาของหลอดเลือดส่วนที่แข็งตัว การศึกษาโดยใช้สัตว์ทดลอง การศึกษาทางด้านอณูชีววิทยา ตลอดจนการศึกษาทางคลินิกโดยให้ยาปฏิชีวนะแก่ผู้ป่วยที่มีการติดเชื้อดังกล่าวพบว่า การติดเชื้อ *คลามิเดีย นิวโมนิอี* มีส่วนสัมพันธ์มากที่สุดกับการเกิดภาวะหลอดเลือดแดงแข็งตัวและภาวะหัวใจขาดเลือด โดยขบวนการที่สำคัญคือการกระตุ้น ที เซลล์ รวมถึงการทำให้ความแข็งแรงของผนังที่ห่อหุ้มพลาคลดลงเกิดการแตกของพลาคได้ง่ายขึ้น ถึงจะมีการศึกษาในเรื่องการติดเชื้อและภาวะหลอดเลือดแดงแข็งไปเป็นจำนวนมาก แม้กระนั้นพยาธิสรีรวิทยาของการเกิดดังกล่าวก็ยังไม่สามารถหาคำตอบได้อย่างชัดเจน ยังคงต้องการค้นหาความจริงอยู่อีกมาก ดังนั้นการวิจัยทางคลินิกที่ให้ยาปฏิชีวนะแก่ผู้ป่วยโรคหัวใจขาดเลือดอยู่ในขณะนี้น่าจะช่วยให้คำตอบดังกล่าวแก่วงการแพทย์ต่อไปในไม่ช้า

คำสำคัญ : การติดเชื้อเรื้อรัง, ภาวะหลอดเลือดแดงแข็ง, โรคหัวใจขาดเลือด, *คลามิเดีย นิวโมนิอี*, ไซโตเมกกาโลไวรัส, *เฮลิโคแบคเตอร์ ไพลอรี*

วัฒนา เลี้ยววัฒนา
จดหมายเหตุทางแพทย์ ฯ 2544; 84 (ฉบับพิเศษ 3): S650–S657

* ภาควิชาพยาธิวิทยาคลินิก, คณะแพทยศาสตร์ศิริราชพยาบาล, มหาวิทยาลัยมหิดล กรุงเทพ ฯ 10700