Endothelial function and inflammation in coronary artery disease

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Abstract
Evidence supports the central role of endothelium and inflammation in all phases of atherosclerotic process, and clinical studies have demonstrated their prognostic potential for the development of ischemic events and for adverse outcome following acute coronary syndromes. Reduction in inflammatory levels and improving endothelial function by traditional and novel therapeutic strategies was associated with a proportional reduction in cardiovascular events. However, randomised controlled trials are required to explore further whether drugs approach targeting inflammatory process and endothelial function will be a reasonable adjunctive treatment for patients with coronary artery disease.
**Introduction**

Coronary artery disease remains the principal cause of death and disability leading to increased burden in health care costs in developed countries. It is characterised by a long asymptomatic phase of development which starts as early as from the first decade of life and progresses eventually to the formation of atherosclerotic plaques. The latter, when they are unstable or become obstructive, lead to ischemic syndromes, the clinical manifestations of atherosclerosis and coronary artery disease (CAD).

Over the last few decades, our understanding of the vascular biology of atherogenesis and its clinical presentations has evolved enormously. It is now clear that inflammatory processes have key role not only in the initiation and progression of atherosclerosis but also in the stability of the established atherosclerotic plaques. In the long preclinical phase the vascular endothelium has been a major focus of research. Traditional and novel risk factors for cardiovascular disease trigger a chronic inflammatory process, which is accompanied by loss of vasodilatory and antithrombotic properties of the vascular endothelium.

In this review the role of endothelial function and inflammatory processes will be assessed as important determinants of the development of coronary artery disease. In addition the exciting potential for treatment that target this disturbed pathology will be discussed.

**2. Endothelium in coronary artery disease**

The endothelium plays important role in vascular homeostasis. It secretes numerous mediators such as nitric oxide (NO), prostacyclin and endothelin that regulate vascular tone, platelet activity and coagulation factors but also influence vascular inflammation and cell migration.

**Risk factors and vascular endothelium**

A variety of insults may damage endothelial structure and function which include physical injuries, biochemical injury and immune mediated damage. These insults cause alteration in endothelial physiology resulting in impairment or loss of its normal functions. The development of an imbalance in the release of vasoconstrictor and vasodilator agents from the endothelium results in impaired endothelium dependent vasodilatation, representing the hallmark of endothelial dysfunction. Over the last decade, it has been made possible to study NO dependent regulation of vascular tone in response to pharmacological and physical stimuli in different vascular beds. By using different invasive and non-invasive techniques it has been demonstrated that patients with CAD and those with increased cardiovascular risk factor profile present with dysfunctional endothelium.

A number of cardiovascular risk factors have been consistently associated with disturbances in normal endothelial physiology. These include non modifiable risk factors such as older age and male sex and modifiable ones. The latter include hypercholesterolaemia which appears as one of the most important contributors for atherosclerotic disease progression and others such as smoking, hypertension and diabetes which have been shown to be major risk factors for both coronary and cerebral events in both men and women irrespective of age and gender.
New risk factors associated with the westernised way of life have also been described. Among them obesity, the introduction of an atherogenic diet and physical inactivity are emerging as important players in this process. Epidemiological data has suggested that infection and chronic inflammation may trigger endothelial dysfunction. Studies performed in adults documented that serological evidence of exposure to multiple intracellular pathogens, particularly in the context of a low grade inflammatory response is associated with increased coronary atherosclerosis. Inflammatory vascular disease is associated with persistent endothelial dysfunction and more recently mild non specific viral infections seem to have a detrimental effect on the vascular endothelium.

While being in the process of identifying the aetiology of endothelial dysfunction and CAD the list of candidate risk factors increases to encompass elevation of serum homocysteine levels, birth weigh and polymorphisms that affect the expression of genes regulating endothelial biology.

### 3. The prognostic role of endothelial function in coronary artery disease

The endothelial vasodilator function was assessed as a test that can integrate the impact of multiple environmental and genetic influences on the vasculature and thus could serve as a useful diagnostic prognostic tool but also as a therapeutic target to improve outcome.

