WHY ARE ANGIOTENSIN CONVERTING ENZYME INHIBITORS EFFECTIVE IN MYOCARDIAL ISCHAEMIA?

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"We know what we are but we know not what we may be" Shakespeare (Ophelia, in Halmet).

Newer indications are being added to the conditions benefiting from Angiotensin converting enzyme inhibitors. They have an extremely successful track record for lowering systolic and diastolic blood pressure and have been employed usefully in the setting of symptomatic and asymptomatic cardiac failure and post myocardial infarction. Their new role of possessing antischaemic properties has come to limelight only recently. This article reviews the evidence and the possible mechanisms for it.

Do angiotensin converting enzyme inhibitors have anti-ischaemic properties? ACE inhibitors do not have any consistent short term anti anginal effects. Attention has been focused on the potential long term benefits of ACE inhibitors in preventing ischemic events in patients with stable CAD. This came as an unexpected finding from large clinical trials conducted in patients with severe, moderate and mild heart failure. The combined arms of the SOLVD study, for example, demonstrated a reduction in the risk of myocardial infarction either first or recurrent) of 23% and the risk of unstable angina by 20% in the enalapril treated group.[1] In the SAVE study, there was also 25% reduction in recurrent myocardial infarction as well as a significant reduction of the rate of revascularization including percutaneous transluminal coronary angioplasty (PTCA) and coronary artery bypass grafting (CABG) in the captopril treated group.[2]

It is unlikely that the observed reduction in ischaemic events can be explained by the blood pressure lowering action of ACE inhibitors alone, since the magnitude of risk reduction was substantially larger than that expected from short term modest reductions in blood pressure. In a recent meta-analysis of 14 randomized clinical trials of antihypertensive therapy, diastolic blood pressure reduction of 5-6 mmHg for about 4-5 years showed a 14% reduction in fatal and non-fatal CHD events.[3] In the combined SOLVD trials, diastolic blood pressure was reduced by an average of 4 mmHg; this was associated with a 23% reduction in fatal or non-fatal myocardial infarction and a 21% reduction in cardiac deaths. Moreover, the risk reduction in ischemic events were similar in patients with different levels of systolic and diastolic blood pressure at baseline. While there was a trend towards larger reductions in the risk for myocardial infarction. In latest study the effects of ACEI were studied on stable patients with CAD, and the results were impressive reduction in MACE.[4,5]

Similar results were obtained in high risk population with and without CAD.[6] As the evidence is accumulating in favour of ACEI as anti atherosclerosis agents. What could be the possible mechanisms and the evidence to support the effects is being mentioned briefly.[8-11]

a. ACE Gene

In humans, the level of ACE is partly under genetic control. The ACE gene is characterized by insertion (I) deletion (D) polymorphism based on the presence (I) or absence (D) within intron 16 of a 287 base pair Alu repeat sequence. Several recent investigations have evaluated associations between the ACE DD genotype, which identifies individuals with higher circulating and tissue levels of ACE and the risk for different manifestations of cardiovascular disease, particularly myocardial infarction. A number of studies found a clear link between the ACE DD genotype and risk of myocardial infarction. This was particularly relevant in individuals otherwise felt to be at low risk for acute ischemic events based on classical cardiovascular risk factors, while other investigations failed to confirm such associations.[12] Further studies evaluating the significance of the ACE gene polymorphism and of other genetic variants in the renin angiotensin system are underway and will help to resolve this important question as well as its potential therapeutic implications.[13]

It has also been recently suggested that the I/D polymorphism might even influence coronary vasomotion and coronary thrombosis, which are both implicated in the genesis of acute myocardial infarction.

b. Haemodynamic effects

Angiotensin II is a potent systemic and coronary vasoconstrictor.[14] In patients with CAD, angiotensin II adversely affects the balance between oxygen supply and demand in patients with CAD, with or without heart failure, ACE inhibitors improve cardiac haemodynamics and energy supply to the myocardium by causing coronary and peripheral dilation in the absence of reflex tachycardia.[14] Despite this positive haemodynamic action, the effects of ACE inhibitors on angina pectoris are not yet well defined.

