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Scientific Update™

Inflammation, Ischemia, and Angiogenesis: New Therapeutic Targets in Cardiovascular Disease

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The relationship between dysfunction of the endothelium and the development of cardiovascular disease (CVD) is well-established. Mediators of the progression of disease include oxidative stress, endothelial dysfunction, and inflammation. It is possible to interrupt this progression using pharmacological, interventional, and other cardioprotective treatments that act on these mediators. Recently completed studies have demonstrated improvement in endothelial dysfunction in patients with CVD who were treated with angiotensin-converting enzyme (ACE) inhibitors, particularly those with high tissue affinity (eg, quinapril). Tissue ACE inhibition leads to a beneficial effect on endothelial dysfunction by reversing associated nitric oxide (NO) and bradykinin deficiency and angiotensin-II (A-II) excess; the latter conditions are important mediators of inflammation, vasoconstriction, vascular remodelling, plaque rupture, and thrombosis.

The cardiovascular continuum: oxidative stress, endothelial dysfunction, inflammation, and angiogenesis

Cardiovascular disease is a continuum of events (Figure 1) and central to this disease continuum is the vascular endothelium.[1] The endothelium plays a central role in maintaining normal vascular function and structure. Evidence suggests that normal endothelial function is predicated on a homeostatic balance between reactive nitrogen species (eg, NO) and reactive oxygen species ([ROS]; eg, superoxide anion). Endothelial cell dysfunction is characterized by an impairment in the capacity of a vessel to dilate and promote an increase in blood flow. This impairment reflects the enhanced catabolism of NO caused by the increased generation of ROS. In addition to its role as an endothelium-derived vasodilator, NO appears to be an endogenous inhibitor of vascular smooth muscle cell growth and migration, transcription factors, and expression of pro-inflammatory molecules. Hence, the two characteristic features of endothelial dysfunction — impaired vasorelaxation and increased adhesiveness — appear to result, in part, from a decrease in NO bioactivity. This relative deficiency in NO activity predisposes vascular tissue to atherosclerotic lesion formation.

Recent evidence indicates that dyslipidemia, hypertension, diabetes, and other cardiovascular risk factors can increase oxidative stress in the vessel wall, especially in the endothelial cells. Oxidative stress induces the expression of redox-sensitive genes (eg, cytokines and vascular cell adhesion molecule-1 [VCAM-1]) that stimulate chemo-attraction and adhesion of leukocytes onto the vessel wall.

Recent data also demonstrate that A-II is a major inducer of vascular oxidative stress, independent of its hemodynamic effect. Thus, A-II increases vascular superoxide anion production, VCAM expression, and leukocyte adhesion, which are key early events in atherogenesis. Tissue ACE in A-II production is increased in early and late atherosclerotic lesions. Accordingly, a positive feedback mechanism involving tissue A-II, decreased NO production, increased oxidative stress, and endothelial dysfunction may play a key role in the pathogenesis of vascular disease.

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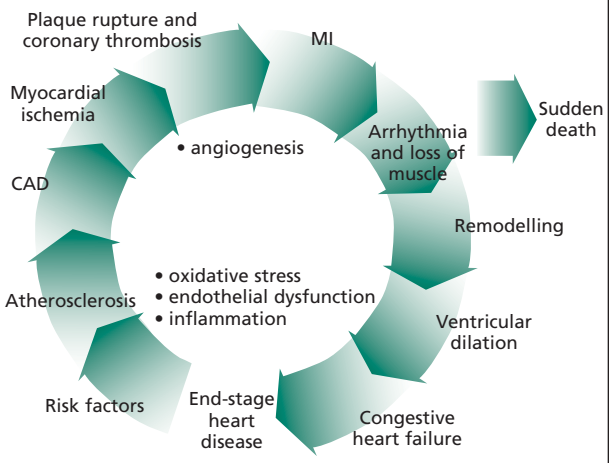
Figure 1: Cardiovascular disease continuum



Adapted from Dzau VJ and Braunwald E[1]

Endothelial dysfunction not only impairs vasodilation, thus reducing coronary reserve, but also attenuates the angiogenic response of the myocardium to chronic ischemia. Recent data suggest that decreased NO activity and possibly increased A-II inhibit angiogenesis in response to vascular endothelial growth factor (VEGF). Indeed, inhibition of tissue ACE stimulates angiogenesis in response to ischemia. Taken together, these data suggest that the balance between tissue A-II and NO determines the long-term myocardial angiogenic compensation in coronary artery disease (Figure 2).[1]

Inflammation, endothelial dysfunction, and coronary risk

Several lines of basic research indicate that inflammation in the vessel wall plays a critical role in the initiation and progression of atherosclerosis and in the conversion of stable

