Effects of ACE inhibitors on coronary atherosclerosis and restenosis

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The renin-angiotensin system was originally regarded as an endocrine system modulating vascular tone and salt and water balance by producing angiotensin II in the circulation and the lungs. More recently, independent tissue bound renin-angiotensin systems have been identified that produce angiotensin II locally in various tissues, including the heart and blood vessels.¹⁻³ Local production of angiotensin II within the blood vessel wall, in addition to stimulating vasoconstriction, may promote smooth muscle growth and proliferation and contribute to the vascular hypertrophy that accompanies chronic hypertension.⁴ Increasing evidence suggests that angiotensin II may also be active in the pathogenesis of other vascular disorders, particularly atheromatous disease. Because the endocrine and tissue production of angiotensin II is amenable to inhibition by angiotensin converting enzyme (ACE) inhibitors, the potential exists to modify the progression of vascular disease pharmacologically.⁵⁻⁷ In this article we will review the evidence that implicates the renin-angiotensin system in the pathogenesis of atheromatous disease and will speculate on the therapeutic role of ACE inhibitors for this condition.

Animal studies

ENDOTHELIAL DYSFUNCTION

The link between atherosclerosis and endothelial dysfunction is well established. Thus, Harrison *et al* showed that in the iliac arteries of normal monkeys acetylcholine stimulates release of endothelium derived relaxation factor and acts as a vasodilator.⁸ In monkeys fed a high cholesterol, atherogenic diet, on the other hand, considerable intimal thickening occurs and endothelial function becomes impaired as reflected by noticeable reductions in the vasodilator response to acetylcholine. Importantly, however, the endothelial dysfunction is reversible and the vasodilator response to acetylcholine normalises after regression of intimal thickening in monkeys switched to a non-atherogenic diet.

ACE inhibitors may also improve endothelial function in atherosclerotic arteries. Becker *et al* found that ramipril given to rabbits fed an atherosclerotic diet preserved the vasodilator response to acetylcholine when compared with atherosclerotic control rabbits not given the ACE inhibitor.⁹ These investigators also showed a dose-dependent increase in cyclic guanine monophosphate concentrations in the aortic segments of the rabbits

treated with ramipril compared with the controls. Cyclic guanine monophosphate concentration in vascular smooth muscle is a marker of release of endothelium derived relaxation factor by the endothelium; the data therefore confirm the value of ACE inhibition for preserving endothelial function in atherosclerotic arteries.

INTIMAL PROLIFERATION AND HYPERTROPHY AFTER ARTERIAL INJURY

Angiotensin II is a potent stimulus for smooth muscle cell growth and proliferation and its part in the atherosclerotic process is a subject of considerable interest.¹⁰ Powell *et al* subjected normotensive rats to balloon injury to the left internal carotid artery by means of a catheter.¹¹ This produces traumatic endothelial denudation of the vessel wall and an injury response which includes migration and proliferation of smooth muscle cells in the arterial intima and synthesis of extracellular protein. These investigators found that treatment with ACE inhibitors produced considerable attenuation of the injury response. Thus, rats treated continuously with cilazapril or captopril had significantly less neointimal formation during the first 14 days after balloon injury compared with untreated control animals, presumably because of suppression of local angiotensin II activity by the ACE inhibitor and removal of the stimulus for smooth muscle migration and proliferation.

If the protective effects of ACE inhibitors against vascular smooth muscle responses to balloon injury are mediated locally by inhibition of the tissue renin-angiotensin system, then treatment with these drugs would be expected to lead to reductions in the density of ACE within the vessel wall. This hypothesis was tested by Johnston *et al*, who subjected spontaneously hypertensive rats to balloon injury resulting in denudation of the aortic endothelium.¹² The density of ACE in the injured arterial segment was measured at necropsy by in vitro autoradiography. The autoradiographs showed an increase in ACE density (and neointimal formation) within the arterial segment eight days after balloon injury, but this was not seen in animals treated with quinapril, an ACE inhibitor that binds particularly strongly to vascular ACE.⁶ These findings suggest that local activation of the renin-angiotensin system is part of the neointimal response to vascular injury, and they raise the possibility that ACE inhibitors such as quinapril may be useful for reducing the neointimal response.