c. Modulation of the sympathetic activity

Angiotensin II modulates local cardiac and vascular sympathetic activity. Inhibition of this effect may potentially account for the cardiac protection and reduction in cardiovascular events. The importance of this mechanism in humans is still controversial. All of the studies have been conducted in patients with heart failure treated with diuretics, digitalis and vasodilators; these treatments exert a significant action on the sympathetic system, which may concede the effect of ACE inhibitors do not seem to influence the neuroendocrine response, but data are scarce.[14,15] The relevance of the antiadrenergic properties of ACE inhibition in humans in the absence of heart failure is even less clear.[16,17]

d. Effects on endothelial function

Balance is meticulously maintained in the endothelium vascular smooth muscles tone by secreting relaxing and contracting factors. There is a constant release of endothelium derived relaxing factors (EDRFs), whose biological activity is provided by nitric oxide (or closely related molecules) and which constantly counteracts vasoconstrictor substance such as noradrenaline, angiotensin II or endothelin I. The normal functioning endothelium is able to increase the release of EDRFin response to physiological stimuli, such as the shear stress exerted by the circulating blood, or to humoral stimulation by vasoactive sub-

stances such as acetylcholine or bradykinin. Thus, the endothelium is both a target and a modulator of blood pressure related and hormonal influence. Alteration of endothelial function, such as an impaired release of EDRFs, develops in many pathological conditions including CAD.[15] Experimental studies have shown that ACE inhibition stimulates endothelial release of nitric oxide and prostacyclin by a bradykinin mediated mechanism, thereby enhancing endothelial dependent vasodilation.[18] These and other studies have raised the question as to whether or not ACE inhibition can improve coronary endothelial function in humans and whether a potential beneficial effect of ACE inhibition is mediated by bradykinin.[19]

The results of the TREND trial support this theory. This study tested the effect of ACE inhibition with quinapril on coronary artery endothelial function in patients with established coronary artery atherosclerosis. In the treated group the initial vasoconstrictor response to intracoronary infusion of acetylcholine was significantly reduced and partly normalized towards a vasodilator response, whereas no change was observed in the placebo group.[20] Perindopril, another ACE inhibitor with high tissue binding affinity, is also able to normalize coronary endothelial function of patients with hypertension subjected to cold pressor tests or after papaverine injection.[17] These beneficial effects of ACE inhibition could be due to a reduction in angiotensin II and/or an increase in bradykinin. Inhibition of the generation of angiotensin II may attenuate smooth muscle contraction and the production of superoxide anions resulting from stimulation of NADH/NADPH oxidase systems of smooth muscle cells.[21] This would inactivate endothelial derived nitric oxide and thereby dysfunction. In addition, bradykinin induced augmentation of nitric oxide release by endothelial cells is promoted by ACE inhibition. By using the selective endothelial dependent vasodilation mediated by ACE inhibitors is indeed related to an increase of bradykinins.[22]

There is evidence that ACE inhibition has the potential to restore abnormal peripheral and coronary artery endothelial function in patient with CAD.

e. Anti-atherogenic effects

There is experimental evidence of anti atherogenic effects of ACE inhibitors in several animal models of atherosclerosis.[24-26] The effects are complex and include protection of the endothelium, antimitogenic action, antithrombotic and plaque stabilizing effects, and possible anti-oxidant properties. Increase in the messenger RNA (mRNA) for ACE and angiotensinogen have been shown in the proliferating tissue of balloon injured vessels of rats.[27] the results of the QUIET trial a[20] failed to show a reduction in mortality or recurrence of angina pectoris in patients with CAD treated with PTCA in combination with quinapril or placebo.[28] Although the low doses of cilazapril or quinapril used in these studies may have been sufficient to reduce blood pressure, animal studies suggest that doses required to inhibit neointimal development are higher than the usual anti hypertensive doses.

