**Name of journal: World Journal of Translational Medicine**

**ESPS Manuscript NO: 5140**

**Columns: REVIEW**

**Impact of viral and bacterial infections in coronary artery disease patients**

Jha HC *et al.* Infectious agents in CAD

Hem Chandra Jha, Aruna Mittal

**Hem Chandra Jha, Aruna Mittal,** National Institute of Pathology-ICMR, New Delhi 110029, India

**Hem Chandra Jha,** Department of Microbiology, University of Pennsylvania, Philadelphia, PA 19104, United States

**Author contributions:** Jha HC and Mittal A solely contributed to this paper.

**Correspondence to: Aruna Mittal, Consultant,** National Institute of Pathology-ICMR, South Extension, New Delhi 110029, India. hemcjha@gmail.com

**Telephone:** +91-11-2619840205 **Fax:** +91-11-2619801

**Received:** August 16, 2013 **Revised:** September 30, 2013

**Accepted:** November 1, 2013

**Published online:**

**Abstract**

Atherosclerosis is becoming an alarming disease for the existence of healthy human being in 21st century. There are growing number of agents either modernized life style generated or competitive work culture related or infection with some bacterial or viral agents documented every year. These infectious agents do not have proper diagnostics or detection availability in many poor and developing countries. Hence as an active medical researcher, we summarize some aspect of infectious agents and their related mechanism in this review which may beneficial for new beginner in this field and update awareness in the field of cardiovascular biology.

© 2013 Baishideng. All rights reserved.

**Key words:** *Chlamydia pneumonia*; *Helicobacter pylori*; *Cytomegalovirus*; Cytokines; Diagnostics

**Core tip:** This paper described the association of atherosclerosis with different infectious agents specifically *Chlamydia pneumonia* (*C. pneumoniae*), *Helicobacter pylori*, Herpesviruses, and periodontal pathogens. There are many other bacteria and viruses as well as life style related factors also described and cited in this review. The manuscript also emphasize on how *C. pneumoniae* modulating human immune system with mimicking some antigenic proteins of host. Overall this report helps in the field of cardiac biology to explore associated risk factors in more details.

Jha HC, Mittal A. Impact of viral and bacterial infections in coronary artery disease patients.

**Available from:**

**DOI:**

**INTRODUCTION**

There are numerous studies supporting the association of coronary artery disease with many infectious agents including bacteria and viruses [1-8]. Several bacterial pathogens have been reported triggering the inflammation of atherosclerosis including *Chlamydia pneumoniae* (*C. pneumoniae*)[7,9,10], *Helicobacter pylori* (*H. pylori*)[11,12], *Chryseomonas sp* [13], *Veillonella* *sp* [13], *Streptococcus sp* [13], *Aggregatibacter actinomycetemcomitans* [14], *Porphyromonas gingivalis* [15], *Prevotella intermedia* [16], *Prevotella nigrescens* [17], *Tannerella forsythia* [18], *Ruminococcus enterotype* [19], *Enterobacter hormaechei* [20], periodontal pathogens [21]. Similarly many viruses known to be associated with atherosclerosis namely- *cytomegalovirus* (CMV) [22,23], *herpesvirus* [24], and *hepatitis A* [25], B [26], and C viruses [27], *Epstein-Barr virus* [28], *Herpes simplex virus* I and II [29]. Thus it would be important to know in which circumstances bacteria and viral infections activate heart disease mechanistically.

**REVIEW OF LITERATURE**

Increasing risk of heart disease is a major cause of concern. In 2008, 30% of all global death is attributed to cardiovascular diseases [30]. It is also estimated that by 2030, over 23 million people will die from cardiovascular diseases annually [30]. The incidence rate of atherosclerotic symptoms increasing exponentially year by year [31]. There are numerous factors involved in the causation of atherosclerosis. Some researcher strongly classified it as a life style disease, where they include body mass weight, smoking, heavy alcoholic, sedentary life style, blood pressure, elevated levels of cholesterol and bad lipids, reduced levels of good lipid and stress full life [32-38]. Although many studies found significant association of atherosclerosis with genetics or hereditary [39] either their close blood relatives were suffering from heart attack or diabetes or hypertension [8,40,41]. Moreover, mainly from last decades various studies were conducted on the association of heart disease with infectious agents. Many type of specimens including blood samples, PBMCs, specific tissue sites were evaluating for the establishment of infection with atherosclerosis [42]. Till now there are hundreds of research studies where by using ELISA, standard PCR, real time quantitative PCR, cell culture, immunohistochemistry, immunocytochemistry methods to find a relevant and authentic answer for the association between infectious agents with atherosclerosis [6-8, 43-49]. Although some controversy existed in this field to completely accept the direct association between infectious agents with atherosclerosis, however there is no question for the enhanced presence of infectious agents in atherosclerosis or accelerated progression of atherosclerosis in presence of infectious agents. To date, some well established infectious agents like bacteria and virus-*C. pneumoniae*, *H. pylori* and *cytomegalovirus* as mentioned below were observed in number of studies and explained the etiology of disease causation in details [50-53].

***C. PNEUMONIAE***

*C. pneumoniae* is an intracellular obligatory bacteria which causing upper and lower respiratory tract infection [54]. Other than respiratory disease, *C. pneumoniae* has been found to be associated with heart disease, Alzimer disease, multiple sclerosis, lung cancer, and arthritis [55-59]. Majority of 95% population have the exposure with *C. pneumoniae* in their life time, however this exposure is asymptomatic while when they get contact with *C. pneumoniae* frequently and exposure with some other co-activator of *C. pneumoniae* infection triggering the establishment of infection and chronicity of disease pathogenesis [60]. There are numerous tissue or body organelles involved in the acceleration of *C. pneumoniae* infection [61,62]. Correct diagnosis of infectious agents are always in question, and many methodological improvements were made in this aspect [63,64]. To date, nested PCR or quantitative probe based real time PCR methods have been largely updated in this field [7,65,66]. 16S rRNA and major outer membrane protein found to be critical for the identification on PCR based methods [7,67,68]. Moreover, immunoglobulin based screening also has significance and capability for the predication of disease occurrence in existing non-symptomatic and close relative population of patients [41]. In many studies, *C. pneumoniae* specific immunoglobulin IgA has been found to be more predictive and robustly observed compared to IgG in the serum of coronary artery disease patients [8,69,70], while some studies reported vice versa as well [71]. In response to *C. pneumoniae* infection many host immune response get manipulated or aggravated to counter the effect of bacterial pathogens and stop the progression of disease, while same time this smart bacteria also activated host signaling by mimicking some of key proteins and start to accelerate disease progression [49,72,73]. These host-pathogen responses are very complex and many studies find some narrative result which suggest the hypothetical model for the infection progression due to *C. pneumoniae* [74]. Moreover details are needed to explore in this field to prevent human population from these kind of opportunistic pathogens.

