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The renin-angiotensin-aldosterone system and cardiac ischaemia

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The renin-angiotensin-aldosterone system is a remarkably complex homoeostatic neuroendocrine entity. It is an endocrine system regulating vascular tone and salt and water balance. It is a tissue based system with paracrine and autocrine effects, and also a neuromodulator. These attributes result in an extensive range of actions on the heart, many of which play an important role in cardiac ischaemia and hence are of immense interest to clinicians and basic scientists.

There are several theoretical reasons why the renin-angiotensin system should play a pivotal role in cardiac ischaemia. Angiotensin II is a potent coronary and systemic vasoconstrictor and a positive inotropic and chronotropic agent. These attributes of angiotensin II promote ischaemia in vulnerable areas of the myocardium. Initial attempts to block these pro-ischaemic effects by angiotensin converting enzyme (ACE) inhibitors produced equivocal results, due largely to inadequacies of experimental design, are were themselves the victims of inadequate knowledge. More recently, with better understanding of the fundamental biophysiology of the renin-angiotensin system and better drugs, blockade of the system in patients after acute myocardial infarction has yielded promising results, especially in patients with impaired systolic left ventricular function. Research has now focused on ways and means of using these newly discovered anti-ischaemic properties of ACE inhibitors as agents for secondary and perhaps also for primary prevention of acute and chronic coronary events. Research into this aspect of the renin-angiotensin system appears set for spectacular growth as knowledge regarding this system in cardiac ischaemia accelerates.

In this article I shall endeavour to review the basic physiological action of angiotensin II on the coronary vasculature and the myocardium as well as the therapeutic use of angiotensin blocking agents in the management of acute and chronic ischaemic conditions.

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Glossary of trials
MARCATOR—Multicenter American Research Trial with Cilazapril after Angioplasty to Prevent Transluminal Coronary Obstruction and Restenosis
MERCATOR—Multicenter European Research Trial with Cilazapril after Angioplasty to Prevent Transluminal Coronary Obstruction and Restenosis
PHYLLIS—Plaque Hypertension Lipid-Lowering Italian Study
PRACTICAL—Placebo-Controlled Randomized ACE Inhibitor Comparative Trial in Cardiac Infarction and LV Function
SAVE—Survival and Ventricular Enlargement Study
SMILE—The Survival of Myocardial Infarction Long-Term Evaluation Study
SOLVD—Studies of Left Ventricular Dysfunction
V-HeFT II—Vasodilator-Heart Failure Trial II

Actions on myocardial oxygen supply: demand ratio

Experimental and clinical data indicate that angiotensin II has a modest action on the heart in normal subjects when the renin-angiotensin system is not activated.[1,2] However, if the system is stimulated by sodium deprivation,[1] diuretic therapy,[3] acute cardiac ischaemia,[4–8] or renovascular hypertension,[9] then the cardiovascular effects are intensified.

The earliest view of the effects of angiotensin II effects on the heart was that it had four major actions. First, it had a direct positive inotropic action on the ventricular myocardium.[10,11] Second, there was a further inotropic effect resulting from its neuromodulator role of augmenting sympathetic tone.[12] Third, angiotensin II increased heart rate directly and through augmentation of sympathetic activity.[13,14] Fourth, there was tonic modulation of sympathetic coronary vasoconstriction.[15]

Left ventricular hypertrophy is a common consequence of systemic hypertension and has been shown to be associated with a considerably enhanced risk of cardiovascular morbid events, including myocardial infarction.[16–18] A consequence of left ventricular hypertrophy is a reduction in the ability of the coronary microvasculature to vasodilate normally in response to usual physiological and pathological stimuli: reduced "coronary vasodilator reserve".[19,20] This is also instrumental in reducing coronary flow, especially in the presence of coronary stenosis, and precipitates or promotes myocardial ischaemia.

At the cellular level, hypertrophy of the myocyte leads to an increasing distance of the centre of the cell nucleus from the periphery where the nutrient capillary blood flow is located. Thus the centre of the cell, that is, the nucleus, becomes progressively ischaemic, ultimately resulting in cell death. Cellular hypertrophy, which is caused by the addition of sarcomeres, results in increased nutritional demands, and since the capillary network cannot keep pace, inevitably produces cellular ischaemia.

