Chapter

8 Inflammation, Atherosclerosis and Coronary Artery Disease

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In 1856, Rudolf Virchow proposed that the atherosclerosis was caused when plasma components (including lipids) elicited an inflammatory response in the arterial wall. Current research also points that inflammation plays a central role in genesis of atherosclerosis and its complications. In early atherosclerotic lesions, immune cells dominate and their effector cells leads to progression of atherosclerosis. The inflammatory process has been implicated in the vulnerability of the plaque leading to plaque rupture, leading to Acute Coronary Syndrome. Understanding the role of inflammation in causation of the atherosclerosis and coronary artery disease will lead to new vistas in prediction, prevention and treatment of cardiovascular diseases.

INFECTION AND CORONARY ARTERY DISEASE

Various microbes have been implicated in the causation of atherosclerosis. Chlamydia pnemoniae, Herpes viruses and Cytomegalovirus have been associated with atherosclerosis because either these microbes have been found in the atherosclerotic lesions or the elevated titers of antibodies against these pathogens have been noted in such situations. However in experimental animals, such pathogens could not initiate atherosclerosis, but they can lead to progression of atherosclerosis and plaque activation[1]. It is possible that a single pathogen may not cause atherosclerosis and total burden of infection may be the factor in initiation and progression of atherosclerosis and finally in causation of acute coronary syndromes.

Does infection play a major role in causation of atherosclerosis and coronary artery disease in developing countries?

PLAQUE VULNERABILITY AND RUPTURE

Inflammatory cells like activated macrophages, T cells and mast cells by releasing cytokines, enzymes like proteases, coagulation factors and certain other molecules leads to destabilization of the stable plaque. Collagen in the stable fibrous caps comes under the attack and weakens the stable cap leads to activation and rupture of the plaque, induce thrombosis and cause ischemia.

Matrix metalloproteinases (MMPs) and Cysteine proteases are the key enzymes that are responsible in degradation of the matrix. They are also important factors in the composition of the plaque formation. In future, therapeutic strategies will target such factors to reduce the plaque vulnerability and consequently avoiding its rupture[2,3].

INFLAMMATORY MARKERS

Various inflammatory markers are elevated in acute coronary syndromes favoring the concept of inflammation playing the pivotal role in the whole process. These markers have also been shown to play an important role in prognosticating the disease process. C-reactive protein is the well established marker. Other inflammatory markers like fibrinogen, interleukin-7, interleukin-8, CD40 ligand, C-reactive protein related protein pentraxin 3 have also been elevated in these patients. Such markers are elevated in acute coronary syndromes and not in stable angina or vasospastic angina hypothesizing that these markers reflect the inflammation as the cause of acute events and not just ischemia[4].

C-REACTIVE PROTEIN, ATHEROSCLEROSIS AND CAD

C-reactive protein (CRP), the classical acute phase protein, represents a highly sensitive mark of inflammation – increasing by several hundred-fold in response to acute injury, infection or other inflammatory stimuli. Robust anti-CRP antibodies and a well-established WHO International reference standard for CRP are available so that precise sensitive clinical plasma / serum assays can be readily undertaken.

The Physicians Health Study examined CRP levels in apparently healthy men in whom myocardial infarction, venous thrombosis or strokes subsequently developed and in a similar number of men in whom vascular disease did not develop – over a follow-up period of at least 8 years[5]. The subjects were assigned to receive placebo or aspirin at the beginning of the study. Base line plasma CRP were higher in men who subsequently had a MI with the men in the quartile with the highest CRP having nearly three times the relative risk for MI compared with those in the lowest quartile. The increased risk remained stable at least 6 years of follow-up. Such an association was similarly found in Women's Health Study by the same group of investigators – with the highest quartile of CRP levels associated with 5 times likelihood to suffer a cardiovascular event compared with those subjects in the lowest quartile[6]. Other studies have reproduced very similar data. In a formal meta-analysis of n=11 prospective studies with almost 2000 cases a relative risk of two-fold, for CHD was found after adjustment of various confounders in the individuals in the top third compared to the bottom third of CRP distribution[7].

Whilst the underlying mechanism that may trigger the low-grade inflammatory response in atherosclerosis remains unclear, CRP can be regarded as the primary surrogate marker for the inflammatory processes. C-reactive protein may behave as a pro-coagulant marker since it is known to induce expression of tissue factor in monocytes. It may exert direct vascular and endothelial effects in that CRP is found within the vessel wall even in the early stage of plaque formation. It is chemotactic for monocytes, avidly binds to human neutrophils and induces complement activation. More recently increased plasma CRP levels were shown to directly impair endothelial cell function[8].

There is on-going debate whether concentrations of CRP will have a role in routine cardiovascular risk assessment. Interestingly the following properties have been noted:

- Consistency of results from 11 prospective population-based studies in apparently healthy subjects is quite remarkable.
- The association between CRP and future coronary events is strong – with a risk ratio 2-fold in those in the upper tertile of CRP distribution compared to those in the lower tertile. This holds true in both men and women
- The association between CRP in coronary risk has proved to be independent of a wide number of potential confounders – including cigarette smoking and social class.
- Other studies seem to demonstrate that the addition of CRP determination to that of total cholesterol dramatically enhances risk prediction[9].
- CRP is relatively stable–measured in plasma or serum and the measurement procedure is standardizing. Automated high sensitive CRP assays have low intra-and inter-assay variability[10].