ACE inhibitors may also exert an indirect anti atherogenic action by reducing vascular smooth muscle growth and proliferation, restoring endothelial function and by reducing the propensity for a plaque to rupture, a crucial mechanism in the genesis and progression of athero-sclerotic lesions. Angiotensin II acts by inducing the protooncogenes c-fos,[29] c-myc[30] and c-jun,[31] as well as the expression of several growth facto gene ultimately resulting in vascular smooth muscle cell growth. In addition, angiotensin II favours the release of a neutrophil chemo-attractant from the endothelium, leading to accumulation of neutrophils.[32] ACE inhibitors reduce the breakdown of bradykinin, which has a vasodilator effect,

and act by releasing nitric oxide and prostacyclin (Prostagladin I_2) from endothelial cell. Besides being a potent vasodilator, nitric oxide has other beneficial effects on endothelial function and integrity by inhibiting platelet adhesion and aggregation and smooth muscle cell mitogenesis. By enhancing kinin accumulation, Ace inhibitors may prevent the development of proliferative atherosclerotic lesions.

ACE inhibitors may also prevent plaque rupture by inhibition of the vasoconstrictive action of angiotensin II, reduction in endothelium release (which is stimulated by angiotensin II) and prevention of hypomagnesaemia, which in turn, leads to coronary artery spasm.

f. Antiproliferative actions

ACE indictors are effective in reducing left ventricular masses in animal models as well as in subjects with hypertension. In general, an increased left ventricular mass is an independent risk factor for CAD, which is associated with increased cardiac mortality and morbidity.[33] Regression and prevention of ventricular hypertrophy is related, in part at least, to the reduction in after load and to reshaping of the elastic and collagen fibers of the myocardium, thus limiting the remodeling process.[34]

Load independent mechanism could also play a role in the antihypertrophic effect of ACE inhibitors are used at doses too low to reduce blood pressure.[35] These findings are attributed to a direct inhibition of cardiac tissue ACE, resulting in blockade of angiotensin II mediate myocyte hypertrophy. Both circulating and locally (cardiac) produced angiotensin II may directly stimulate cardiac hypertrophy via induction of proto-oncogene and growth factor expression. Though there is consistent evidence of the antiproliferative effect of ACE inhibitors, a clear reduction in the cardiovascular events associated with this effect has not been demonstrated.[36]

g. Antithrombotic activity

Experimental studies have shown that angiotensin II selectively induces the production and secretion of plasminogen activator inhibitor I (PAI-I) in endothelial cells, which is the inhibitor of tissue type plasminogen activator (tPA) in plasma[37] Elevated levels of tPA are at the basis of thromboembolic disease. This indicated that angiotensin II may be prothrombotic by increasing PAI-I and consequently reducing the activity of the fibrinolytic system. There are some preliminary observations that ACE inhibits improve endogenous fibrinolytic function in CAD patients, suggesting a potential link between the rennin-angiotensin system and the risk of thrombosis.[38] It is also suggested that an indirect effect of ACE inhibitors on platelet function may result from a prospective action on the arterial wall.[39]

To conclude ACE seem to possess some anti ischemic properties and confer the beneficial effects through various mechanisms but more direct evidence should be sought from large clinical trials to further clear the picture.[40,41] The question that should all patients with CAD should be receiving ACE inhibitors has now entered into a practical phase and needs serious consideration.[42]

REFERENCES

1. SOLVD investigators. Effects of Enalapril on survival in patients with reduced left ventricular ejection fraction and congestive heart failure. N Eng J Med 1991; 325: 293.
2. Pfeiffer MA, Braunwald E, Moye LA, et al: Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. N Engl J Med 1992; 327:669
3. Ambrosioni E, Borghi C. Early and late angiotensin-converting enzyme inhibition after myocardial infarction: an overview of randomized clinical trials. Am J Med. 2003; 115(6): 503