***H. PYLORI***

*H. pylori* has been known to be an active initiator of gastric carcinoma [75]. Moreover these days presence of *H. pylori* has been found to be associated significantly in atheromatous plaque [76]. In our study we found significantly *H. pylori* IgA antibody titer in CAD patients compared to controls, levels of H. pylori IgG was also high [8]. Further we also detected *H. pylori* DNA in atheromatous plaque by using quantitative real time PCR [6]. There are many other reports also suggesting the active involvement of H. pylori in the development of atherosclerosis [11,77,78]. However it would be important to know that in which circumstances this bacteria activating oncogenesis and heart disease.

**CMV**

CMV is an important pathogenic virus which causes many chronic diseases such as cancer and atherosclerosis [79-82]. There are growing evidences supporting the synergistic effect of infectious agents in the progression of heart disease [50,83]. In our antibody titer detection assay and PCR assay, we found higher positivity for CMV in CAD patients compared to controls [6]. However, there is lots of space where we can identify the initiator organism or activator organism among many infection which may alter the immune response of system.

**HUMAN HERPESVIRUSES**

A number of evidences suggests that human herpesviruses have potential link to arterial injury [83]. This hypothesis proven in animal model studies as well as clinical epidemiological association between herpes viral infection and accelerated arteriosclerosis [84]. Studies suggested that eight members of the herpesvirus family member may infect humans [85]. *Herpes simplex virus*-1 (HSV-1), *herpes simplex virus*-2 (HSV-2), *Epstein–Barr virus* (EBV) and CMV are widespread in the general population; they are primary candidates for investigations into viruses related to atherosclerosis [86].

A definite association was found for HSV-2 and subclinical coronary atherosclerosis [87]. This organism has been shown to be responsible for thrombogenic and atherogenic changes to host cells [88]. Earlier association of HSV-2 with hypertension has been reported [89]. These days many studies emphasis on role of inflammatory pathways in atherosclerosis development [90]. Further recently Horvath *et al*[91] suggesting that long-term HSV-2 infection may contribute to development of atherosclerosis.

Earlier many studies demonstrated that only atherosclerotic tissues are majorly have multiple infections [86]. Researcher also suggested the synergistic impact of infection on atherogenesis related to the aggregate number of pathogens with human being infected [92]. Several serological studies demonstrated that these all pathogens (CMV, EBV, *hepatitis A virus*, HSV-1, HSV-2 and *C. pneumoniae*) are variably associated with the risk of CAD [4]. Shi *et al*[86] was detected HSV-1, EBV and CMV DNA in the upper part of the non-atherosclerotic aortic wall and also these viral DNA was detected more extensively in atherosclerotic lesions compared to non-atherosclerotic tissue.

**DENTAL PATHOGENS IN ATHEROSCLEROSIS**

There are several reports given emphasis on the association of dental disease with elevated risk of myocardial infarction [93], and also metabolic activity of the gut microbiota has been shown to be related with blood pressure [94]. Several other studies also suggested an oral source for atherosclerotic plaque-associated bacteria [95,96]. *Chryseomonas sp* was present in endocarditis and all atherosclerotic plaque samples [97].

Many species namely *Porphyromonas gingivalis*, *Tannerella forsythia*, and *Actinobacillus actinomycetemcomitans* are actively involved in periodontal disease and also have been reported for potential risk for the development of atherosclerosis [98]. Animal studies were proven this association as well [99].

Beside these infectious agents, other factors that may incite vessel inflammation are oxidized low-density lipoprotein cholesterol and the metabolic syndrome, which are associated with proinflammatory condition characterized by elevations of C-reactive protein or high sensitive C-reactive protein (hs-CRP) [100-102]. Metabolic syndrome is a cluster of abnormalities caused by elevation of multiple metabolic pathways, hyperinsulinemia, insulin resistance in body organelle, hyperglycemia, atherogenic dyslipidemia, abdominal obesity, and hypertension [103-104]. In our study we found the association of hs-CRP with elevated levels of *C. pneumoniae* IgA and H. pylori IgA [8]. We also observed higher proinflammatory cytokines interleukin-6 positively associated with hs-CRP [100]. Further our study extend the knowledge in respect of association between C. pneumoniae IgA with Th-1, Th-2, Th-3 or adhesion molecules [101]. Although these markers labeled as independent markers for CAD in our study [105]. There are many studies which suggesting that Th-1 cytokines or proinflammatory cytokines expressing earlier after *C. pneumoniae* infection followed by Th-2 kind of cytokines [106-107], however mechanistically how it moving in case of human is still invaded. We draw a schematic for *C. pneumoniae* in atherosclerosis (Figure 1).