Studies performed at the time of cardiac catheterization, although some limited by small number of studied patients or by the lack of a thorough multivariable assessment of other potentially important independent predictors of risk, clearly demonstrate a direct association between endothelial dysfunction and event rates (Table 1). On the other hand the peripheral endothelial assessment gave contradictory results (Table 2). Perticone et al, and Heitzer et al, by using invasive forearm venous occlusion plethysmography highlighted the prognostic importance of endothelial dysfunction. Three other groups using non-invasive methods shared similar findings while others failed to do so when detailed multivariate analysis was performed. It is possible that differences in the population studied, treatment regimens used, the underlying inflammatory response or finally differences in the variability of different methods used might account for these discrepancies.

### 4. Inflammatory mechanisms in atherosclerosis

In the presence of risk factors the vascular endothelium responds and the activation of protein kinase C and transcriptional messenger nuclear factor-kB (NF-kB) are the primary events. This leads to upregulation of genes that code for and induce angiotensin converting enzyme activity, local production of angiotensin II and expression of endothelial cell surface adhesion molecules. These events in turn initiate and amplify cellular and subcellular responses in conduit coronary arteries that lead to endothelial dysfunction. This may lead to intimal thickening, plaque formation and ultimately disruption of plaque and clinical events.

Three cellular components of the circulation, monocytes, platelets and lymphocytes together with endothelial and smooth muscle cells interact in multiple ways in concert with low density lipoprotein (LDL) cholesterol in generating atherosclerotic lesions. In addition, pro-inflammatory cytokines and cellular adhesion molecules,
involved in the attachment of monocytes to the endothelial wall, appear to be critical in atherogenesis.

3.1 Adhesion molecules and monocytes

One early phase of atherosclerosis involves the recruitment of inflammatory cells from the circulation and their transendothelial migration. This process is mediated by cellular adhesion molecules, which are expressed on the vascular endothelium and on circulating leukocytes in response to several inflammatory stimuli. Adhesion is a multistep process that starts with leukocyte rolling on the endothelial surface. This is due to selectin ligation, whereas the subsequent firm adhesion depends on interactions between immunoglobulin like molecules (vascular cell adhesion molecules (VCAM-1), intercellular cell adhesion molecules (ICAM-1)) on the endothelium and integrins on the leukocyte surface 20(Figure 1).

Monocytes/macrophages play key roles both in the initiation and progression of atherosclerosis. Recruitment of monocytes into the arterial wall is one of the earliest events in atherosclerosis. Intimal monocytes develop into macrophages, which are important mediators of inflammation and the innate immune response in atherosclerotic lesions. Macrophages contribute to the local inflammatory responses through production of cytokines, free oxygen radicals, proteases and complement factors. The uptake of modified lipoproteins by macrophages leads to the accumulation of cholesterol esters and formation of macrophage derived foam cells, the hallmark of the fatty streak. Macrophages also contribute to lesion remodelling and to plaque rupture by secreting matrix metalloproteinases and thus contribute to the evolution of atherosclerosis in diverse ways.

3.2 B and T lymphocytes

A diverse lymphocyte population is found in atherosclerotic lesions with substantial number of T lymphocytes detected. T lymphocytes may enter the vessel wall prior to monocytes during the earliest stages of lesion formation and become activated as demonstrated by the presence of activation markers on these cells21. The presence of activated lymphocytes at each stage of the human lesion formation provides compelling evidence for a role of this cell type in the orchestration of the disease process.

3.3 Cytokines and inflammatory markers in atherosclerosis

Cytokines differentially affect atherogenesis with distinct cytokines directing pro and anti-atherogenic processes, modulating plaque characteristics and clinical outcomes22. The classical pro-inflammatory cytokines, interleukin (IL)-1 and tumor necrosis factor (TNF)-a typically mediate proatherogenic processes while IL-10 mediates anti-atherogenic pathways.