There are several issues, which require confirmation and clarification before a full clinical role could be established. The causal relevance of CRP in atherothrombosis remains uncertain. Quartiles, tertiles and quintiles are sample- and population-dependent therefore not universally applicable. The lowering of CRP by various intervention strategies (e.g. statins / aspirin) is shown promising results but further studies are required[11].

Whilst local inflammatory processes are linked with the elevation of CRP in atherothrombosis, it may also be that inflammation elsewhere is relevant. *Chlamydia pneumoniae* and *Helicobacter pylori* infections have been linked with CHD[12,13]. Whether the CRP levels are a reflection of chronic infection is debatable. Higher levels of CRP have also been strongly associated with increased body mass index and more specifically with many features of the insulin resistance / metabolic syndrome (including frank diabetes mellitus). Interestingly the oral contraceptive and hormone replacement therapy are also associated with significantly raised base line CRP concentrations[14].

Accumulating data suggest that CRP is a useful predictor of short and long-term outcome in previously unrecognized cardiac disease and established acute coronary syndromes. In daily clinical practice the choice of cut off levels for appropriate differentiation of lowering high-risk patients remains problematic. As patients with different clinical presentations have been studied using different assays the data and literature cannot be fully comparable. It is reasonable to suspect

that levels less than 3 mg/l are associated with low risk of events. Emerging data suggest that statins reduce CRP levels – indicative of the pleiotropic properties of such agents. The use of biochemical markers such as CRP in the setting of both primary and secondary prevention risk assessment is steadily creeping into clinical practice. Defining the causal relationship, the degree of detrimental risk and the effects of interventions still require further research. Exciting times lie ahead.

THERAPEUTIC INTERVENTIONS

Inflammation as the cause of atherosclerosis opens up new vistas for the management of acute coronary syndromes. Immunosuppressants or anti-inflammatory drugs may become the frontline attractive options. Lipid-lowering statins have shown the anti-inflammatory properties – most important pleiotropic effect. Reduction of inflammation, depicted by lowering of CRP levels in patients receiving statins, improved the clinical outcome independent of cholesterol lowering.

In conclusion, the knowledge acquired about the role of inflammation in pathogenesis of atherosclerosis and coronary artery disease has led to better diagnostic and prognostic criterias for the disease and may offer newer solutions to this life threatening disease.

REFERENCES

1. Hu H, Pierce GN, Zhong G. The atherogenic effects of Chlamydia are dependent on serum cholesterol and specific to Chlamydia pneumoniae. J Clin Invest 1999;103:747-53.
2. Jones CB, Sane DC, Herrington DM. Matrix metalloproteinases: A review of their structure and role in acute coronary syndrome. Cardiovasc Res 2003;59:812-23.
3. Liu J, Sukhova GK, Sun JS, Xu WH, Libby P, Shi GP. Lysosomal cysteine proteases in atherosclerosis. Arterioscler Thromb Vasc Biol 2004;24:1359-66.
4. Damas JK, Waehre T, Yndestad A, et al. Interleukin-7 mediated inflammation in unstable angina : possible role of chemokines and platelets. Circulation 2003;107:2670-6.
5. Ridker P, Cushman M, Stampfer M, et al. Inflammation, aspirin and risk of cardiovascular disease in apparently healthy men. N Engl J Med 1997; 336:973-9.
6. Ridker P, Buring J, Shih J, et al. Prospective study of C-reactive protein and risk of future cardiovascular events among apparently healthy women. Circulation 1998; 98: 836-43.
7. Danesh J, Whincup P, Walker M, et al. Low grade inflammation and coronary heart disease: prospective study and updated meta-analyses. BMJ 2000; 321: 194-204.
8. Koenig W. C-reactive protein: risk assessment in the primary prevention of atherosclerotic disease. Has the time come for including it in the risk profile? Ital Heart J 2001; 2: 157-63.
9. Ridker P, Glynn R, Hennekens C. C-reactive protein adds to the predictive value of total and HDL cholesterol in determining risk of myocardial infarction. Circulation 1998;97:2001-11.
10. Rifai N, Tracy R, Ridker P. Clinical efficacy of an automated high-sensitivity C-reactive protein assay. Clin Chem 1999;45: 2136-41.
11. Ridker P, Rifai N, Pfeffer M, et al. Long-term effects of pravastatin on plasma concentration of C-reactive protein. Circulation 1999;100:230-5.
12. Gupta S, Kaski J. Chlamydia causes coronary heart disease: an inflammatory idea? Acute Coronary Syndromes 1999; 2: 42-8.
13. Gupta S. Chronic infection in the aetiology of atherosclerosis - focus on Chlamydia pneumoniae. [The John French Memorial Lecture] Atherosclerosis 1999;143:1-6.
14. Ridker P, Hennekens C, Rifai N, et al. Hormone replacement therapy and increased plasma concentration of C-reactive protein. Circulation 1999; 100: 713-6.