**REFERENCES**

1 **Muhlestein JB**, Anderson JL. Chronic infection and coronary artery disease. *Cardiol Clin* 2003; **21**: 333-362 [PMID: 14621450 DOI: 10.1016/S0733-8651(03)00054-7]

2 **Roivainen M**, Viik-Kajander M, Palosuo T, Toivanen P, Leinonen M, Saikku P, Tenkanen L, Manninen V, Hovi T, Mänttäri M. Infections, inflammation, and the risk of coronary heart disease. *Circulation* 2000; **101**: 252-257 [PMID: 10645920 DOI: 10.1161/01.CIR.101.3.252]

3 **Rosenfeld ME**, Campbell LA. Pathogens and atherosclerosis: update on the potential contribution of multiple infectious organisms to the pathogenesis of atherosclerosis. *Thromb Haemost* 2011; **106**: 858-867 [PMID: 22012133 DOI: 10.1160/TH11-06-0392]

4 **Rupprecht HJ**, Blankenberg S, Bickel C, Rippin G, Hafner G, Prellwitz W, Schlumberger W, Meyer J. Impact of viral and bacterial infectious burden on long-term prognosis in patients with coronary artery disease. *Circulation* 2001; **104**: 25-31 [PMID: 11435333 DOI: 10.1161/hc2601.091703]

5 **Watt S**, Aesch B, Lanotte P, Tranquart F, Quentin R. Viral and bacterial DNA in carotid atherosclerotic lesions. *Eur J Clin Microbiol Infect Dis* 2003; **22**: 99-105 [PMID: 12627283]

6 **Jha HC**, Srivastava P, Divya A, Prasad J, Mittal A. Prevalence of Chlamydophila pneumoniae is higher in aorta and coronary artery than in carotid artery of coronary artery disease patients. *APMIS* 2009; **117**: 905-911 [PMID: 20078556]

7 **Jha HC**, Vardhan H, Gupta R, Varma R, Prasad J, Mittal A. Higher incidence of persistent chronic infection of Chlamydia pneumoniae among coronary artery disease patients in India is a cause of concern. *BMC Infect Dis* 2007; **7**: 48 [PMID: 17537253 DOI: 10.1186/1471-2334-7-48]

8 **Jha HC**, Prasad J, Mittal A. High immunoglobulin A seropositivity for combined Chlamydia pneumoniae, Helicobacter pylori infection, and high-sensitivity C-reactive protein in coronary artery disease patients in India can serve as atherosclerotic marker. *Heart Vessels* 2008; **23**: 390-396 [PMID: 19037586 DOI: 10.1007/s00380-008-1062-9]

9 **Sessa R**, Nicoletti M, Di Pietro M, Schiavoni G, Santino I, Zagaglia C, Del Piano M, Cipriani P. Chlamydia pneumoniae and atherosclerosis: current state and future prospectives. *Int J Immunopathol Pharmacol* 2009; **22**: 9-14 [PMID: 19309547]

10 **Shor A**, Phillips JI. Chlamydia pneumoniae and atherosclerosis. *JAMA* 1999; **282**: 2071-2073 [PMID: 10591391 DOI: 10.1001/jama.282.21.2071]

11 **Ameriso SF**, Fridman EA, Leiguarda RC, Sevlever GE. Detection of Helicobacter pylori in human carotid atherosclerotic plaques. *Stroke* 2001; **32**: 385-391 [PMID: 11157171 DOI: 10.1161/01.STR.32.2.385]

12 **Mayr M**, Kiechl S, Mendall MA, Willeit J, Wick G, Xu Q. Increased risk of atherosclerosis is confined to CagA-positive Helicobacter pylori strains: prospective results from the Bruneck study. *Stroke* 2003; **34**: 610-615 [PMID: 12624280 DOI: 10.1161/01.STR.0000058481.82639]

13 **Koren O**, Spor A, Felin J, Fåk F, Stombaugh J, Tremaroli V, Behre CJ, Knight R, Fagerberg B, Ley RE, Bäckhed F. Human oral, gut, and plaque microbiota in patients with atherosclerosis. *Proc Natl Acad Sci U S A* 2011; **108 Suppl 1**: 4592-4598 [PMID: 20937873 DOI: 10.1073/pnas.1011383107]

14 **Zhang T**, Kurita-Ochiai T, Hashizume T, Du Y, Oguchi S, Yamamoto M. Aggregatibacter actinomycetemcomitans accelerates atherosclerosis with an increase in atherogenic factors in spontaneously hyperlipidemic mice. *FEMS Immunol Med Microbiol* 2010; **59**: 143-151 [PMID: 20482627 DOI: 10.1111/j.1574-695X.2010.00674.x]

15 **Hayashi C**, Viereck J, Hua N, Phinikaridou A, Madrigal AG, Gibson FC, Hamilton JA, Genco CA. Porphyromonas gingivalis accelerates inflammatory atherosclerosis in the innominate artery of ApoE deficient mice. *Atherosclerosis* 2011; **215**: 52-59 [PMID: 21251656 DOI: 10.1016/j.atherosclerosis.2010.12.009]

16 **Gaetti-Jardim E**, Marcelino SL, Feitosa AC, Romito GA, Avila-Campos MJ. Quantitative detection of periodontopathic bacteria in atherosclerotic plaques from coronary arteries. *J Med Microbiol* 2009; **58**: 1568-1575 [PMID: 19679682 DOI: 10.1099/jmm.0.013383-0]

17 **Yakob M**, Söder B, Meurman JH, Jogestrand T, Nowak J, Söder PÖ. Prevotella nigrescens and Porphyromonas gingivalis are associated with signs of carotid atherosclerosis in subjects with and without periodontitis. *J Periodontal Res* 2011; **46**: 749-755 [PMID: 21793826 DOI: 10.1111/j.1600-0765.2011.01398.x]

18 **Rivera MF**, Lee JY, Aneja M, Goswami V, Liu L, Velsko IM, Chukkapalli SS, Bhattacharyya I, Chen H, Lucas AR, Kesavalu LN. Polymicrobial infection with major periodontal pathogens induced periodontal disease and aortic atherosclerosis in hyperlipidemic ApoE(null) mice. *PLoS One* 2013; **8**: e57178 [PMID: 23451182 DOI: 10.1371/journal.pone.0057178]

19 **Karlsson FH**, Fåk F, Nookaew I, Tremaroli V, Fagerberg B, Petranovic D, Bäckhed F, Nielsen J. Symptomatic atherosclerosis is associated with an altered gut metagenome. *Nat Commun* 2012; **3**: 1245 [PMID: 23212374 DOI: 10.1038/ncomms2266]