In addition recent evidence suggests that C-reactive protein (CRP) a marker of underlying inflammation might have a direct role in the pathophysiology of atherosclerosis. Thus in the presence of CRP there is increased uptake of low density lipoprotein (LDL) cholesterol by macrophages that contributes to foam cell formation. CRP can activate complement in atherosclerotic plaques leading potentially to plaque instability23-25. It can induce adhesion molecule expression on human coronary endothelial cells26. Finally increased CRP is also associated with endothelial dysfunction and the progression of atherosclerosis27.

5. The prognostic role of inflammation in coronary artery disease
In the process of identifying a reliable and independent predictor of the risk of an acute coronary event the endothelium has not been the only candidate. Inflammatory mediators which have instrumental role in the pathology of CAD have also been thoroughly tested. The inflammatory response may influence the prognosis of CAD patients by accelerating atherosclerosis but also by sudden development of instability in already established atherosclerotic plaques. Furthermore in the presence of an acute event inflammatory processes can modulate the consequences of ischaemia and necrosis. However, the contribution of each of these secondary and primary mechanisms of inflammation to prognosis may vary in different groups of patients.

The total white blood cell count is an inexpensive, reliable, easy to interpret inflammatory marker which has been associated with adverse prognosis in patients who have stable coronary heart disease after a myocardial infarction\textsuperscript{28}. Experimental evidence suggests numerous mechanisms through which leukocytes may affect the stability of plaques in acute coronary syndromes\textsuperscript{29-31}. One potential participant in this process is the leukocyte enzyme myeloperoxidase. Myeloperoxidase levels are increased in persons with angiographically documented cardiovascular disease and within culprit lesions prone to rupture\textsuperscript{32}. Myeloperoxidase has been linked to the development of lipid laden soft plaque, the activation of protease cascades affecting the stability and thrombogenicity of plaque, the production of cytotoxic and prothrombogenic oxidised lipids and the consumption of nitric oxide leading to vasoconstriction. Given its pathophysiological role myeloperoxidase seems to be a good prognostic marker of the incidence of a coronary event (Table 3)\textsuperscript{32, 33}.

Elevated values of other circulating inflammatory markers, such as CRP, serum amyloid A protein, IL-6 and IL-1 receptor antagonist, are also commonly found in ACS (Table 3). These markers have been shown to be reflective of the extent of myocardial necrosis, ischaemia/reperfusion damage and have also been considered as triggers of coronary instability\textsuperscript{1, 22}.

However at the moment the most attractive candidate marker of cardiovascular outcome is CRP. Commercially available high sensitivity assays allow the accurate and reproducible determination of CRP levels both in fresh and frozen plasma. In addition the absence of circadian variation makes it applicable for comparisons in large population studies. Liuzzo et al, were the first to demonstrate a direct association between elevated CRP levels and adverse short term prognosis independently of necrosis and ischaemia\textsuperscript{34}. Since then, a number of population based studies have demonstrated that baseline CRP levels predict future cardiovascular events and implied that CRP testing may thus have a major adjunctive role in the global assessment of cardiovascular risk over and above the already used Framingham risk score (Tables 4,5). However this strong association does not seem to hold in all studies after adjusting for a number of potential confounders. It is still possible that these discrepancies reflect differences in the studied endpoints or the confounding effect of medications usually administered in patients with CAD. Indeed, in the Physicians Health Study aspirin reduced the levels of plasma CRP in apparently healthy men and this effect was associated with a reduction in the risk of a first myocardial infarction\textsuperscript{35}. In addition, data from the CARE trial showed that patients with evidence of low grade vascular inflammation as measured by increased levels of CRP and serum amyloid A had more than 50% reduction in recurrent events while receiving pravastatin therapy\textsuperscript{36}. Randomised controlled trials are required to explore further
whether a drug approach targeting CRP will be a reasonable adjunctive treatment for patients with CAD.

