**Do ACE inhibitors modulate atherosclerosis?**

**Atherosclerosis and the ACE–angiotensin II–bradykinin system**

The disease process known as atherosclerosis can now be seen to cover a spectrum extending from subclinical endothelial dysfunction, via coronary artery stenosis associated with myocardial ischaemia and infarction, to heart failure. At the sub-clinical end of this spectrum, it is now recognized that there is a characteristic loss of endothelium-dependent relaxation, seen in both animal models and in human coronary arteries, which represents a marker for subsequent structural disease. Atherosclerosis itself is a fibroproliferative and inflammatory process occurring in response to a variety of vascular 'insults', including particularly hypercholesterolaemia, hypertension, diabetes and smoking (Fig. 1). Early lesions are the result of an accumulation of lipids, often in macrophages, within the arterial intima. There is subsequently progression with the accumulation of further macrophages and smooth muscle cells, which proliferate and then migrate into the intimal layer. Finally, these lesions acquire a superficial layer of connective tissue mixed with smooth muscle cells to become fibrous plaques. Myocardial ischaemia and infarction occur as a result of these obstructive lesions together with thrombus formation and localized vasoconstriction. Angiotensin converting enzyme (ACE) inhibitors are well equipped to interfere with this pathophysiological machinery at several levels. ACE inhibitors have two main mechanisms of action: the simultaneous prevention of angiotensin II production and bradykinin degradation (Fig. 2).

Several strands of evidence implicate the ACE/angiotensin II/bradykinin system as having a role in the atherosclerotic process. There is persuasive, although largely circumstantial, clinical evidence. Plasma renin levels, for example, have been positively correlated with risk of myocardial infarction in both normotensive subjects and in patients with hypertension. In addition, the DD genotype for ACE is associated with an increased risk of myocardial infarction, regardless of other risk factors. The same polymorphism has also been shown to be associated with the presence and extent of coronary artery disease in both Welsh and Japanese populations. Preliminary data also suggest that the DD genotype is associated with augmented neurohumoral activation and cardiac dilatation following myocardial infarction. There is also a large volume of laboratory-derived data. The activity of ACE itself has now unequivocally been shown to be present at tissue level, as well as in the circulation. Specifically, ACE activity has been demonstrated in macrophages and vascular smooth muscle cells in atherosclerotic lesions. Furthermore, messenger RNA coding for angiotensinogen, the angiotensin precursor, is also identifiable in all three layers of the arterial vessel wall, and is also detectable in neointimal lesions, thus providing further evidence for the existence and importance of local vascular ACE/angiotensin II/bradykinin systems. Angiotensin II binds to receptors on vascular smooth muscle cells and stimulates contraction as a result of an increase in intracellular free calcium (Fig. 2). Binding initiates the activity of several intracellular secondary messenger systems, including phospholipase C and subsequently protein kinase C. Via these and other, calcium-sensitive, mechanisms, angiotensin II stimulates the production of autocrine–paracrine growth factors, including basic fibroblast growth factor and platelet-derived growth factor, both of which mediate smooth muscle cell mitogenesis and proliferation, and the anti-proliferative transforming growth factor-β. An imbalance of these factors, for example as a result of chronic endothelial injury, can induce an increase in local smooth muscle division and proliferation. Angiotensin II also stimulates the release of the potent vasoconstrictor and mitogenic peptide, endothelin-1, from endothelial cells. There is also evidence that angiotensin II stimulates the release of prothrombotic agents including plasminogen activator inhibitor (PAI-1). By contrast, bradykinin stimulates release of endothelially-derived nitric oxide and prostacyclin, whose activation of secondary messenger systems in vascular smooth muscle cells leads to an increase in both cAMP and cGMP concentrations, causing not only vasorelaxation, but also antiproliferative effects on vascular smooth muscle as well as potent anti-aggregatory effects on platelets.
Figure 1  Atherosclerosis is thought to be a response to chronic vascular injury from a variety of common causes that can all produce endothelial dysfunction. Several of the subsequent inflammatory and proliferative responses involve the ACE/angiotensin II/bradykinin system. There is also evidence that local inflammation itself can also initiate endothelial dysfunction. VSM=vascular smooth muscle.