20 **Rafferty B**, Dolgilevich S, Kalachikov S, Morozova I, Ju J, Whittier S, Nowygrod R, Kozarov E. Cultivation of Enterobacter hormaechei from human atherosclerotic tissue. *J Atheroscler Thromb* 2011; **18**: 72-81 [PMID: 20972353 DOI: 10.5551/jat.5207]

21 **Fiehn NE**, Larsen T, Christiansen N, Holmstrup P, Schroeder TV. Identification of periodontal pathogens in atherosclerotic vessels. *J Periodontol* 2005; **76**: 731-736 [PMID: 15898933 DOI: 10.1902/jop.2005.76.5.731]

22 **Xenaki E**, Hassoulas J, Apostolakis S, Sourvinos G, Spandidos DA. Detection of cytomegalovirus in atherosclerotic plaques and nonatherosclerotic arteries. *Angiology* ; **60**: 504-508 [PMID: 18818234 DOI: 10.1177/0003319708322390]

23 **Zhu J**, Quyyumi AA, Norman JE, Csako G, Epstein SE. Cytomegalovirus in the pathogenesis of atherosclerosis: the role of inflammation as reflected by elevated C-reactive protein levels. *J Am Coll Cardiol* 1999; **34**: 1738-1743 [PMID: 10577564 DOI: 10.1016/S0735-1097(99)00410-6]

24 **Alber DG**, Powell KL, Vallance P, Goodwin DA, Grahame-Clarke C. Herpesvirus infection accelerates atherosclerosis in the apolipoprotein E-deficient mouse. *Circulation* 2000; **102**: 779-785 [PMID: 10942747 DOI: 10.1161/01.CIR.102.7.779.]

25 **Zhu J**, Quyyumi AA, Norman JE, Costello R, Csako G, Epstein SE. The possible role of hepatitis A virus in the pathogenesis of atherosclerosis. *J Infect Dis* 2000; **182**: 1583-1587 [PMID: 11069227 DOI: 10.1086/317613]

26 **Ishizaka N**, Ishizaka Y, Takahashi E, Toda Ei E, Hashimoto H, Ohno M, Nagai R, Yamakado M. Increased prevalence of carotid atherosclerosis in hepatitis B virus carriers. *Circulation* 2002; **105**: 1028-1030 [PMID: 11877348 DOI: 10.1161/hc0902.105718]

27 **Butt AA**, Xiaoqiang W, Budoff M, Leaf D, Kuller LH, Justice AC. Hepatitis C virus infection and the risk of coronary disease. *Clin Infect Dis* 2009; **49**: 225-232 [PMID: 19508169 DOI: 10.1086/599371]

28 **Binkley PF**, Cooke GE, Lesinski A, Taylor M, Chen M, Laskowski B, Waldman WJ, Ariza ME, Williams MV, Knight DA, Glaser R. Evidence for the role of Epstein Barr Virus infections in the pathogenesis of acute coronary events. *PLoS One* 2013; **8**: e54008 [PMID: 23349778 DOI: 10.1371/journal.pone.0054008]

29 **Kotronias D**, Kapranos N. Herpes simplex virus as a determinant risk factor for coronary artery atherosclerosis and myocardial infarction. *In Vivo* 2005; **19**: 351-357 [PMID: 15796197]

30 **Robinson JG**, Fox KM, Bullano MF, Grandy S. Atherosclerosis profile and incidence of cardiovascular events: a population-based survey. *BMC Cardiovasc Disord* 2009; **9**: 46 [PMID: 19754940 DOI: 10.1186/1471-2261-9-46]

31 **Ambrose JA**, Barua RS. The pathophysiology of cigarette smoking and cardiovascular disease: an update. *J Am Coll Cardiol* 2004; **43**: 1731-1737 [PMID: 15145091 DOI: 10.1016/j.jacc.2003.12.047]

32 **Burnett JR**. Lipids, lipoproteins, atherosclerosis and cardiovascular disease. *Clin Biochem Rev* 2004; **25**: 2 [PMID: 18516207]

33 **Huszar D**, Varban ML, Rinninger F, Feeley R, Arai T, Fairchild-Huntress V, Donovan MJ, Tall AR. Increased LDL cholesterol and atherosclerosis in LDL receptor-deficient mice with attenuated expression of scavenger receptor B1. *Arterioscler Thromb Vasc Biol* 2000; **20**: 1068-1073 [PMID: 10764675 DOI: 10.1161/01.ATV.20.4.1068]

34 **Kiechl S**, Willeit J, Rungger G, Egger G, Oberhollenzer F, Bonora E. Alcohol consumption and atherosclerosis: what is the relation? Prospective results from the Bruneck Study. *Stroke* 1998; **29**: 900-907 [PMID: 9596232 DOI: 10.1161/01.STR.29.5.900]

35 **Mainous AG**, Everett CJ, Diaz VA, Player MS, Gebregziabher M, Smith DW. Life stress and atherosclerosis: a pathway through unhealthy lifestyle. *Int J Psychiatry Med* 2010; **40**: 147-161 [PMID: 20848872 DOI: 10.2190/PM.40.2.b]

36 **Rossi R**, Iaccarino D, Nuzzo A, Chiurlia E, Bacco L, Venturelli A, Modena MG. Influence of body mass index on extent of coronary atherosclerosis and cardiac events in a cohort of patients at risk of coronary artery disease. *Nutr Metab Cardiovasc Dis* 2011; **21**: 86-93 [PMID: 19939651 DOI: 10.1016/j.numecd.2009.09.001]

37 **van Leeuwen R**, Ikram MK, Vingerling JR, Witteman JC, Hofman A, de Jong PT. Blood pressure, atherosclerosis, and the incidence of age-related maculopathy: the Rotterdam Study. *Invest Ophthalmol Vis Sci* 2003; **44**: 3771-3777 [PMID: 12939290 DOI: 10.1167/iovs.03-0121]