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Clinical trials

Clinical trials investigating the influence of ACE inhibitors on the progression of coronary artery disease have not yet been reported. In progress, however, is the quinapril ischaemic event trial (QUIET), a prospective double blind, placebo controlled study designed to assess the ability of quinapril to reduce the rate of ischaemic events and to slow the progression of angiographic coronary artery disease in a normotensive, normolipidaemic population without left ventricular dysfunction.¹³ Quinapril was selected for this trial because it binds strongly to the tissue ACE within the vascular wall and may, therefore, be well suited to modify endothelial and neointimal changes that are driven by angiotensin II and form part of the atherosclerotic process.⁶ The results of QUIET will not be available until after the three year treatment phase has finished (projected for 1995). Meanwhile, clinical evidence that ACE inhibition may influence progression of coronary artery disease remains hypothetical and is based on analysis of the results of three major randomised trials (figure).

MULTICENTRE EUROPEAN RESEARCH TRIAL WITH CILAZAPRIL AFTER ANGIOPLASTY TO PREVENT TRANSLUMINAL CORONARY OBSTRUCTION AND RESTENOSIS (MERCATOR)

The antiproliferative effects of cilazapril in the rat model of intimal balloon injury suggested a potential role for the drug for prevention of restenosis after coronary angioplasty. The MERCATOR investigators tested this hypothesis in 735 patients after successful angioplasty. They found that cilazapril did not prevent coronary restenosis at six months, patients randomly allocated to the ACE inhibitor showing reductions of minimal lumen diameter between angiograms after angioplasty and those at follow up of -0.27 (0.51) mm compared with -0.29 (0.49) mm in the control group.¹⁴ The failure of cilazapril to prevent restenosis was disappointing, particularly in view of the encouraging results

in animals. However, the low dose of cilazapril (5 mg twice daily) chosen for this study may have been insufficient. Thus, although 5 mg cilazapril in humans reduces plasma ACE activity to almost undetectable amounts for up to eight hours during short term treatment,¹⁵ inhibition of neointima formation is dose-dependent; in addition, the data of Powell *et al* in rats suggest that a higher dose may be necessary to influence the process of restenosis.¹⁶

Notwithstanding the low dose of cilazapril used in MERCATOR, it should not be inferred that because ACE inhibition has no effect on restenosis it will have no effect on the progression of coronary disease. We emphasise that MERCATOR was a restenosis trial and quite apart from the fact that restenosis is not a clinical surrogate of atherosclerotic disease, the six months of follow up was scarcely long enough to detect differences in the progression of disease between the two groups. Nevertheless, in MERCATOR the active treatment group showed a trend towards fewer clinical cardiac end points at 12 months, such as death, myocardial infarction, and coronary revascularisation (figure).¹⁷ It is possible to speculate, therefore, that had the dose of ACE inhibitor been higher and the treatment period longer, a more substantial effect on these cardiac end points might have been seen.

STUDIES OF LEFT VENTRICULAR DYSFUNCTION (SOLVD)

After publication of the results of the cooperative north Scandinavian enalapril survival study (CONSENSUS) showing that treatment with enalapril could improve survival in patients with advanced heart failure,¹⁸ interest turned to the potential benefits of ACE inhibition in patients with less severe disease. The SOLVD studies were designed to assess this potential by randomly allocating 2569 patients with predominantly class II or III heart failure according to the New York Heart Association's classification ("treatment trial") and 4228 patients with predominantly class I heart failure ("prevention trial") to treatment with enalapril or placebo.^{19 20} Follow up in both trials was for four years. The treatment trial confirmed that enalapril significantly reduced mortality in patients with symptomatic (class II to III) heart failure. Improved outcome using a combined end point (death and admission to hospital for heart failure) was also observed for the asymptomatic patients recruited in the prevention trial.