**Conclusion**

In recent years the understanding of the pathophysiology of CAD has evolved enormously. Current evidence supports the central role of endothelium and inflammation in all phases of atherosclerotic process and clinical studies have demonstrated their prognostic potential for the development of ischemic events and for adverse outcome following acute coronary syndromes. Reduction in inflammatory levels and improving endothelial function by traditional and novel therapeutic strategies was associated with a proportional reduction in cardiovascular events. However, the identification of a single putative trigger for acute coronary syndrome seems unlikely in a disease with diverse aetiology and such a complexity in presentation of clinical symptoms. Further studies are needed to evaluate whether combination of therapies will provide additional anti-inflammatory effects and protection from cardiovascular events.
Reference List


36. Ridker PM, Rifai N, Pfeffer MA, Sacks FM, Moye LA, Goldman S et al. Inflammation, pravastatin, and the risk of coronary events after myocardial


47. Brevetti G, Silvestro A, Schiano V, Chiariello M. Endothelial dysfunction and cardiovascular risk prediction in peripheral arterial disease: additive value of


68. Kistorp C, Raymond I, Pedersen F, Gustafsson F, Faber J, Hildebrandt P. N-terminal pro-brain natriuretic peptide, C-reactive protein, and urinary albumin
levels as predictors of mortality and cardiovascular events in older adults. *JAMA* 2005;**293**:1609-16.


<table>
<thead>
<tr>
<th>Author</th>
<th>Patients</th>
<th>Study type and duration</th>
<th>Outcome studied</th>
<th>Predictive value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Al Suwaidi</td>
<td>157 patients with mild CAD</td>
<td>Retrospective (28 months)</td>
<td>Cardiac death, MI, CHF, CABG and PCI</td>
<td>+</td>
</tr>
<tr>
<td>Schachinger</td>
<td>147 patients with CAD</td>
<td>Retrospective (7.7 years)</td>
<td>MI, UA, ischemic stroke, CABG, PTCA, peripheral bypass</td>
<td>+</td>
</tr>
<tr>
<td>Hollenberg</td>
<td>73 orthotopic heart transplant recipients</td>
<td>Prospective (32 months)</td>
<td>Cardiac death</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Cardiac allograft vasculopathy</td>
<td></td>
</tr>
<tr>
<td>Halcox</td>
<td>308 patients referred for cardiac catheterization</td>
<td>Retrospective (46 months)</td>
<td>CVD death, MI, ischemic stroke, UA</td>
<td>+</td>
</tr>
<tr>
<td>Targonski</td>
<td>503 patients without angiographic CAD</td>
<td>Retrospective (90 months)</td>
<td>Cerebrovascular events</td>
<td>+</td>
</tr>
<tr>
<td>Schindler</td>
<td>130 patients with normal coronary angiograms</td>
<td>Prospective (45 months)</td>
<td>CVD death, UA, MI, PTCA, CABG, stroke, peripheral bypass</td>
<td>+</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Author</th>
<th>Patients</th>
<th>Study type and duration</th>
<th>Outcome studied</th>
<th>Predictive value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neunteufü17</td>
<td>73 patients with CAD</td>
<td>Retrospective (5 years)</td>
<td>Death, MI, PTCA, CABG</td>
<td>+</td>
</tr>
<tr>
<td>Heitzer18</td>
<td>281 patients with CAD</td>
<td>Prospective (4.5 years)</td>
<td>CVD, stroke, MI, CABG, PTCA, peripheral bypass</td>
<td>+</td>
</tr>
<tr>
<td>Perticone17</td>
<td>225 patients with hypertension</td>
<td>Prospective (32 months)</td>
<td>CVD death, MI, stroke, TIA, UA, CABG, PTCA, PVD</td>
<td>+</td>
</tr>
<tr>
<td>Gokce44</td>
<td>187 patients undergoing vascular surgery</td>
<td>Prospective (30 months)</td>
<td>CVD death, MI, UA, stroke</td>
<td>+</td>
</tr>
<tr>
<td>Modena45</td>
<td>400 hypertensive postmenopausal women</td>
<td>Prospective (67 months)</td>
<td>CVD event</td>
<td>+</td>
</tr>
<tr>
<td>Gokce46</td>
<td>199 patients undergoing vascular surgery</td>
<td>Prospective (1.2 years)</td>
<td>CVD death, MI, UA, stroke</td>
<td>+</td>
</tr>
<tr>
<td>Brevetti47</td>
<td>131 patients with peripheral vascular disease</td>
<td>23 months</td>
<td>CVD death, MI, Coronary revascularization, UA, stroke, TIA,</td>
<td>+</td>
</tr>
<tr>
<td>Chan48</td>
<td>152 coronary patients</td>
<td>34 months</td>
<td>CVD death, MI, Coronary revascularisation, UA, Stroke, TIA, Carotid endarterectomy</td>
<td>+</td>
</tr>
<tr>
<td>Fathi49</td>
<td>444 patients at risk of coronary events</td>
<td>24 months</td>
<td>Cardiovascular death, MI, Stroke, Revascularization</td>
<td>–</td>
</tr>
</tbody>
</table>