38 **Kovacic S,** Bakran M. Genetic susceptibility to atherosclerosis. *Stroke Res Treat* 2012: 362941 [doi: 10.1155/2012/362941]

39 **O'Donnell CJ**. Family history, subclinical atherosclerosis, and coronary heart disease risk: barriers and opportunities for the use of family history information in risk prediction and prevention. *Circulation* 2004; **110**: 2074-2076 [PMID: 15477424 DOI: 10.1161/01.CIR.0000145539.77021.AC]

40 **Jha HC**, Mittal A. Coronary artery disease patient's first degree relatives may be at higher risk for atherosclerosis. *Int J Cardiol* 2009; **135**: 408-49; author reply 410 [PMID: 18572262 DOI: 10.1016/j.ijcard.2008.03.031]

41 **Gómez-Hernández A**, Martín-Ventura JL, Sánchez-Galán E, Vidal C, Ortego M, Blanco-Colio LM, Ortega L, Tuñón J, Egido J. Overexpression of COX-2, Prostaglandin E synthase-1 and prostaglandin E receptors in blood mononuclear cells and plaque of patients with carotid atherosclerosis: regulation by nuclear factor-kappaB. *Atherosclerosis* 2006; **187**: 139-149 [PMID: 16212965 DOI: 10.1016/j.atherosclerosis.2005.08.035]

42 **Estrada R**, Giridharan G, Prabhu SD, Sethu P. Endothelial cell culture model of carotid artery atherosclerosis. *Conf Proc IEEE Eng Med Biol Soc* 2011; **2011**: 186-189 [PMID: 22254281 DOI: 10.1109/IEMBS.2011.6089925]

43 **Kosierkiewicz TA**, Factor SM, Dickson DW. Immunocytochemical studies of atherosclerotic lesions of cerebral berry aneurysms. *J Neuropathol Exp Neurol* 1994; **53**: 399-406 [PMID: 8021714 DOI: 10.1097/00005072-199407000-00012]

44 **Mallat Z**, Corbaz A, Scoazec A, Besnard S, Lesèche G, Chvatchko Y, Tedgui A. Expression of interleukin-18 in human atherosclerotic plaques and relation to plaque instability. *Circulation* 2001; **104**: 1598-1603 [PMID: 11581135 DOI: 10.1161/hc3901.096721]

45 **Pedretti M**, Rancic Z, Soltermann A, Herzog BA, Schliemann C, Lachat M, Neri D, Kaufmann PA. Comparative immunohistochemical staining of atherosclerotic plaques using F16, F8 and L19: Three clinical-grade fully human antibodies. *Atherosclerosis* 2010; **208**: 382-389 [PMID: 19699478 DOI: 10.1016/j.atherosclerosis.2009.07.043]

46 **Smith BW**, Strakova J, King JL, Erdman JW, O'Brien WD. Validated sandwich ELISA for the quantification of von Willebrand factor in rabbit plasma. *Biomark Insights* 2010; **5**: 119-127 [PMID: 21151589 DOI: 10.4137/BMI.S6051]

47 **van Eck M**, Bos IS, Kaminski WE, Orsó E, Rothe G, Twisk J, Böttcher A, Van Amersfoort ES, Christiansen-Weber TA, Fung-Leung WP, Van Berkel TJ, Schmitz G. Leukocyte ABCA1 controls susceptibility to atherosclerosis and macrophage recruitment into tissues. *Proc Natl Acad Sci U S A* 2002; **99**: 6298-6303 [PMID: 11972062 DOI: 10.1073/pnas.092327399]

48 **Jha HC**, Srivastava P, Vardhan H, Singh LC, Bhengraj AR, Prasad J, Mittal A. Chlamydia pneumoniae heat shock protein 60 is associated with apoptotic signaling pathway in human atheromatous plaques of coronary artery disease patients. *J Cardiol* 2011; **58**: 216-225 [PMID: 21889313 DOI: 10.1016/j.jjcc.2011.07.010]

49 **Latsios G**, Saetta A, Michalopoulos NV, Agapitos E, Patsouris E. Detection of cytomegalovirus, Helicobacter pylori and Chlamydia pneumoniae DNA in carotid atherosclerotic plaques by the polymerase chain reaction. *Acta Cardiol* 2004; **59**: 652-657 [PMID: 15636450 DOI: 10.2143/AC.59.6.2005249]

50 **Bloemenkamp DG**, Mali WP, Tanis BC, Rosendaal FR, van den Bosch MA, Kemmeren JM, Algra A, Ossewaarde JM, Visseren FL, van Loon AM, van der Graaf Y. Chlamydia pneumoniae, Helicobacter pylori and cytomegalovirus infections and the risk of peripheral arterial disease in young women. *Atherosclerosis* 2002; **163**: 149-156 [PMID: 12048133 DOI: 10.1016/S0021-9150(01)00761-4]

51 **Witherell HL**, Smith KL, Friedman GD, Ley C, Thom DH, Orentreich N, Vogelman JH, Parsonnet J. C-reactive protein, Helicobacter pylori, Chlamydia pneumoniae, cytomegalovirus and risk for myocardial infarction. *Ann Epidemiol* 2003; **13**: 170-177 [PMID: 12604160 DOI: 10.1016/S1047-2797(02)00276-4]

52 **Virok D**, Kis Z, Kari L, Barzo P, Sipka R, Burian K, Nelson DE, Jackel M, Kerenyi T, Bodosi M, Gönczol E, Endresz V. Chlamydophila pneumoniae and human cytomegalovirus in atherosclerotic carotid plaques--combined presence and possible interactions. *Acta Microbiol Immunol Hung* 2006; **53**: 35-50 [PMID: 16696549]

53 **Grayston JT**. Infections caused by Chlamydia pneumoniae strain TWAR. *Clin Infect Dis* 1992; **15**: 757-761 [PMID: 1445972 DOI: 10.1093/clind/15.5.757]