Angiotensin II is a potent coronary vasoconstrictor agent with an in vivo potency 40 times that of noradrenaline. Therefore activation of the renin-angiotensin system results in constriction of epicardial coronary arteries. The smaller, intramural arteries and capillaries are also influenced by angiotensin II, but their tone is largely governed by local metabolic and nervous influences, with angiotensin II playing a lesser role. Modulation of sympathetic vasoconstrictor tone amplifies this vasoconstrictor action further.

The combination of inotropic, chronotropic, and coronary vasoconstrictor actions results in an adverse coronary oxygen demand to supply ratio. This becomes of major clinical significance in regions of the myocardium where the blood supply is affected by critical coronary vascular stenosis. Conversely, angiotensin II blockade should improve the supply/demand balance, and hence ameliorate myocardial ischaemia.

Actions on cardiac loading conditions

Angiotensin II influences the heart through its propensity to cause vasoconstriction in systemic arteries and veins. Arterial vasoconstriction causes increased afterload as a result of vasoconstriction of the medium sized resistance arteries and also because of early wave reflection in the aorta and large conductance vessels.[21] Increased afterload promotes cardiac ischaemia by increasing left ventricular wall tension, a major determinant of myocardial oxygen requirements, in accordance with LaPlace's law (wall tension = radius × pressure/2 × wall thickness). Increase in afterload is a major signal for left ventricular hypertrophy which also promotes ischaemia, as described previously.

The normal heart can cope with increases in afterload by means of its considerable contractile reserve, but the failing heart becomes exquisitely sensitive to afterload changes, and as described by Sarnoff and Mitchell,[22] left ventricular stroke output and afterload develop a linear relation. This means that activation of the renin-angiotensin system, as happens in cardiac failure, will result in further falls in output of the failing heart and hence accentuation of ischaemia. It also provides therapeutic opportunity in that reduction in afterload through blockade of the renin-angiotensin system will have the reverse effect of improving cardiac output and hence myocardial ischaemia.

The renin-angiotensin system also influences ventricular preload. Angiotensin II, by inducing venoconstriction,[23] increases venous return and hence increases left ventricular wall tension according to the LaPlace formula. More importantly, increased production of aldosterone due to activation of this system results in sodium and water retention which increases intracardiac volumes. These increases in preload result in increased wall tension and will result in increased myocardial oxygen demands, which may not be possible to meet in the areas of the myocardium where blood supply is already compromised.

Effects on coronary vasomotion

There has been a long standing argument as to whether coronary vasoconstriction can coexist with cardiac ischaemia, ischaemia being regarded as the most potent physiological vasodilator influence normally present. However, this is now known to be not the case, and additional vasodilatation can be achieved by ACE inhibition even in the presence of cardiac ischaemia.[4]

Normal regulation of coronary blood flow is a complex process. It depends on three interrelated factors: myocardial oxygen consumption, coronary vasomotor tone, and perfusion pressure. Coronary vasoconstrictive effects of angiotensin II, either directly or through modulation of sympathetic tone, may be counteracted by other mechanisms, hence masking its effects. In the rat heart Langendorf preparation, coronary blood flow increased when ACE inhibitors were added to the perfusate.[24,25] Pretreatment with ACE inhibitors resulted in flow increase in vitro throughout the experiments. In vivo experiments produced more complex results. When captopril was given to anaesthetised dogs under conditions of normal oxygenation, no significant changes in coronary blood flow were noted.[26] However, under conditions of myocardial ischaemia, there was redistribution of blood flow in favour of the brain and heart. Changes occurred especially in conditions where the renin-angiotensin system was stimulated.[27] Several studies have shown that myocardial ischaemia results in renin release,[28,29] although there is no direct proof that this is due to ischaemia rather than the consequent systemic haemodynamic alterations. In various models of cardiac ischaemia, saralasin and captopril acted as coronary vasodilators.[4]

Several investigators have reported that myocardial ischaemia is produced or exacerbated by activation of the renin-angiotensin system. Ertl[4] showed in an animal preparation, where the heart remained in situ, that ischaemia was produced by elevation or depression of a reservoir attached cannula in the anterior descending coronary artery, that ischaemia produced activation of the renin-angiotensin system which in turn produced further ischaemia by coronary vasoconstriction. Furthermore, this ischaemic response could be attenuated by pretreatment with ACE inhibitors.