Figure 2: The pathological mechanisms associated with atherosclerosis

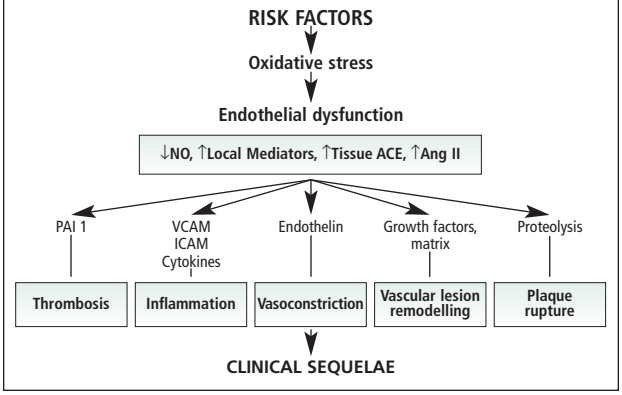
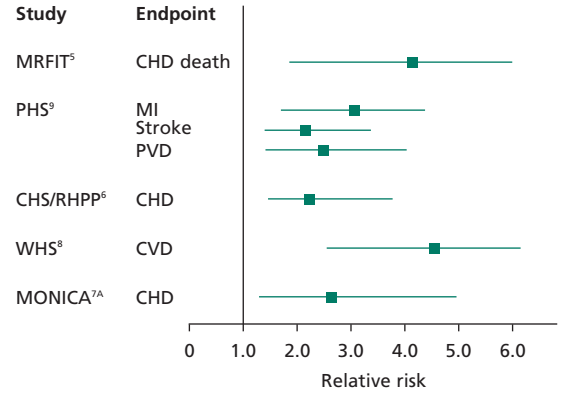


Figure 3: Prospective studies of hs-CRP as a risk factor for future cardiovascular disease in populations free of clinical disease



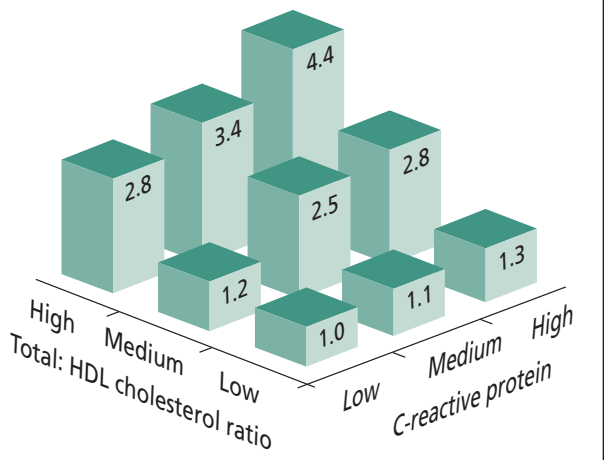
plaques to unstable lesions.[2] With respect to clinical practice, recent prospective data indicate that markers of inflammation can be used to predict the future occurrence of cardiovascular events. In particular, high-sensitivity (hs) assays for C-reactive protein (CRP) capable of detecting low-grade "microinflammation" appear to provide a novel method of detecting pre-clinical atherosclerosis in both stable and unstable patients (Figure 3).[3, 4, 5, 6, 7,7A]

For example, data from healthy middle-aged men[3] and women[8] demonstrate that those with elevated baseline risks of CRP have significantly increased risk of future myocardial infarction (MI) and stroke, an effect independent of traditional cardiovascular risk factors. Moreover, the assessment of CRP appears to add to the predictive value of total and HDL cholesterol (Figure 4), data that raise the possibility that this marker of inflammation may have clinical utility in both primary and secondary prevention.[9] Recent data also indicate that preventive therapies such as ASA[3] and HMG-CoA reductase inhibition[10] may modify the effects of inflammation on vascular risk. Whether elevations of CRP reflect underlying lipid oxidation, increased release of vascular cytokines, or alterations in cellular adhesion molecule function is under investigation. Some studies indicate, however, that baseline levels of soluble adhesion molecules such as intracellular adhesion molecule (ICAM)-1, E-selectin, and interleukin-6 are elevated among individuals at risk for future coronary events.[11,12]

Angiotensin as a mediator of coronary artery disease

There is also evidence that an increase in the plasma level of renin is associated with a higher risk of MI.[13] In contrast, ACE inhibition appears to reduce the risk of recurrent MI as suggested by data derived from secondary analyses of the

Figure 4: Relative risks of future MI as predicted by the simultaneous assessment of hs-CRP and a standard lipid profile



Adapted from Ridker PM, et al[9]

SAVE[14] and SOLVD[15] trials. In addition, polymorphisms in the genes encoding ACE and the angiotensin II AT_1 receptor have been shown to be potent risk factors for MI.[16,17]

There may be an important interaction between the activated renin-angiotensin system and proinflammatory cytokines in acute coronary syndromes. A-II is known to interact with a number of receptor subtypes found in vascular smooth muscle cells. By binding to the AT-I receptor subtype, A-II elicits the activation of various biochemical pathways leading to cell proliferation and hypertrophy, vasoconstriction, and inflammation.