54 **Belland RJ**, Ouellette SP, Gieffers J, Byrne GI. Chlamydia pneumoniae and atherosclerosis. *Cell Microbiol* 2004; **6**: 117-127 [PMID: 14706098 DOI: 10.1046/j.1462-5822.2003.00352.x]

55 **Campbell LA**, Kuo CC, Grayston JT. Chlamydia pneumoniae and cardiovascular disease. *Emerg Infect Dis* 1998; **4**: 571-579 [PMID: 9866733 DOI: 10.3201/eid0404.980407]

56 **Chaturvedi AK**, Gaydos CA, Agreda P, Holden JP, Chatterjee N, Goedert JJ, Caporaso NE, Engels EA. Chlamydia pneumoniae infection and risk for lung cancer. *Cancer Epidemiol Biomarkers Prev* 2010; **19**: 1498-1505 [PMID: 20501758 DOI: 10.1158/1055-9965.EPI-09-1261]

57 **Fainardi E**, Castellazzi M, Seraceni S, Granieri E, Contini C. Under the microscope: focus on Chlamydia pneumoniae infection and multiple sclerosis. *Curr Neurovasc Res* 2008; **5**: 60-70 [PMID: 18289023 DOI: 10.2174/156720208783565609]

58 **Hammond CJ**, Hallock LR, Howanski RJ, Appelt DM, Little CS, Balin BJ. Immunohistological detection of Chlamydia pneumoniae in the Alzheimer's disease brain. *BMC Neurosci* 2010; **11**: 121 [PMID: 20863379 DOI: 10.1186/1471-2202-11-121]

59 **Karunakaran KP**, Blanchard JF, Raudonikiene A, Shen C, Murdin AD, Brunham RC. Molecular detection and seroepidemiology of the Chlamydia pneumoniae bacteriophage (PhiCpn1). *J Clin Microbiol* 2002; **40**: 4010-4014 [PMID: 12409367 DOI: 10.1128/JCM.40.11.4010-4014.2002]

60 **Gieffers J**, Füllgraf H, Jahn J, Klinger M, Dalhoff K, Katus HA, Solbach W, Maass M. Chlamydia pneumoniae infection in circulating human monocytes is refractory to antibiotic treatment. *Circulation* 2001; **103**: 351-356 [PMID: 11157684 DOI: 10.1161/01.CIR.103.3.351]

61 **Mosorin M**, Surcel HM, Laurila A, Lehtinen M, Karttunen R, Juvonen J, Paavonen J, Morrison RP, Saikku P, Juvonen T. Detection of Chlamydia pneumoniae-reactive T lymphocytes in human atherosclerotic plaques of carotid artery. *Arterioscler Thromb Vasc Biol* 2000; **20**: 1061-1067 [PMID: 10764674 DOI: 10.1161/01.ATV.20.4.1061]

62 **Boman J**, Hammerschlag MR. Chlamydia pneumoniae and atherosclerosis: critical assessment of diagnostic methods and relevance to treatment studies. *Clin Microbiol Rev* 2002; **15**: 1-20 [PMID: 11781264 DOI: 10.1128/CMR.15.1.1-20.2002]

63 **Ieven MM**, Hoymans VY. Involvement of Chlamydia pneumoniae in atherosclerosis: more evidence for lack of evidence. *J Clin Microbiol* 2005; **43**: 19-24 [PMID: 15634945 DOI: 10.1128/JCM.43.1.19-24.2005]

64 **Hardick J**, Maldeis N, Theodore M, Wood BJ, Yang S, Lin S, Quinn T, Gaydos C. Real-time PCR for Chlamydia pneumoniae utilizing the Roche Lightcycler and a 16S rRNA gene target. *J Mol Diagn* 2004; **6**: 132-136 [PMID: 15096569 DOI: 10.1016/S1525-1578(10)60501-6]

65 **Tondella ML**, Talkington DF, Holloway BP, Dowell SF, Cowley K, Soriano-Gabarro M, Elkind MS, Fields BS. Development and evaluation of real-time PCR-based fluorescence assays for detection of Chlamydia pneumoniae. *J Clin Microbiol* 2002; **40**: 575-583 [PMID: 11825973 DOI: 10.1128/JCM.40.2.575-583.2002]

66 **Meijer A**, Roholl PJ, Gielis-Proper SK, Ossewaarde JM. Chlamydia pneumoniae antigens, rather than viable bacteria, persist in atherosclerotic lesions. *J Clin Pathol* 2000; **53**: 911-916 [PMID: 11265175 DOI: 10.1136/jcp.53.12.911]

67 **Meijer A**, van Der Vliet JA, Roholl PJ, Gielis-Proper SK, de Vries A, Ossewaarde JM. Chlamydia pneumoniae in abdominal aortic aneurysms: abundance of membrane components in the absence of heat shock protein 60 and DNA. *Arterioscler Thromb Vasc Biol* 1999; **19**: 2680-2686 [PMID: 10559011 DOI: 10.1161/01.ATV.19.11.2680]

68 **Apfalter P**. Chlamydia pneumoniae, stroke, and serological associations: anything learned from the atherosclerosis-cardiovascular literature or do we have to start over again? *Stroke* 2006; **37**: 756-758 [PMID: 16424375 DOI: 10.1161/01.STR.0000201970.88546.5e]

69 **Wolf SC**, Mayer O, Jürgens S, Vonthein R, Schultze G, Risler T, Brehm BR. Chlamydia pneumoniae IgA seropositivity is associated with increased risk for atherosclerotic vascular disease, myocardial infarction and stroke in dialysis patients. *Clin Nephrol* 2003; **59**: 273-279 [PMID: 12708567 DOI: 10.5414/CNP59273]

70 **Podsiadły E**, Przyłuski J, Kwiatkowski A, Kruk M, Wszoła M, Nosek R, Rowiński W, Ruzyłło W, Tylewska-Wierzbanowska S. Presence of Chlamydia pneumoniae in patients with and without atherosclerosis. *Eur J Clin Microbiol Infect Dis* 2005; **24**: 507-513 [PMID: 16133407]