Lindpainter *et al*[30] studied another model of cardiac ischaemia using an isolated perfused rat heart. This differs importantly from intact animal models in that the removal of the kidneys eliminates the circulating renin-angiotensin system. Hence any changes in cardiac and coronary functional properties are due to alterations in the renin-angiotensin system confined to the heart. This model produced virtually identical results. Ischaemia resulted in increased activity of the tissue renin-angiotensin system with increased coronary vascular resistance. Administration of ACE inhibitors resulted in reversal of these effects on the myocardium and vasculature.

Clinical studies on the effect of ACE inhibi-

tion on coronary blood flow suggest that these theoretical considerations and experimental findings may also be relevant in human beings. In patients with heart failure and hypertension, a reduction in coronary blood flow was observed as a part of the acute effects of ACE inhibitors, corresponding to a reduction in myocardial oxygen consumption due primarily to a reduction in heart rate times systolic pressure product.[31] Variable results were achieved in patients without heart failure. Captopril increased coronary blood flow in healthy subjects and patients with hypertension but without coronary disease, provided that the renin-angiotensin system was activated. Foult *et al*[32] showed evidence of coronary vasodilating action by intracoronary injection of enalaprilat, which produced coronary vasodilatation independent of systemic effects. Remme *et al*[33] confirmed that ACE inhibitors preferentially dilated the coronary vasculature in patients with coronary artery disease in the absence of heart failure. Ikram *et al* [34] demonstrated coronary vasodilatation by captopril in patients with coronary artery disease subjected to incremental atrial pacing induced myocardial ischaemia. Similar findings were reported by cold pressor and diving stress testing in coronary patients.

Blockade of the renin-angiotensin system will have opposite effects, reducing contractility, heart rate, and excitability while increasing coronary blood flow—a desirable state of affairs in patients with ischaemic heart disease. If the renin-angiotensin system is blocked at the level of the angiotensin II receptor, the observed effects will be those solely due to blockade of this system. However, if blockade occurs at the step involving converting enzyme, then there are additional effects due to inhibition of bradykinin degradation (which is also mediated by kininase II (converting enzyme)) and vasodilator prostaglandins. The net result will be more intense vasodilation, involving both the systemic and coronary vessels.

Cellular growth promoting action

These observations are further developed by the recently discovered ability of angiotensin II to promote cellular growth.[35,36] Experimental data show that angiotensin II can promote growth of vascular smooth muscle. This is highly relevant to adaptive and maladaptive changes of "remodelling" in the heart and arterial system following ischaemic injury and increased haemodynamic loads. The growth promoting actions of angiotensin II are mediated by the induction of proto-oncogenes: c-*fos*, c-*myc* and c-*jun*.[37-39] Other growth factor genes which are also induced by angiotensin II include thrombospondin, platelet derived growth factor, and transforming growth factor β.[40,41]

In addition to stimulating vascular cellular proliferation, angiotensin II has been shown to stimulate the release of an endothelial chemoattractant principle which promotes the accumulation of neutrophils at certain sites.[42] Experiments in hypertensive rats have shown that accumulation of foam cells in the subendothelial layers, which are intimately involved in the development of atheromatous plaque, are reduced by ACE inhibitor treatment.[41] Several studies have demonstrated that ACE inhibitors reduce cellular proliferation/migration in the experimental situation, and hence may be expected to have a beneficial effect on the development of atheroma.

