

The evidence for a role of bacteria and viruses in cardiovascular disease



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Abstract:

Inflammation plays a critical role in atherosclerosis and cardiovascular disease. Bacteria and viruses are major causative agents of inflammation in the body which normally develops as a response to infection. It is a logical extension, therefore, to believe bacterial and viral infections may be involved in a variety of presentations of cardiovascular diseases. The purpose of this review is to describe the data and conclusions to date on the involvement of these infectious agents in the induction of cardiovascular disease. The review also discusses the various specific bacteria and viruses that have been implicated in cardiovascular disease and the mechanisms, if known, that these agents induce cardiovascular disease.

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INFECTIONS ASSOCIATED WITH CARDIOVASCULAR DISEASE

A number of risk factors have been identified as important in determining the expression of cardiovascular disease (CVD). Some are modifiable and others like genetic predisposition, time and race are not. Among the more recent environmental factors that are modifiable is infection. Over time, it has become dogma in the cardiovascular research field that infection and its associated inflammatory reactions are principle factors in the development of many CVDs. The primary type of CVD in which this presents itself is atherosclerotic CVD. The hypothesis that infection and inflammation plays a critical role in atherosclerosis created an initial surge of research to identify the specific infectious agents that may cause atherosclerotic disease. The results from these studies were somewhat surprising and disbelieved for many years. One concern for the studies was that these causative infectious agents identified were from very unlikely sources. Bacteria and viruses commonly associated with diseases of non-cardiac origin were implicated in CVD. However, the evidence to strongly support their involvement has accumulated over many years and now even includes the virus in-

involved in the most recent COVID-19 pandemic. The purpose of this review is to discuss the various bacteria and viruses that have been implicated in CVD and the mechanisms, if known, that these agents induce CVD.

BACTERIAL INFECTIONS ASSOCIATED WITH CARDIOVASCULAR DISEASE

A variety of bacteria, commonly associated with diseases of non-cardiac origin, have nonetheless been implicated in CVD. All are Gram-negative bacteria. For example, although *Helicobacter pylori* is most commonly associated with persistent gastritis [1], these bacteria have also been identified as causative agents in CVD. *Porphyromonas gingivalis* and *Actinobacillus actinomycetemcomitans* are causative bacteria for periodontal disease but have also been implicated in CVD. *Chlamydia pneumoniae* and *Mycobacterium tuberculosis* are well known for their respiratory complications [2], however, these bacteria have also been identified as causative agents in CVDs.

Chlamydia pneumoniae is the most intensely studied pathogen with regard to its role in CVD. *C pneumoniae* antibodies have been detected within the serum of

patients with coronary artery disease [3][4]. DNA and elementary bodies of *C pneumoniae* have also been found in the atherosclerotic plaque [2]. Most importantly, a causal relationship and the mechanisms of action for *C pneumoniae* infection and atherogenesis has been tested and established in some cases [5][6][7][8][9], although some aspects remain in dispute [10][11]. Heat inactivated *C pneumoniae* is not atherogenic [12].

H pylori has been strongly correlated with atherosclerotic heart disease and coronary artery disease and stroke clinically [13][14][15], particularly in patients with hyperhomocysteinaemia [16]. Causal evidence for a role for *H pylori* in atherogenesis and coronary artery disease is lacking.

P gingivalis is one of several bacterial pathogens commonly associated with dental plaque and gum disease. This includes *Actinobacillus actinomycetemcomitans*, *Treponema denticola* and *Bacteroides forsythus*. Again, there is strong evidence of a close correlation of *P gingivitis* with coronary artery disease with DNA evidence of its presence in up to 30 % of carotid atheromas [17][18]. Furthermore, CVD risk has been correlated with the severity of the periodontal infection [19].