Effects on vascular dysfunction: A review of clinical trials with ACE inhibitors

In the healthy state with normal endothelial function, vascular ACE maintains a balance between constrictor and dilator substances, so that blood vessel tone is minimal. In the pathological state with endothelial dysfunction, however, the vascular ACE system is upregulated to modulate the formation of excess local A-II. Blocking these effects with ACE inhibitors has become an attractive therapeutic target. While several small clinical studies suggest that ACE inhibition improves endothelial function in patients with CAD, the most compelling data come from recent studies using ACE inhibitors with more potent tissue effects. For example, Hornig, et al[18] demonstrated that quinaprilat – but not enalaprilat – improved flow-mediated dilation in congestive heart failure patients. Similarly, in the QUO VADIS study,[19] quinapril – but not captopril – improved vascular response and significantly reduced ischemic events. In a small cohort (n=149) of post-bypass patients randomized to treatment with either quinapril or placebo, there were fewer ischemic events (MI, recurrent angina, coronary angioplasty/repeat bypass surgery, stroke/transient ischemic attack) in quinapril-treated patients (4% versus 18%, p=0.03). The TREND study, conducted in patients with CAD and preserved left ventricular function,[20] showed that quinapril improved coronary endothelial function independent of blood pressure changes. The BANFF trial[21] found that brachial artery endothelial function in patients with CAD improved with quinapril, but not with enalapril, losartan, or amlodipine.

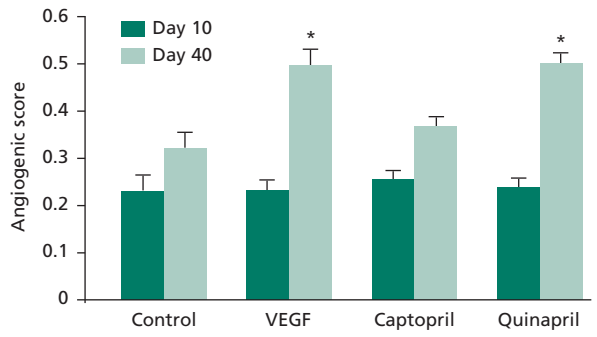
In an abstract presented at the ACC Scientific Session, Uehata, et al[22] investigated the precise mechanisms underlying the benefit of quinapril on endothelial dysfunction. They studied 16 hypertensive patients treated with quinapril (20 mg daily) and 10 patients treated with the calcium channel blocker nitrendipine (10 mg daily). Despite similar blood pressure reductions with both active antihypertensive agents, there were marked differences in flow-mediated dilation of the brachial artery (as measured by high resolution ultrasound) and in plasma levels of bradykinin. Flow-mediated dilation improved following quinapril, but not nitrendipine (6.7 ± 3.6% versus 2.0 ± 3.6%, p<0.001). While a slight increase in bradykinin levels was noted following quinapril, but not nitrendipine treatment, this increase did not correlate with the increase in flow-mediated dilation (r=0.14). Thus, endothelial dysfunction in this small group of hypertensive patients was restored only by quinapril. Since reductions in blood pressure and an increase in plasma bradykinin did not modulate this beneficial effect, these results suggest that local tissue ACE inhibition may be independent of its inhibition of bradykinin breakdown or its antihypertensive effect.

ACE inhibition and angiogenesis

The identification of angiogenic growth factors has generated the opportunity for novel therapies in the treatment of a variety of diseases, including cardiovascular disease. Indeed, clinical trials of therapeutic angiogenesis have already been initiated in patients with myocardial ischemia and peripheral vascular disease. These include trials of recombinant-protein therapy as well as gene transfer. It has been demonstrated that ACE inhibition may favourably affect endothelial function, suggesting that ACE inhibition might have similarly favourable effects on angiogenesis.

In a study investigating the effect of quinaprilat and captopril in a rabbit model of chronic hindlimb ischemia, data showed that both VEGF and quinaprilat stimulated angiogenesis, extending the vascular network to a higher degree than in spontaneous or captopril-treated animals (Figure 5). This raises the hypothesis that captopril's apparent inability to stimulate angiogenesis may be linked to its relatively low inhibitory effect in tissues. In contrast,

Figure 5: ACE inhibition and angiogenesis



*p<0.05 compared with control and captopril

quinapril's high tissue-affinity may lead to greater upregulation of NO in the vascular endothelium. Upregulation of NO by VEGF or quinapril may lead to a number of vasculoprotective effects.

Conclusion

Endothelial dysfunction is an early and frequent manifestation of atherosclerotic heart disease. Administration of ACE inhibitors, particularly those with higher affinity for tissue ACE (eg, quinapril) appears to be an effective means of altering endothelial dysfunction and may also play a role in angiogenesis. Whether such treatment specifically targeted at endothelial dysfunction in patients with coronary artery disease, hypertension, and congestive heart failure translates into better long-term clinical outcome awaits further large-scale trial results.

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