Interactions with endothelial function

Important interactions between the renin-angiotensin system and endothelium derived vasoconstricting and dilating factors, which have a major bearing on cardiac ischaemic syndromes, have recently been elucidated. Angiotensin II stimulates the production of endothelin,[43] which has powerful vasoconstrictor actions and has a major adverse effect on cardiac ischaemia.[44] It has been speculated that Cleopatra's death was due to coronary insufficiency caused by asp venom sarafotoxins, compounds which are very similar to endothelins.[45] Endothelial function in vessels with extensive atheromatous involvement is severely compromised even in the absence of critical stenosis. In such situations, normal physiological stimuli such as cold, or abnormal but widely prevalent vascular stress factors such as cigarette smoke, could precipitate cardiac ischaemia. ACE inhibitors have been shown to improve endothelial function, although the major mechanism appears to be through their effects in preventing the breakdown of bradykinin rather than inhibition of angiotensin II.[46] There is in addition the potential of improved vascular function through increased production of vasodilator prostaglandins, which is also mediated by bradykinin.[47] Aldosterone also has interactions with the endothelium in that endothelial function is abnormal in patients with primary hyperaldosteronism and is normalised by removal of the aldosterone producing tissue.[48]

Interaction with the autonomic nervous system

Angiotensin II affects the heart through important interactions with the autonomic nervous system. It augments the sympathetic system by direct actions, as well as increasing release of catecholamines from the adrenal medulla and facilitating transmission in the sympathetic ganglia.[49] The resulting increase in heart rate and myocardial contractility are additional to its direct inotropic and chronotropic actions, which are thought to be mediated through activation of voltage sensitive calcium channels and stimulation of phospholipase C.[50]

There are angiotensin II receptors located in the central structures of the brain concerned with control of autonomic function. These include the paraventricular nucleus, the parabrachial nucleus, and the nucleus of the tractus solitarius.[51] These receptors are significantly increased in number in experimental

animals with genetic hypertension. Their precise function is unknown but one suggestion is that they are concerned with the central connection of the baroreceptor reflex arc.[52]

There is some evidence that angiotensin II also interacts with the parasympathetic system and inhibits vagal tone.[53] This would also increase heart rate and contractility. While these effects are relatively modest in the normal state, activation of the renin-angiotensin system by cardiac ischaemia leads to significant increases in all these actions.

Interactions with bradykinin

There is growing evidence that some of the vascular effects of ACE inhibitors may be mediated by the kallikrein-kinin system. The kinins are the vasoactive principles of the kallikrein-kinin system. Bradykinin has many effects that are opposite to angiotensin II. It is a coronary vasodilator, reduces myocardial ischaemic damage, and has an antiproliferative action. Kinins are oligopeptides with an exceedingly brief half life. They are degraded by kininase II which is the same enzyme as ACE—hence the close link with the renin-angiotensin system. The vascular actions of the kinins are mediated through the endothelial secretion of several autacoids. Activation of endothelial B_2 kinin receptors leads to the formation of nitric oxide (endothelium derived relaxing factor), prostacyclin, and platelet activating factor.[54]

There is an endogenous tissue kallikrein-kinin system in the heart and coronary vessels, and blockade of kininase II (ACE) with ACE inhibitors may produce kinins locally. Vasodilator and antiproliferative actions attributed to ACE inhibitors may, in reality, be due to increased accumulation of kinins due to reduced degradation, rather than reduced levels of angiotensin II.[55]

The availability of a specific antagonist of the B_2 kinin receptors, HOE 140, a bradykinin antagonist, has enabled the testing of this hypothesis at least in the experimental laboratory. In the dog and rabbit model of acute myocardial infarction produced by coronary arterial ligation, the ACE inhibitor ramipril reduced the size of the infarct in a dose that did not have systemic effects. However, this effect was abolished by the concomitant administration of HOE 140.[56] The findings of these studies suggest that the increase in local bradykinin by ACE inhibitors protects the heart by its own actions, or results in the release of a cardioprotective second messenger, cyclic guanosine monophosphate (cGMP), through increases in nitric oxide and prostacyclin. Whatever the mechanism, it is increasingly apparent that the kallikrein-kinin system is a major player in the cardioprotective effects of ACE inhibition in myocardial ischaemia.