Table 3: Relationship between IL6, myeloperoxidase and CD40 and cardiovascular risk

<table>
<thead>
<tr>
<th>Inflammatory biomarkers</th>
<th>Predictive value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL6</td>
<td>Early marker for outcome in acute ischemic stroke&lt;sup&gt;50&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Adverse in hospital prognosis in ACS patients&lt;sup&gt;51&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Increased mortality in unstable CAD&lt;sup&gt;52, 53&lt;/sup&gt;</td>
</tr>
<tr>
<td>MPO</td>
<td>Increased risk for cardiovascular events&lt;sup&gt;54, 55&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Risk of recurrent cardiovascular events&lt;sup&gt;56, 57&lt;/sup&gt;</td>
</tr>
<tr>
<td>CD40</td>
<td>Independent increased risk of major cardiovascular events&lt;sup&gt;54, 58&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

**Abbreviations:** AIS: acute ischemic stroke, MPO: myeloperoxidase, IL-6: interleukin 6, ACS: acute coronary syndrome, CAD: coronary artery disease
<table>
<thead>
<tr>
<th>Author</th>
<th>No of patients</th>
<th>Yrs of follow up</th>
<th>Endpoint measured</th>
<th>Predictive value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agewall et al</td>
<td>131 (56-77yrs)</td>
<td>3 yrs</td>
<td>Fatal &amp; non fatal MI, SCD</td>
<td>+</td>
</tr>
<tr>
<td>Koenig et al</td>
<td>936 (45-64yrs)</td>
<td>8.2 yrs</td>
<td>Fatal or non fatal AMI</td>
<td>+</td>
</tr>
<tr>
<td>Jager et al</td>
<td>631 (50-70 yrs)</td>
<td>5 yrs</td>
<td>CVD death ICD</td>
<td>+</td>
</tr>
<tr>
<td>Ridker et al</td>
<td>5742 (45-73yrs)</td>
<td>5 yrs</td>
<td>Non fatal MI, UA, SCD</td>
<td>+</td>
</tr>
<tr>
<td>Rost et al</td>
<td>1462 (59-91yrs)</td>
<td>12-14 yrs</td>
<td>First ischemic stroke, TIA</td>
<td>+</td>
</tr>
<tr>
<td>Harris et al</td>
<td>675 (above 65yrs)</td>
<td>4.6 yrs</td>
<td>CVD death, ICD</td>
<td>–</td>
</tr>
<tr>
<td>Mendall et al</td>
<td>1239 (45-59yrs)</td>
<td>13.7 yrs</td>
<td>First fatal or non fatal IHD</td>
<td>–</td>
</tr>
<tr>
<td>Lowe et al</td>
<td>1595 (49-67yrs)</td>
<td>6.25 yrs</td>
<td>First fatal or non fatal IHD</td>
<td>–</td>
</tr>
<tr>
<td>Piro et al</td>
<td>2037 (35-64yrs)</td>
<td>5.2 yrs</td>
<td>Angina, CI, non fatal MI, coronary death</td>
<td>–</td>
</tr>
<tr>
<td>Strandberg</td>
<td>455 (75-85yrs)</td>
<td>10 yrs</td>
<td>CVD mortality</td>
<td>–</td>
</tr>
<tr>
<td>Kirstop et al</td>
<td>764 (50-89 yrs)</td>
<td>5 yrs</td>
<td>CVD mortality and first major CV event</td>
<td>–</td>
</tr>
</tbody>
</table>