Evidence that ACE inhibitors can modulate atherosclerosis

Experimental evidence suggests that in animal models of atherosclerosis it is possible to retard the development of atherosclerotic lesions by the administration of ACE inhibitors. For example, 9 months of captopril therapy in hyperlipidaemic rabbits reduced the total aortic intimal area affected by atheroma, as well as reducing the cellularity and cholesterol content of the lesions themselves\(^\text{[13]}\). This effect was independent of blood pressure and serum lipid profile. Similar results were obtained in cholesterol-fed rabbits when they were treated by enalapril, but importantly not when they were given an angiotensin II receptor antagonist\(^\text{[14]}\). The same attenuation in the development of atherosclerotic lesions has also been reported in the coronary arteries of cholesterol-fed monkeys after captopril treatment\(^\text{[15]}\). Clearly, therefore, the structural end-point of the atherosclerotic process can be retarded/attenuated by ACE inhibition in these animal models. However, can this therapeutic regimen alter vasoreactivity, the marker of early atherosclerosis? In rabbits exposed to an atherogenic diet for 17 weeks, this question has been addressed by testing acetylcholine-induced, endothelium-dependent vasorelaxation of pre-constricted isolated aortic rings. The rings from control animals (i.e. no ACE inhibitor) exhibited severely impaired endothelium-dependent relaxation, whereas this dilation response was preserved in those animals treated with the ACE inhibitor, ramipril\(^\text{[16]}\). Further investigation implies that loss of endothelial nitric oxide production explains this phenomenon, thus supporting the hypothesis that endothelial dysfunction and injury represent an important component of the atherosclerotic process. It seems likely, in view of this evidence, together with the lack of effect of an angiotensin II receptor antagonist, that it is inhibition of bradykinin breakdown that confers this protection by the ACE inhibitors. Experimental animal data thus support the hypothesis that inhibition of ACE can modulate the pathophysiological mechanism of atherosclerosis. But...
Angiotensin converting enzyme mediates the conversion of angiotensin I to angiotensin II, and also the conversion of bradykinin to inactive metabolites. The activity of ACE inhibitors therefore results in reduced local levels of angiotensin II, but increased amounts of bradykinin. The net effect is to reduce local vasoconstriction, as well factors stimulating smooth muscle and fibroblast proliferation, and to increase local release of nitric oxide and prostacyclin which promote vasorelaxation, and inhibit platelet adhesion and aggregation. ET-1=endothelin-1; NO=nitric oxide; PGI₂=prostacyclin; Ca²⁺=intracellular free calcium; PLC=phospholipase C; PKC=protein kinase C; bFGF=basic fibroblast growth factor; PDGF=platelet-derived growth factor; TGF-β1=transforming growth factor β.

what about in man? In the TREND study[17], 129 patients who had single or double vessel coronary artery disease, for which they underwent non-surgical revascularization, were randomized to receive either quinapril 40 mg once daily or placebo for 6 months. One of their main coronary arteries had to contain no greater than 40% stenosis, and this vessel was then used as the target for the study of vasoactive response to acetylcholine, which, in order to qualify for the study, had to be constriction. Baseline responses were no different between the two groups. At 6 months, however, the degree of acetylcholine-induced constriction was significantly reduced in the ACE inhibitor group, but was unchanged in controls. For the first time, therefore, a double-blind, placebo-controlled study has demonstrated that ACE inhibition (albeit at a high dose) can favourably alter one of the functional markers of early atherosclerosis. Although this is a promising result, it is a long way from the two ideal therapeutic outcomes: namely, regression of established structural and functional atherosclerotic disease, or, even more attractively, the prevention of such lesions in the first place.