Stabilisation of atheromatous plaque

Several properties of angiotensin II promote plaque rupture. These include its direct vasoconstrictor actions, and those acting through the sympathetic nervous system. Furthermore, it stimulates the release of endothelin, another intensely vasoconstrictor substance which may also promote plaque rupture.[57 58] Therefore antagonism of angiotensin II production, either locally or in the body as a whole, would reduce the propensity to plaque rupture. Experimental hypomagnesaemia has also been shown to promote plaque rupture,[59] and theoretically ACE inhibitors (which increase serum and tissue magnesium levels) may be protective against plaque rupture through this additional mechanism. Definitive evidence remains to be obtained to support these claims.

Interaction with clotting mechanisms

Angiotensin II interacts with plasminogen activating factor (PAF_1), a part of the clotting cascade which promotes clotting.[60 61] ACE inhibitors, which reduce circulating and tissue angiotensin II concentrations, inhibit the release of this factor and thereby reduce the propensity to clot. This is an important attribute in the production of vascular atheroma and cardiac protection from ischaemia.

Therapeutic implications

ACUTE MYOCARDIAL INFARCTION

Following acute myocardial infarction there are several structural changes that occur in both the infarcted and non-infarcted myocardium. Immediately after infarction the infarcted area undergoes infarct expansion and thinning. The ventricular cavity enlarges and the non-infarcted myocardium rapidly hypertrophies. The ventricular cavity tends to become more spherical in shape. These changes are collectively termed "remodelling". In addition, beginning from the onset of infarction there is intense neuroendocrine activation, with very high levels of catecholamines, arginine vasopressin, corticosteroids, natriuretic peptides, and other hormones.

In general terms, it has been shown that the immediate administration of ACE inhibitors to an unselected group of patients with acute myocardial infarction will result in an improvement in mortality,[62–65] with one exception,[66] or improved left ventricular function[67 68] over and above that from all other conventional treatments—a saving of three to four lives per 1000 patients treated. If these drugs are given to patients with acute infarction with clinical evidence of heart failure,[69] or asymptomatic patients with reduced ejection fractions,[70] in the early phase of infarction (3–11 days) they can attenuate the remodelling process, resulting in reduced mortality and morbidity from subsequent heart failure. Administration of ACE inhibitors to patients with impaired systolic function and a history of heart failure several months or years after the infarction resulted in improved mortality and morbidity.[71] The PRACTICAL study[67] was a head to head comparison of two ACE inhibitors with significantly different structural

and pharmodynamic properties. The results of this study showed that the ACE inhibitors had similar effects on left ventricular function, suggesting that the cardioprotective actions are a generic property of all ACE inhibitors rather than being drug specific.

Overall, these are intriguing and important observations which deserve further examination since they fit well into the extensive body of knowledge—theoretical, experimental, and clinical—regarding the anti-ischaemic properties of these drugs. If confirmed, it will open up the possibility of the use of these drugs in the secondary prevention of myocardial infarction as well as heart failure, with major economic and clinical benefits.

CHRONIC STABLE ANGINA

Blockade of the renin-angiotensin system in normal individuals[72] and experimental animals[1] usually has relatively little effect on coronary blood flow. However, if the system is activated by haemorrhage or diuretic treatment, then administration of agents that block the system at the level of converting enzyme or angiotensin receptors results in coronary vasodilatation.[1 3]

Similar observations have been made in patients with coronary artery disease. Resting coronary blood flow is generally within normal limits in such patients. However, global coronary blood flow changes are of little relevance to a condition dependent on regional supply versus demand alterations. Induction of ischaemia/angina by atrial pacing in such patients is ameliorated, coronary blood flow is increased, and neuroendocrine activation is attenuated by ACE inhibitors.[29 34] There is a paucity of information concerning the effects of ACE inhibition on regional coronary blood flow in patients with coronary artery disease. There is also a growing appreciation that in angina pectoris endothelial function is of critical importance. This is invariably abnormal in patients with diffuse atherosclerotic disease which is the usual substrate for chronic stable angina.