4. Fox KM; European trial On reduction of cardiac events with Perindopril in stable coronary Artery disease Investigators. Efficacy of perindopril in reduction of cardiovascular events among patients with stable coronary artery disease: randomised, double-blind, placebo-controlled, multicentre trial (the EUROPA study). Lancet. 2003; 362(9386): 782
5. Owen OG. EUROPA shows role for ACE inhibition in low-risk CHD. Int J Clin Pract. 2003; 57(8): 726
6. Yusuf S, Sleight P, Pogue J, et al. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. *N Engl J Med* 2000;342(3):145-53.
7. Pitt B. The anti-ischemic potential of angiotensin-converting enzyme inhibition: insights from the heart outcomes prevention evaluation trial. Clin Cardiol. 2000; 23(7 Suppl 4): IV9-14.
8. Vogt M, Motz W, Strauer BE. ACE-inhibitors in coronary artery disease? Basic Res Cardiol. 1993; 88 Suppl 1: 43-64.
9. Pepine CJ. Rationale for ACE inhibition as an anti-ischaemic therapy. Eur Heart J. 1998 Jul; 19 Suppl
10. Prasad A, Mincemoyer R, Quyyumi AA Anti-ischemic effects of angiotensin- converting enzyme inhibition in hypertension. J Am Coll Cardiol. 2001; 38(4): 1116.
11. Pepine CJ.Potential role of angiotensin-converting enzyme inhibition in myocardial ischemia and current clinical trials.

Clin Cardiol. 1997 Nov; 20(11 Suppl 2): II-58-.

12. Cambien F, Poirier O, Lecerf L, et. al. Deletion polymorphism in the gene for angiotensin converting enzyme is a potent risk factor for myocardial infarction. Nature 1992; 359: 661.
13. Lindpaintner K, Pfeffer MA, Kreutz R, et al. Angiotennsin converting enzyme inhibitors. N Eng J Med 1995; 332: 706.
14. Agerholm-Larsen B, Nordestgaard BG, Stenffensen R, et al. Novel neurohormonal modulators in cardiovascular disorders. The therapeutic potential of endopeptidase inhibitors. Circulation 1997; 95: 2358.
15. GaveA h, Brown JJ, Lever AF, et al. Repression of angiotensin II and potentiation of bradykinin contribute to the synergistic effects of dual metalloprotease inhibition in heart failure. Lancet 2003; 122: 1382.
16. Anand IS, Karla GS, Ferrari R, et al. Neutral endopeptidase 24.11: Structure, inhibition, and experimental and clinical pharmacology. Circulation 1998; 80: 299.
17. Remme WJ. Effect of ACE inhibition on neurohormones. Eur Heart J. 1998;19 Suppl J: J16
18. Mombouli JV, Illiano S, Nagao T, et al. Prostaglandins in severe congestive heart failure. Relation to activation of the renin-angiotensin system and hyponatremia. Circ Res 2003; 71: 137. Groves P, Kurz S, Just H, et al. Circulation 1999; 92: 3424
19. Pepine CJ. Improved endothelial function with angiotensin-converting enzyme inhibitors.Am J Cardiol. 1997 Mar 6; 79(5A): 29-32
20. Mancini GBJ, Henry GC, Macaya C, et al. Angiotensin-converting enzyme inhibition with quinapril improves endothelial vasomotor dysfunction in patients with coronary artery disease. The TREND (Trial on Reversing ENdothelial Dysfunction) Study.Circulation 1996; 94: 258.
21. Anand IS, Karla GS, Ferrari R, et al. Neutral endopeptidase 24.11: Structure, inhibition, and experimental and clinical pharmacology. Circulation 1998; 80: 299.
22. Rajagopalan S, Kurz S, Munzel T, et al. Angiotensin II medical hypertension in the rat increase vascular superoxide production via membrane NADH/NADPH oxidase activation: contribution to alterations of vascular tone. J Clin Invest 1996; 97: 1916.
23. Messerli FH. Vascular protection of ACE inhibitors. Arch Intern Med. 2003; 163(22): 2791
24. Michael JB, Plisonier D, Bruneval P. Effect of perindopril on th immune arterial wall remodeling in the rat model of arterial graft rejection. Am J Med 1999; 92(suppl 4B) 39S.
25. Rakugi H, Wang DS, Dzau YJ. Potential importance of tissue angiotensin converting enzyme inhibition in preventing neointima formation. Circulation 1994; 90: 449.
26. Rakugi H, Jacob HJ, Krieger JE, et al. Vascular injury induces angiothensiogen gene expression in the media and neointima. Circulation 1993; 87: 283.