THE MECHANISMS WHEREBY BACTERIAL INFECTIONS INDUCE CARDIOVASCULAR DISEASE

Further studies have clearly demonstrated that the relationship between infection and atherosclerosis is not a simple indirect association but an important cause and effect relationship [5][6][7][20][21][22][23][24][25]. The mechanism whereby infections induce an atherogenic lesion is unclear. Many of these infectious agents either have stimulatory effects on cellular proliferation [8][9][23][26][27] or inhibitory effects on apoptosis [28]. These actions may be involved in their atherogenic effects [23][26][28]. The susceptibility of atherogenesis to such a broad spectrum of infectious agents, however, suggests that a pathway common to infection in general may be a key player in this phenomenon. Heat shock proteins have been identified as one potential mediator that would link the atherosclerosis process with the infection/inflammatory condition [28][29][30][31][32]. It is also clear that lipids have an important role to play in modifying the atherogenic effects of infections [5][9][33]. It has been identified that the atherogenic potential of *C pneumoniae* is dependent upon a high cholesterol environment [5][7]. Feeding the LDL receptor knockout mouse a high cho-

lesterol diet induced atherosclerotic plaque formation. Conversely, infection of mice on a normal diet with *C pneumoniae* did not induce an atherosclerotic effect. However, if the animals were placed on the cholesterol-enriched diet to induce atherosclerosis and then infected with *C pneumoniae*, a significantly greater stimulation of atherosclerotic plaque formation [5][7] than cholesterol could induce on its own was observed. These data strongly suggested a synergistic interaction between the infection and cholesterol. This model is attractive because it links an important conventional atherogenic risk factor (cholesterol) with the infection process and may explain why some people develop clinically significant atherosclerosis after an infection and others do not. Relevant to the present topic, it also strongly points to the importance of diet in modulating the atherogenic action of an infectious agent. Significantly, a clinical investigation has documented the potent stimulatory effect of additional risk factors like hypercholesterolaemia on the cardiovascular effects of infection with *C pneumoniae* in a clinically relevant patient population [34].

ANTIBIOTIC USE TO PREVENT CVD

If these bacteria do play a role in atherosclerotic CVD, the next logical step would be to determine if antibiotic usage can prevent or deter the clinical symptoms of CVD. *C pneumoniae* strains are susceptible to antibiotics like tetracycline, fluoroquinolones and macrolides in *in vitro* studies [35][36]. However, the results from clinical trials testing the capacity of antibiotics to prevent major CVD events have been disappointing. Retrospective studies in patients treated with antibiotics prior to a myocardial infarction have yielded no clear conclusions [37][38]. A detailed description of the clinical trials using antibiotics to prevent CVD is found elsewhere [39]. In summary, although the first few small antibiotic trials with azithromycin on patients with cardiovascular disease resulted in a positive protective effect versus the incidence of myocardial infarctions and indices of CVD [40][41][42][43], several more extensive trials like the ACADEMIC study (The Azithromycin in Coronary Artery Disease: Elimination of Myocardial Infection with Chlamydia) [44], the WIZARD trial (Weekly Intervention With Azithromax Against Atherosclerotic-Related Disorders) [45], the CLARICOR trial (CLARithromycin for patients with stable CORonary heart disease) [46], the ACES trial (Azithromycin and Coronary Events Study) [47], the ANTIBIO trial (Antibiotic Therapy in Acute Myocardial Infarction) [48], the AZACS trial (Azythromycin in Acute Coronary Syndrome) [49] and the PROVE-IT trial (Pravastatin Or Atorvastatin Evaluation and Infection