In chronic stable angina, clinical trials on the effects of ACE blockade have produced variable results, depending on the degree of activation of the renin-angiotensin system and other local influences that are operating. Initial studies reported favourable results in patients undergoing bicycle or treadmill stress testing.[73 74] These were largely uncontrolled trials in very small numbers of patients treated with ACE inhibitors for relatively brief periods. Larger, controlled studies could not consistently replicate these beneficial effects of ACE inhibitors on exercise performance.[75] Most showed some small statistically insignificant benefits overall. However, in most studies there were large numbers of patients who did show benefit. It became clear that the effects of blocking the renin-angiotensin system in patients with chronic stable angina were quite variable,[76] and it is generally not possible reliably to predict in advance which patients will respond. There was some evidence to suggest that if the renin-angiotensin system had been activated then this would be beneficial.[77] However, patients with heart failure and angina were likely to experience deterioration in their anginal status with the use of ACE inhibitors unassociated with specific antianginal treatment.[78]

In the light of emerging information on the natural history of post-infarction ischaemia, it is likely that these trials in chronic angina may have been the victims of inadequate experimental design. All the reported trials on the therapeutic use of ACE inhibitors in angina have been underpowered, with patient numbers in double figures only. The duration of these studies has been relatively brief, up to a few weeks at most. Data from the SAVE and SOLVD studies show that beneficial effects on coronary events were seen late, usually after a year of treatment. In the SMILE study[65] there was a significant reduction in the recurrence of angina, both early (8·9% *v* 27·1%) and late (9·8% *v* 21·7%) after acute myocardial infarction, followed for over a year. With the emergence of the concept of vascular remodelling by these agents,[79] which takes quite a long time, it may be that these trials were not of sufficient duration to discover the benefits.

The anginal end point under investigation also has an important bearing in determining whether the outcome is positive or negative. Exercise testing has produced variable results but ambulatory electrocardiographic assessment of ischaemia has generally shown that ACE inhibitors have worthwhile anti-ischaemic effects.[75 77 80] There is a dichotomy in anti-ischaemic effects as assessed by maximal exercise testing and the total 24 hour ischaemic burden by ambulatory electrocardiography, which is seen in the case of nitrates and nifedipine.[81]

In general, most of the double blind investigations into the anti-anginal effects of ACE inhibition have used near maximal exercise stress testing in order to induce myocardial ischaemia. This—although a perfectly valid experimental technique—is not easily extrapolated to everyday ambulatory activity. Ambulatory electrocardiographic studies in patients with chronic angina have favoured the anti-ischaemic action of ACE inhibitors. They have also been shown to have a favourable influence on the circadian cycle of cardiac ischaemia, diminishing the peaks in the morning and evening significantly.[77 82]

The conclusions from trials in chronic stable angina, most of which are of relatively small size (n = 50) and short duration (six months), are that a variable proportion of patients show therapeutic benefit, defined as fewer attacks of angina and improved treadmill exercise performance. These patients are usually those in whom there is activation of the renin-angiotensin system. However, there is a considerable number of patients that do not show therapeutic benefit. Hence the agents are not suitable as first line antianginal drugs.

There is evidence that ACE inhibitors reduce ambulatory ischaemia and the circadian patterns of cardiac ischaemia, and that these effects are most likely to be noted after

three months or more of treatment. This would suggest that beneficial effects are consequent upon effects on vascular remodelling and thrombogenesis.

With this predominantly favourable anti-ischaemic profile, ACE inhibitors merit consideration as adjunctive therapy in chronic stable angina, especially in patients with impaired cardiac function after myocardial infarction, where their anti-ischaemic properties have been demonstrated.

"Anti-atheroma" actions

There are sound theoretical reasons why inhibition of the renin-angiotensin system may exert antiatheroma effects. Several animal studies have suggested the possibility that ACE inhibitors have a direct antiatherogenic action. Chobanian *et al*[83] studied the effects of captopril in the Watanabe rabbit model of heritable hyperlipidaemia. Captopril reduced the area of aorta intima affected by atheroma and also decreased the cellularity of the lesions. The implications of these studies were that both extent and instability of atheromatous plaques were reduced by captopril treatment.