Table 4: Nested case control studies examining relationship between CRP and CVD

<table>
<thead>
<tr>
<th>Author</th>
<th>Study population/ Age</th>
<th>Follow-up period</th>
<th>Endpoint</th>
<th>Predictive value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albert et al</td>
<td>289 (97 men cases) 40-84 yrs</td>
<td>17 yrs</td>
<td>SCD</td>
<td>+</td>
</tr>
<tr>
<td>Danesh et al</td>
<td>1531 (506 men cases) 40-59 yrs</td>
<td>9.5 yrs</td>
<td>Fatal CHD, non fatal MI</td>
<td>+</td>
</tr>
<tr>
<td>Folsom et al</td>
<td>1205 (615 cases) 45-64 yrs</td>
<td>3.6-4.3 yrs</td>
<td>MI, CHD, death, revascularization</td>
<td>+</td>
</tr>
<tr>
<td>Gram et al</td>
<td>391 (133 cases) &gt;40 yrs</td>
<td>7-15 yrs</td>
<td>MI, CHD</td>
<td>–</td>
</tr>
<tr>
<td>Gussekloo et al</td>
<td>163 (80 cases) &gt;85 yrs</td>
<td>&lt;5 yrs</td>
<td>Stroke death</td>
<td>+</td>
</tr>
<tr>
<td>Kervinen et al</td>
<td>300 (150 cases) 40-55 yrs</td>
<td>&lt;17 yrs</td>
<td>MI or coronary death</td>
<td>+</td>
</tr>
<tr>
<td>Kuller et al</td>
<td>444 (148 cases) 35-57 yrs</td>
<td>&lt;17 yrs</td>
<td>CHD mortality</td>
<td>+</td>
</tr>
<tr>
<td>Roivainen et al</td>
<td>430 (215 cases) 48 yrs</td>
<td>&lt;8.5 yrs</td>
<td>MI or coronary death</td>
<td>+</td>
</tr>
<tr>
<td>Packard et al</td>
<td>1740 (580 cases) 56.8 (5.2) yrs</td>
<td>&lt;6 yrs</td>
<td>Fatal CHD, non fatal MI</td>
<td>+</td>
</tr>
<tr>
<td>Ridker et al</td>
<td>789 (246 men cases) 40-84 yrs</td>
<td>&lt;14 yrs</td>
<td>MI</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>697 (154 men cases) 40-84 yrs</td>
<td></td>
<td>Ischemic stroke</td>
<td></td>
</tr>
<tr>
<td>Ridker et al</td>
<td>366 (122 women cases) 59.3(8.4)</td>
<td>&lt;3 yrs</td>
<td>MI, stroke, PTCA, CABG, CVD death</td>
<td>+</td>
</tr>
<tr>
<td>Sakkinen et al</td>
<td>1717 (369 men cases) 45-68</td>
<td>20 yrs</td>
<td>MI</td>
<td>+</td>
</tr>
<tr>
<td>Tice et al</td>
<td>394 (52 women cases) &gt;65 yrs</td>
<td>6 yrs</td>
<td>CVD death</td>
<td>+</td>
</tr>
<tr>
<td>Tracy et al</td>
<td>292 (146 cases) &gt;65 yrs</td>
<td>&lt;3 yrs</td>
<td>MI, AP, CHD death</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>382 (237 cases) 65-79 yrs</td>
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</table>
Legends to figures

Figure 1: Leukocyte-endothelial cell interactions in atherosclerosis. Selectins mediate the initial rolling of leukocytes on the endothelial surface. Subsequent adhesion requires interaction between integrins expressed on leukocytes (leukocyte function-associated antigen (LFA-1) and very late antigen (VLA)-4) and immunoglobulin like molecules (vascular cell adhesion molecule (VCAM-1), intercellular cell adhesion molecule (ICAM-1) on the endothelium. The final step then is the transmigration of leukocytes in the intima. Abbreviations: PSGL-1: P-selectin glycoprotein ligand-1.
STATEMENT

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