27. Lees RS, Pitt B, Chan RC, et al. Baseline clinical and angiographic data in the Quinapril Ischemic Event (QUIET) Trial. Am J Cardiol 1996; 78: 1011.

28. Pitt B, O'Neill B, Feldman R, Ferrari R, et al QUIET Study GrouThe QUinapril Ischemic Event Trial (QUIET): evaluation of chronic ACE inhibitor therapy in patients with ischemic heart disease and preserved left ventricular. Am J Cardiol. 2001 ; 87(9): 1058

29. Naftilan AJ, Gilliand GK, Eldridges CS, et al. Enhancing cardiac protection after myocardial infarction: Rationale for newer clinical trials of angiotensin receptor blockers. J Hypertens 1990; 10: 5536.

30. Paquet JL, Giilliand GK, Eldridge CS, et al. Induction of the proto oncogene c-jun by angiotensin Mol Cell Biol. 1990; 8: 565.

31. Lyall F, Morton JJ, Gillespie D. Angiotensin II stimulates c-jun experession in cultured vascular smooth muscle cells: superinduction by emetine. Eur J Intern Med 1992; 2: 271.

32. Farber HW, Center DM, Rounds S et al. components of the angiotensin system cause release of neutrophil chemoattractant from cultured bovin and human endothelial cells. Eur Heart J 1990; 11 (suppl B): 100.

33. Kannel WB, Gordon T, Castelli WP, et al. Electrocardiographic left ventricular hypertrophy and risk of coronary heart disease : the Framingham study. Ann Intern Med 1970: 72: 813.

34. Weber KT, Sun Y. Cardiac remodeling by fibrous tissue: role of local factors and circulating hormones. Ann Med 1998; 1: 3.

35. Linz W, Scholkens BA, Ganten D. Converting enzyme inhibition specifically prevents the development and induces regression of cardiac hypertrophy in rats. Clin Exp Hypertension 1989; 11: 1325.

36. Schwartizkopt B, Boerrigter G, Brehm MU, et al. Regression of interstitial fibrosis by chronictreatment with ACE inhibitors in patients with hypertensive heart disease. Circulation 1998; 98: 14154.

37. Olson JA Jr, Shiverick KT, Ogilives S, et al. Angiotensin II induces secretion of plasminogen activator inhibitor I and a tissue metalloprotease inhibitor related protein from rat brain astrocytes. Neurobiology 2003; 88: 1928.

38. Luskutoff DJ, Swadey M, Mimuro J. Type-I plasminogen activator inhibitor. Prog Hemost Thromb 1989; 9: 87.

39. Okruucka A, Pechan J, Kratochvilova H. Effects of the agniotensin converting enzyme (ACE) inhibitor perindopril on endothelial and platelet functions in essential hypertension. Platelets 2002; 9: 63.

40. Rollins G. Acute myocardial infarction care improved, but still inadequate. Rep Med Guidel Outcomes Res. 2003 Aug 8; 14(15): 1-2, 5.

41. N J Wald, ,M R Law..A strategy to reduce cardiovascular disease by more than 80%. BMJ. 2003 ; 326 (7404): 1419

42. White HD. Should all patients with coronary disease receive angiotensin-converting-enzyme inhibitors? Lancet. 2003; 362 (9386): 755.

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