71 **Huittinen T**, Hahn D, Anttila T, Wahlström E, Saikku P, Leinonen M. Host immune response to Chlamydia pneumoniae heat shock protein 60 is associated with asthma. *Eur Respir J* 2001; **17**: 1078-1082 [PMID: 11491147 DOI: 10.1183/09031936.01.00089001]

72 **Jha HC**, Srivastava P, Prasad J, Mittal A. Chlamydia pneumoniae heat shock protein 60 enhances expression of ERK, TLR-4 and IL-8 in atheromatous plaques of coronary artery disease patients. *Immunol Invest* 2011; **40**: 206-222 [PMID: 21192737 DOI: 10.3109/08820139.2010.534217]

73 **Di Pietro M**, Filardo S, De Santis F, Sessa R. Chlamydia pneumoniae infection in atherosclerotic lesion development through oxidative stress: a brief overview. *Int J Mol Sci* 2013; **14**: 15105-15120 [PMID: 23877837 DOI: 10.3390/ijms140715105]

74 **Sugiyama T**, Hige S, Asaka M. Development of an H. pylori-infected animal model and gastric cancer: recent progress and issues. *J Gastroenterol* 2002; **37 Suppl 13**: 6-9 [PMID: 12109668 DOI: 10.1007/BF02990092]

75 **Kowalski M**. Helicobacter pylori (H. pylori) infection in coronary artery disease: influence of H. pylori eradication on coronary artery lumen after percutaneous transluminal coronary angioplasty. The detection of H. pylori specific DNA in human coronary atherosclerotic plaque. *J Physiol Pharmacol* 2001; **52**: 3-31 [PMID: 11795863]

76 **Ayada K**, Yokota K, Hirai K, Fujimoto K, Kobayashi K, Ogawa H, Hatanaka K, Hirohata S, Yoshino T, Shoenfeld Y, Matsuura E, Oguma K. Regulation of cellular immunity prevents Helicobacter pylori-induced atherosclerosis. *Lupus* 2009; **18**: 1154-1168 [PMID: 19880562 DOI: 10.1177/0961203309106600]

77 **Khalil MZ**. The association of Helicobacter pylori infection with coronary artery disease: fact or fiction? *Saudi J Gastroenterol* 2004; **10**: 132-139 [PMID: 19861836]

78 **Bentz GL**, Yurochko AD. Human CMV infection of endothelial cells induces an angiogenic response through viral binding to EGF receptor and beta1 and beta3 integrins. *Proc Natl Acad Sci U S A* 2008; **105**: 5531-5536 [PMID: 18375753 DOI: 10.1073/pnas.0800037105]

79 **Mariguela VC**, Chacha SG, Cunha Ade A, Troncon LE, Zucoloto S, Figueiredo LT. Cytomegalovirus in colorectal cancer and idiopathic ulcerative colitis. *Rev Inst Med Trop Sao Paulo* 2008; **50**: 83-87 [PMID: 18488086]

80 **Sambiase NV**, Higuchi ML, Nuovo G, Gutierrez PS, Fiorelli AI, Uip DE, Ramires JA. CMV and transplant-related coronary atherosclerosis: an immunohistochemical, in situ hybridization, and polymerase chain reaction in situ study. *Mod Pathol* 2000; **13**: 173-179 [PMID: 10697275 DOI: 10.1038/modpathol.3880032]

81 **Utrera-Barillas D**, Valdez-Salazar HA, Gómez-Rangel D, Alvarado-Cabrero I, Aguilera P, Gómez-Delgado A, Ruiz-Tachiquin ME. Is human cytomegalovirus associated with breast cancer progression? *Infect Agent Cancer* 2013; **8**: 12 [PMID: 23557440 DOI: 10.1186/1750-9378-8-12]

82 **Al-Ghamdi A**, Jiman-Fatani AA, El-Banna H. Role of Chlamydia pneumoniae, helicobacter pylori and cytomegalovirus in coronary artery disease. *Pak J Pharm Sci* 2011; **24**: 95-101 [PMID: 21454155]

83 **Morre SA,** Stooker W, Lagrand WK, van den Brule AJ, Niessen HW. Microorganisms in the aetiology of atherosclerosis. *J Clin Pathol* 2000; **53:** 647-654[PMID: 11041053]

84 **Minick CR**, Fabricant CG, Fabricant J, Litrenta MM. Atheroarteriosclerosis induced by infection with a herpesvirus. *Am J Pathol* 1979; **96**: 673-706 [PMID: 382868]

85 **Frenkel N**, Schirmer EC, Wyatt LS, Katsafanas G, Roffman E, Danovich RM, June CH. Isolation of a new herpesvirus from human CD4+ T cells. *Proc Natl Acad Sci U S A* 1990; **87**: 748-752 [PMID: 2153965 DOI: 10.1073/pnas.87.2.748]

86 **Shi Y**, Tokunaga O. Herpesvirus (HSV-1, EBV and CMV) infections in atherosclerotic compared with non-atherosclerotic aortic tissue. *Pathol Int* 2002; **52**: 31-39 [PMID: 11940204 DOI: 10.1046/j.1440-1827.2002.01312.x]

87 **Benditt EP**, Barrett T, McDougall JK. Viruses in the etiology of atherosclerosis. *Proc Natl Acad Sci U S A* 1983; **80**: 6386-6389 [PMID: 6312457 DOI: 10.1073/pnas.80.20.6386]

88 **Epstein SE**, Zhou YF, Zhu J. Infection and atherosclerosis: emerging mechanistic paradigms. *Circulation* 1999; **100**: e20-e28 [PMID: 10421626 DOI: 10.1161/01.CIR.100.4.e20]

89 **Sun Y**, Pei W, Wu Y, Jing Z, Zhang J, Wang G. Herpes simplex virus type 2 infection is a risk factor for hypertension. *Hypertens Res* 2004; **27**: 541-544 [PMID: 15492472 DOI: 10.1291/hypres.27.541]

90 **Libby P,** Ridker PM, Maseri A. Inflammation and atherosclerosis. *Circulation* 2002; **105:** 1135-1143 [DOI: 10.1161/hc0902.104353]