Therapy) [50] all concluded that antibiotic treatments did not result in any reduction in cardiovascular events. As a result, the use of antibiotics to prevent CVD have been largely abandoned as a viable approach. The reason for the lack of prevention may be multifactorial. It is clear that macrolides do not impact persistent *Chlamydial* infection during its persistent stage [39] and this persistence of bacterial infection would negate any antibiotic effect of the macrolides tested. Murine models of atherosclerosis have identified a high cholesterol environment as being critical to the atherogenic effects of *C pneumoniae* infection [5]. It is possible, therefore, that antibiotic treatment may be best utilised in a clinical population with high circulating cholesterol levels prior to the appearance of clinically significant cardiovascular disease. Some clinical studies would lend support to this hypothesis [34] but further work is required to substantiate this conclusively. Additionally, it is possible that a critical window of time exists for the preventative effect of the antibiotics. Antibiotics delivered to rabbits shortly after bacterial inoculation inhibited *C pneumoniae*-induced atherosclerosis but was ineffective if delivered 6 weeks post-inoculation [51]. Clinical trials using antibiotics were delivered in patients with well established cardiovascular disease. The alternative approach of testing the delivery of antibiotics chronically in order to prevent the appearance of atherosclerotic plaque formation before it is established has been proposed but never tested. Today, with the ever growing emergence of multidrug resistance in pathogenic bacteria as a serious health problem, an approach of using antibiotics over an extended period of time when there is an absence of clinical evidence of an infection would not be feasible. This strategy for the prevention of cardiovascular disease would undoubtedly promote the acceleration of antibiotic resistance in pathogenic bacteria and this would be an unacceptable consequence.

Other approaches besides antibiotics for the treatment of infection-induced atherosclerotic disease could be advanced. The afore-mentioned relationship of cholesterol with *C pneumoniae*-induced infection may offer intriguing options. An oxidation mechanism has been proposed to be involved in the association of cholesterol with *C pneumoniae*-induced atherogenesis. It is well known that *C pneumoniae* can induce a stimulation of intracellular oxidative processes [52][53]. For example, *C pneumoniae* and other infectious processes can induce oxidation of LDL in *in vitro* and *in vivo* settings [52][53][54][55][56]. Oxidized LDL is thought to play an important role in atherosclerosis [57][58][59]. Oxidized LDL can potentiate the mitogenic actions of *C pneumoniae* [9]. It is possible, therefore, that the ox-

idation induced by infectious agents like *Chlamydia pneumoniae* [9] is critical to the atherogenic event and preventing this process may retard or block the atherogenic action of *Chlamydia* and other infectious organisms. Blocking the oxidation by treating the *C pneumoniae*-induced cardiovascular disease with antioxidants has not been tested but may provide positive results.

Other alternative pathways have been identified as associated with the atherogenic actions of infectious stimuli like *C pneumoniae*. It has been suggested [39] for example, that it may be more effective to target downstream pathways induced by the *Chlamydial* infection rather than the bacteria itself. Targeting the inflammatory and mitogenic pathways that are activated by the infection to generate the atherogenesis may be more beneficial, particularly those involving heat shock protein 60 [27][29], specific pattern recognition receptors, transporters or other target proteins [39].

VIRAL INFECTIONS ASSOCIATED WITH CARDIOVASCULAR DISEASE

Bacteria are not the only infectious agents that have been associated with cardiovascular diseases. Herpes simplex virus (HSV) [23][24], Epstein-Barr virus DNA and cytomegalovirus (CMV) [28][60], have been tied to both atherosclerotic cardiovascular and cerebrovascular lesions. More recently, another viral infection, the Coronavirus 2019 (COVID-19), has also been strongly linked to a variety of cardiovascular diseases by a host of new studies.

Siscovick and colleagues found that herpes simplex virus type 1 (HSV) IgG antibodies were associated with a 2 fold increase in the risk of incident myocardial infarction and coronary heart disease in older adults [61]. Another study discovered elevated levels of HSV, CMV and Epstein-Barr virus DNA in coronary artery atherosclerotic plaques obtained by end-arterectomy [62]. A large investigation, the ARIC study (Atherosclerosis Risk in Communities), reported that high levels of CMV antibodies were significantly associated with incident coronary heart disease [63]. In another large study of over 14,000 patients, CMV was associated with a significant increase in the risk for all-cause mortality and, when combined with elevated CRP levels, the risk for all-cause mortality and CVD-associated mortality also increased [64]. Serum antibody levels to HSV and two periodontal infections were measured in over 1100 Finnish and Russian participants [65]. They found the risk for CVD was increased when the antibody levels

for the three infectious agents were elevated. These studies have led to the hypothesis that the entire burden of simultaneous chronic infectious disease may be the most important factor in the induction of CVD [19].