Other models of atheroma and vascular injury (for example, the balloon injury[84] and immune injury[85] mediated models of this condition) have shown that ACE inhibitors have antiatheroma actions. Perindopril in the miniswine and cilazapril in the rat both reduced atheromatous lesion severity.[86 87] Studies in non-human primates have also been suggestive. In the cholesterol-fed cynomolgus monkey, Aberg and Ferrer[88] reported a reduction in the extent and cellularity of atheromatous plaques by captopril. However, there are also contradictory findings in the same species which show little or no benefits.[89]

Two recent human studies, MERCATOR[90] and MARCATOR,[91] on the effect of ACE inhibitors on restenosis following balloon angioplasty failed to show any benefits. Additionally, the PHYLLIS study used carotid B-mode ultrasound to explore the possible antiatherosclerotic effect of fosinopril.[92] This whole area is in a state of flux, and further studies using refined evaluation techniques and drug regimes may provide conclusive results.

The renin-angiotensin system, cardiac ischaemia and arrhythmias

Activation of the renin-angiotensin system promotes cardiac arrhythmogenesis by several mechanisms. Angiotensin II is a positive inotropic and chronotropic agent both directly and via its action on the sympathetic nervous system. These tendencies are greatly exaggerated in conditions of ischaemia where the tendency to develop cardiac arrhythmia is already very high, and intensification of ischaemia by angiotensin II induced coronary vasoconstriction and increased myocardial contractility makes the situation worse. The myocardial and coronary actions are mediated by specialised angiotensin II receptors located on the appropriate cells. It has recently been shown that angiotensin II receptors are present on the cells of the specialised cardiac conducting tissue.[93] This raises the possibility that the chronotropic action of angiotensin II may be due to a direct effect which is antagonised by ACE inhibitors.

Administration of ACE inhibitors before coronary artery ligation in the experimental animal protects against major ventricular arrhythmias.[94] Clinical observations in patients with heart failure have shown a reduction in ventricular premature beat frequency and complexity.[95] However, direct proof of antiarrhythmic action or reduction in sudden cardiac death has not, to date, been convincing. The V-HeFT II trial showed that there was a reduction in sudden death mortality in the enalapril treated group in many of the patients who had coronary artery disease as the basis for heart failure.[96] However, in a non-heart-failure setting any direct antiarrhythmic action remains to be established, despite the positive experimental results.

Conclusions

In this review I have attempted to describe the extensive and expanding corpus of knowledge concerning the intimate relation of the renin-angiotensin system and cardiac ischaemia, in its widest sense. The paradigm has expanded from a circulating endocrine system regulating vasomotor tone and fluid/electrolyte homoeostasis, to a ubiquitous system regulating cellular growth and function with wide ranging autocrine and paracrine interactions with other important neuroendocrine and clotting systems. Furthermore, this is almost certainly not the end of the story and other important areas, for example, the cerebral renin-angiotensin system, will have a bearing on the heart, as demonstrated by Rademaker *et al*.[97] Another rapidly growing area of interest is the discovery that there are pathways for generation of angiotensin II in the heart which do not involve the classical pathway of renin and converting enzyme. Chymases[98] located in the heart offer an alternative pathway for angiotensin II generation and afford a means for "escape" from the therapeutic actions of ACE inhibitors. Our understanding of the significance of this pathway is still in its infancy. New information is emerging as to the role of the renin-angiotensin system in electrical cell to cell communication.[99]

The therapeutic yields based on this new knowledge are already impressive in the areas of acute myocardial infarction, heart failure, and hypertensive left ventricular hypertrophy. The fields of antiatheroma, restenosis, and plaque stabilisation are being actively explored. Genetic studies on the renin-angiotensin system and its relation to cardiac ischaemia are still in their infancy, but if confirmed, offer the prospect of targeted cardiac and vascular protection, especially if gene therapy becomes a reality.

While significant gaps remain in our understanding of the renin-angiotensin system and

cardiac ischaemia, this field of knowledge is set to undergo very rapid expansion, so this review is really an exhortation to "watch this space".

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