The SOLVD trials were not designed to evaluate the effects of ACE inhibition on the progression of coronary artery disease; recurrent myocardial infarction was recorded as part of the safety data for this trial as ACE inhibitors might cause hypotension and increase the rate of vascular occlusion. Surprisingly, enalapril reduced not only the frequency of myocardial infarction but also admission for unstable angina, even though about 30% of the patients did not have (or were not known to have) ischaemic heart disease (figure). Again, therefore, the SOLVD

Percentage reduction in ischaemic events compared with placebo in MERCATOR,¹⁴ SOLVD,^{19 20} and SAVE²⁴ trials. a, Admission to hospital for congestive heart failure; b, development of congestive heart failure; CABG, coronary artery bypass grafting; PTCA, percutaneous transluminal coronary angioplasty. Reproduced with permission of Texter *et al*.¹³

trials have led to speculation that ACE inhibition may protect against cardiovascular events by favourably influencing the progression of coronary artery disease in susceptible people.

SURVIVAL AND VENTRICULAR ENLARGEMENT (SAVE) TRIAL

Laboratory and clinical studies of acute myocardial infarction have shown that ACE inhibition can attenuate left ventricular dilatation and remodelling.²¹⁻²³ The SAVE trial tested the hypothesis that this might reduce morbidity and mortality during long term follow up.²⁴ Recurrent myocardial infarction was identified prospectively as a secondary outcome, although the way it was defined changed during the course of the study. A total of 2231 patients with left ventricular dysfunction (ejection fraction $\leq 40\%$), most of whom were not receiving a diuretic, were randomly allocated to treatment with captopril or placebo three to 16 days after acute myocardial infarction. Significant reductions in cardiovascular end points were observed in the active treatment group, including death and progressive heart failure. Of particular interest, however, was the 25% reduction in the risk of recurrent infarction in the active treatment group, a benefit not readily explained by the effects of ACE inhibition on left ventricular remodelling (figure).

Like MERCATOR and SOLVD, therefore, the SAVE trial provides evidence to support the hypothesis that progression of coronary artery disease might be amenable to modification by ACE inhibition. We emphasise, however, that these trials were conducted only in patients with severe ventricular dysfunction. These patients may have an activated circulating or tissue renin-angiotensin system, or both. Moreover, myocardial infarction was not the primary outcome measure and definitions varied during the course of the trial. Until the results of QUIET become available, the exciting possibility that treatment of this type might reduce ischaemic events by slowing the progression of coronary disease remains an untested hypothesis.

Genetic factors

Recent observations on the relation between ACE gene polymorphism and the risk of myocardial infarction lend weight to the hypothesis that the renin-angiotensin system may be active in the pathogenesis of coronary artery disease. Although ACE activities are fairly stable within individual people, they show considerable variation between people.²⁵ About 50% of this variability is determined genetically.²⁶ Thus the gene which codes for ACE²⁷ is associated with an insertion (I)-deletion (D) polymorphism in intron 16.²⁸ People with the DD genotype (one in four of the population) have plasma ACE activities that are on average twice those of people with the II genotype, the ID genotype being associated with intermediate values. Cambien

et al compared patients after myocardial infarction with controls and found that the DD genotype was significantly more frequent in patients with myocardial infarction.²⁹ Indeed, in those with no other risk factors for myocardial infarction (smoking, hypertension, hyperlipidaemia) the DD genotype increased the risk by a factor of 3.6. They concluded that the DD ACE gene variant, which codes for high activities of ACE, is a potent new risk factor for myocardial infarction. They also postulated that the most likely mechanism by which this ACE gene variant influences the risk of myocardial infarction is by increasing the concentration of angiotensin II locally within the coronary arterial wall.

More recently, these same investigators have reported that in the original study population the DD genotype was associated with excess deaths from ischaemic heart disease in parents, strengthening the hypothesis that genetically determined ACE activity may have a role in the pathogenesis of coronary artery disease.³⁰ In response to these new findings, a substudy of QUIET will genetically type all the patients to determine whether the DD variant is indeed a risk factor for ischaemic events and whether administration of the ACE inhibitor quinapril shows differential protective effects in subgroups with and without this variant. If differential effects are identified then it may be possible in future to characterise genetically those patients at special risk of progressive atherosclerosis who would benefit from ACE inhibition.

Conclusion

A body of experimental, clinical, and genetic evidence implicates the tissue renin-angiotensin system in the pathogenesis of coronary artery disease and myocardial infarction. Whether treatment with ACE inhibitors can modify the progression of coronary artery disease is an exciting hypothesis that is currently being tested in the QUIET study, whose results will be available in 1996.

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