Conflicting evidence arguing against a role for HSV and CMV in CVD has been reported. The prevalence of CMV and HSV in coronary artery disease patients was not elevated [66]. Siscovick et al [61] did not find that an elevation in IgG antibodies to CMV was associated with CVD risk among the elderly. Ridker et al [67] also found no correlation between HSV or CMV IgG antibody titers and subsequent risk for CVD in postmenopausal women. More negative results have been reported for CMV in another recent study [68]. The conflicting evidence, particularly for CMV, would lead one to conclude that there is a need for further large controlled studies to resolve this situation.

The emergence of the COVID-19 pandemic has resulted in the evolution of strong evidence for another association between an infectious agent and CVD. Indeed, it may be argued that the controversy that has arisen in the field as to the involvement of viruses in CVD has been answered unquestionably by the clear association of the COVID-19 virus with both acute and chronic manifestations of CVD. The COVID-19 zoonotic viral protein acts initially by binding to the angiotensin converting enzyme 2 (ACE2) receptor to ultimately gain entry to the cell [69]. The strong evidence for a role for the ACE2 receptors in the CVD induced by COVID-19 infection should not come as too big a surprise. ACE2 receptors have long been associated with CVD independently of COVID-19 infection [70][71][72]. This includes the overexpression of ACE2 activity in failing hearts [72]. The resultant systemic inflammation caused by COVID-19 infection induces an intense immune and cytokine response followed by plaque destabilisation, acute coronary syndrome, hypoxia, myocarditis, arrhythmias, cardiomyopathy, cardiogenic shock, myocardial damage, cardiac arrest and ultimately heart failure [73]. Venous thromboembolism and platelet aggregation have also been observed in COVID-19-infected patients [69].

Some 20-30 % of patients admitted to hospitals with COVID-19 infections have cardiovascular complications [74]. Pre-existing CVD appears to exacerbate the effects of COVID-19 infection [74]. Even in patients who had recovered from COVID-19 infection, magnetic resonance imaging detected myocardial damage and myocardial inflammation in 78 % and 60 %, respectively, of these patients [75][76]. The cardiovascular pathologies may be linked to an increased risk of venous and

arterial thromboembolic events [76]. Arrhythmias persist post COVID-19 recovery and the emergence of cardiomyopathies subsequent to infection have also been reported [74]. This further supports the contention that COVID-19 infection is associated with a persistent and chronic CVD [74]. Furthermore, the strikingly higher male mortality incidence in COVID-19 infected patients may be explained by the sexual dimorphism in pre-existing cardiovascular comorbidities [77].

CONCLUSION

The majority of evidence over decades of investigation supports the involvement of both bacterial and viral infection as having an important role to play in inducing CVD. It is also possible now to come to a tentative conclusion that different bacteria and different viruses have very different capacities to induce CVD and, furthermore, they will induce varying severities of CVD. Perhaps the most dramatic example of a viral infection being associated with CVD is the recent pandemic with COVID-19. The infection has been associated with both an immediate as well as a chronic manifestation of a panoply of CVDs. This is likely due to its uniquely facile access to the cardiovascular tissue through the ACE-2 receptor. Unfortunately, the serious vascular and cardiac effects of the current COVID-19 pandemic may only be a harbinger of the future challenges facing the cardiovascular system when multidrug resistance to antibiotics escalates even further and unleashes a horde of pathogenic bacteria on a defenceless cardiovascular system [78].

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Conflict of interest

None.

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