ACE inhibitors and the prevention of neointimal proliferation after PTCA

Following balloon angioplasty, a process of myointimal proliferation occurs at the site, which, in its more aggressive form, leads to restenosis. It is currently thought that this process represents a response to vascular injury, and in particular to an imbalance in the local concentration of growth promoters and inhibitors, vasodilators and pressor agents. The endothelium releases nitric oxide and prostacyclin, both potent vasodilators and anti-platelet molecules, as well as direct inhibitors of growth including heparan sulphate and transforming growth factor β. Endothelial damage and denudation at the time of angioplasty can therefore remove these antiproliferative forces, and also allow direct access of pro-inflammatory and growth-promoting factors to the underlying vascular smooth muscle. Angiotensin II, via basic fibroblast growth factor, is an important component of this part of the process. Simultaneously, platelet activation initiates release of serotonin, thromboxane, platelet-derived growth
factor which contribute to local vasoconstriiction, proliferation and thrombus formation\(^\text{[18]}\).

In some animal models of balloon-induced arterial injury, including rat carotid artery and rabbit iliac and carotid arteries, this myointimal response is suppressed by treatment with ACE inhibitors prior to injury\(^\text{[19]}\). This effect is almost certainly due to a bradykinin-mediated process, because it was not mimicked in one of these studies by the angiotensin II receptor antagonist, losartan\(^\text{[20]}\). Rakugi and colleagues have reported a correlation between residual levels of lesion ACE and the size of neointima formation in a rat carotid artery–balloon injury model\(^\text{[21]}\).

Clearly, ACE/angiotensin II/bradykinin systems are involved in this process. However, these ACE inhibitor properties are not reproduced in models of balloon injury involving larger animals such as pig and baboon\(^\text{[22]}\). More importantly, studies looking for evidence that ACE inhibitors can prevent restenosis after PTCA in humans have proved negative. In the MERCATOR study\(^\text{[23]}\), patients were randomized to receive cilazapril or placebo on the evening after PTCA. After 6 months treatment, there was no difference in the rate of clinical or angiographic restenosis. These findings were reinforced in the MARCATOR study\(^\text{[24]}\), which used a higher dose of ACE inhibitor, and in the as yet unpublished QUIET study (see below). There are several possible explanations for these inter-species differences. Firstly, the ACE inhibitor treatment was started after PTCA in the human studies, but before injury in the small animal experiments. Secondly, there is some evidence that the dose of ACE inhibitor required to suppress neointimal formation is higher than the antihypertensive dose\(^\text{[21]}\), and that the doses utilized in the two clinical studies were therefore too low. Thirdly, the local balance between angiotensin II, bradykinin and the proliferative and anti-proliferative growth factors is likely to differ between species both under normal conditions, and particularly following balloon dilatation. These explanations for the discrepancy between experimental and clinical data are all feasible and certainly not mutually exclusive. More evidence is therefore required from clinical studies that address specific questions such as whether treatment of patients with ACE inhibitors for some time before PTCA will significantly reduce restenosis rate. As long as the patients recruited into such a trial have no history of hypertension or heart failure, they could be randomized to ACE inhibitor or placebo (in addition to their standard anti-anginal treatment) at the time their name was added to a standardized PTCA waiting list. Further data regarding the effects of ACE Inhibition in patients with coronary disease and no heart failure will be provided by the multicentre EUROPA study.

### ACE inhibitors and heart failure: do they reduce ischaemia?

The benefits, both symptomatic and prognostic, of ACE inhibitors in the context of ischaemic heart failure have been unequivocally demonstrated in a large number of clinical trials conducted in patients with severe, moderate and mild heart failure (CONSENSUS-1, VHeFT-I, VHeFT- II, SOLVD–treatment arm), as well as in those with asymptomatic left ventricular dysfunction (SOLVD–prevention arm) and after acute myocardial infarction (ISIS-4, GISSI-3, SAVE, AIRE, SMILE, TRACE\(^\text{[25]}\)).