91 **Horváth R**, Cerný J, Benedík J, Hökl J, Jelínková I, Benedík J. The possible role of human cytomegalovirus (HCMV) in the origin of atherosclerosis. *J Clin Virol* 2000; **16**: 17-24 [PMID: 10680737 DOI: 10.1016/S1386-6532(99)00064-5]

92 **Zhu J**, Quyyumi AA, Norman JE, Csako G, Waclawiw MA, Shearer GM, Epstein SE. Effects of total pathogen burden on coronary artery disease risk and C-reactive protein levels. *Am J Cardiol* 2000; **85**: 140-146 [PMID: 10955367 DOI: 10.1016/S0002-9149(99)00653-0]

93 **Mattila KJ**, Nieminen MS, Valtonen VV, Rasi VP, Kesäniemi YA, Syrjälä SL, Jungell PS, Isoluoma M, Hietaniemi K, Jokinen MJ. Association between dental health and acute myocardial infarction. *BMJ* 1989; **298**: 779-781 [PMID: 2496855 DOI: 10.1136/bmj.298.6676.779]

94 **Holmes E**, Loo RL, Stamler J, Bictash M, Yap IK, Chan Q, Ebbels T, De Iorio M, Brown IJ, Veselkov KA, Daviglus ML, Kesteloot H, Ueshima H, Zhao L, Nicholson JK, Elliott P. Human metabolic phenotype diversity and its association with diet and blood pressure. *Nature* 2008; **453**: 396-400 [PMID: 18425110 DOI: 10.1038/nature06882]

95 **Haraszthy VI**, Zambon JJ, Trevisan M, Zeid M, Genco RJ. Identification of periodontal pathogens in atheromatous plaques. *J Periodontol* 2000; **71**: 1554-1560 [PMID: 11063387 DOI: 10.1902/jop.2000.71.10.1554]

96 **Stelzel M**, Conrads G, Pankuweit S, Maisch B, Vogt S, Moosdorf R, Flores-de-Jacoby L. Detection of Porphyromonas gingivalis DNA in aortic tissue by PCR. *J Periodontol* 2002; **73**: 868-870 [PMID: 12211495 DOI: 10.1902/jop.2002.73.8.868]

97 **Casalta JP**, Fournier PE, Habib G, Riberi A, Raoult D. Prosthetic valve endocarditis caused by Pseudomonas luteola. *BMC Infect Dis* 2005; **5**: 82 [PMID: 16221303 DOI: 10.1186/1471-2334-5-82]

98 **Ford PJ**, Gemmell E, Chan A, Carter CL, Walker PJ, Bird PS, West MJ, Cullinan MP, Seymour GJ. Inflammation, heat shock proteins and periodontal pathogens in atherosclerosis: an immunohistologic study. *Oral Microbiol Immunol* 2006; **21**: 206-211 [PMID: 16842503 DOI: 10.1111/j.1399-302X.2006.00276.x]

99 **Lockhart PB**, Bolger AF, Papapanou PN, Osinbowale O, Trevisan M, Levison ME, Taubert KA, Newburger JW, Gornik HL, Gewitz MH, Wilson WR, Smith SC, Baddour LM. Periodontal disease and atherosclerotic vascular disease: does the evidence support an independent association?: a scientific statement from the American Heart Association. *Circulation* 2012; **125**: 2520-2544 [PMID: 22514251 DOI: 10.1161/CIR.0b013e31825719f3]

100 **Jha HC**, Srivastava P, Sarkar R, Prasad J, Mittal A. Chlamydia pneumoniae IgA and elevated level of IL-6 may synergize to accelerate coronary artery disease. *J Cardiol* 2008; **52**: 140-145 [PMID: 18922388 DOI: 10.1016/j.jjcc.2008.07.001]

101 **Jha HC,** Srivastava P, Sarkar R, Prasad J, Mittal AS. Association of plasma circulatory markers, Chlamydia pneumoniae, and high sensitive C-reactive protein in coronary artery disease patients of India. *Mediators Inflamm* 2009; **2009:** 561532 [DOI: 10.1155/2009/561532]

102 **Johnston SC**, Messina LM, Browner WS, Lawton MT, Morris C, Dean D. C-reactive protein levels and viable Chlamydia pneumoniae in carotid artery atherosclerosis. *Stroke* 2001; **32**: 2748-2752 [PMID: 11739967 DOI: 10.1161/hs1201.099631]

103 **Paneni F,** Beckman JA, Creager MA, Cosentino F. Diabetes and vascular disease: pathophysiology, clinical consequences, and medical therapy: part I. Eur Heart J, 2013 [DOI: 10.1093/eurheartj/eht142]

104 **Semenkovich CF**. Insulin resistance and atherosclerosis. *J Clin Invest* 2006; **116**: 1813-1822 [PMID: 16823479 DOI: 10.1172/JCI29024]

105 **Jha HC**, Divya A, Prasad J, Mittal A. Plasma circulatory markers in male and female patients with coronary artery disease. *Heart Lung* 2010; **39**: 296-303 [PMID: 20561855 DOI: 10.1016/j.hrtlng.2009.10.005]

106 **Ait-Oufella H**, Taleb S, Mallat Z, Tedgui A. Recent advances on the role of cytokines in atherosclerosis. *Arterioscler Thromb Vasc Biol* 2011; **31**: 969-979 [PMID: 21508343 DOI: 10.1161/ATVBAHA.110.207415]

107 **Tedgui A**, Mallat Z. Cytokines in atherosclerosis: pathogenic and regulatory pathways. *Physiol Rev* 2006; **86**: 515-581 [PMID: 16601268 DOI: 10.1152/physrev.00024.2005]

**P-Reviewers:** Han Q, Niculescu M **S-Editor:** Song XX **L-Editor:** **E-Editor:**



**Figure 1 A schematic representation of *Chlamydia pneumoniae* infection from lungs to heart.** IL: Interleukin-6; CMV: *Cytomegalovirus*; CRP: C-reactive protein.