Excluding the effects on left ventricular function and remodelling, of particular interest is the apparent ability of ACE inhibitors to reduce the rates of reinfarction and recurrent ischaemia in this context. For example, the combined arms of the SOLVD study demonstrated a reduction in risk of myocardial infarction (either first or recurrent) of 23% and the risk of unstable angina by 20% in the enalapril group\(^\text{[26]}\). There was also a 25% reduction in recurrent myocardial infarction, as well as a significant reduction in the rate of revascularization (including PTCA and CABG) in the captopril group. In both AIRE and TRACE, there was a trend for a reduced risk of recurrent infarction, but there was no reduction at all in CONSENSUS-II, GISSI-3 or ISIS-4. Finally, the QUIET trial (Quinapril Ischaemic Events Trial), whose results are not yet published (but were presented at the European Society of Cardiology Meeting in Birmingham, U.K., 1996) recruited 1750 patients who were undergoing PTCA, and randomized them to either quinapril or placebo for 3 years\(^\text{[27]}\). At follow-up there was no statistically significant difference in the composite clinical end-point of cardiac death, myocardial infarction, resuscitated ventricular tachycardia/ventricular fibrillation, although there was a trend in favour of the ACE inhibitor group. Sub-group analysis also demonstrated a non-significant reduction in lesion progression at angiography. These data are therefore essentially negative in terms of benefit from this particular dose and type of ACE inhibitor. The same theoretical explanations for a lack of benefit can be raised as have already been discussed regarding neointimal proliferation post-PTCA. Again further clinical data are required.

Clearly, the therapeutic and prognostic potential for a medical treatment that could reduce the rate of recurrent ischaemia and infarction is enormous. In addition to the anti-proliferative and anti-inflammatory properties conferred by ACE inhibitor treatment that have been discussed above, there may be additional specific benefits in the setting...
of acute coronary syndromes because angiotensin II appears to stimulate the release of PAI-1, a prothrombotic agent, so that such therapy would be expected to inhibit thrombus formation, as discussed above. In addition, in one study of myocardial infarction survivors, the group treated with enalapril had lower plasma concentrations of tissue type plasminogen activator antigen than those treated with placebo[28], a situation associated with better prognosis in patients with established coronary heart disease. Once again, more clinical research is required to understand the role of the ACE/bradykinin/angiotensin II system in clotting mechanisms associated with ischaemic syndromes.

Summary

The ACE/angiotensin II/bradykinin system is inextricably linked to some of the processes that contribute to the generation of atherosclerosis at genetic, molecular, biochemical and pharmacological levels. There is a large body of laboratory-derived experimental data that suggests that inhibition of ACE activity has antiproliferative, anti-inflammatory and vasodilatory effects that can modulate this atherosclerotic process from the earliest form of endothelial dysfunction, to delay of lesion formation in primary atherosclerosis or in myointimal proliferation after PTCA. The clinical evidence for these potential benefits is so far sparse. There are several possible explanations for these discrepancies. Firstly, the role of the ACE/bradykinin/angiotensin II system in the local vascular response to either the primary process of atherosclerosis, or to the injury induced by balloon angioplasty is likely to vary between species and models. Secondly, there is a tendency to ensure the presence of ACE inhibitor in high concentration before or during the vascular insult in animal models, whereas this has not been the case in the clinical studies of post-PTCA restenosis. Whilst the animal studies therefore offer potentially valuable insights into the mechanics of local vascular response, the ability of ACE inhibitors to interfere with such mechanisms now needs to be tested in clinical trials that are each aimed at precisely answering specific questions. The experimental data so far lend considerable support to the fact that drugs acting solely by interference with the angiotensin II receptor complex are at a theoretical disadvantage, when compared with ACE inhibitors, since the former would be expected to have little effect on bradykinin-mediated activities.

To the established benefits of ACE inhibitors in left ventricular dysfunction, and the interesting possibility that there may be an anti-ischaemic action in these circumstances, we may add the promise of the TREND study. In the coming years, there is an urgent requirement for intensive investigation into the ability of ACE inhibitors to modulate the various stages of the atherosclerotic spectrum. For now though, the jury remains out.

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References


