The renin-angiotensin system and the heart: a historical review

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Early observations on a possible link between the kidney and the cardiovascular system

In 1836 an English clinician Richard Bright observed that patients dying with contracted kidneys often had a hard, full pulse and cardiac hypertrophy.¹ In 1889 Brown-Sequard, the "father" of endocrinology, showed that injections of extracts from guinea pig testicles were able to produce systemic effects of vigour and the perception of rejuvenation.² On this background, in 1896 the Finnish physiologist Robert Tigerstedt and his student Per Bergman began to explore the possibility that kidney extracts from rabbits may have some systemic effects on the cardiovascular system. In 1898 their classic paper was published showing that intravenous injection of these renal extracts exerted a pressor effect. Moreover they postulated that the substance responsible for this effect was a protein which they named renin. They further suggested that renin was released from the kidney into the blood to produce an effect on blood vessels at a distance: another of the earliest ideas on blood borne chemical messengers.^{3,4} Eight years later Tigerstedt described a pressor effect of renal venous blood although he admitted that the evidence for this was weak.⁵ Other groups could not reproduce Tigerstedt's results, probably because they failed to prevent proteolysis in the preparation of the renal extracts. Therefore enthusiasm for the concept of renin as a pressor substance waned. Tigerstedt died in 1923 without any real acknowledgment of the significance of his contribution to the fields of both endocrinology and cardiovascular homeostasis. In fact for 30 years there were few references to the pressor effects of renin in the literature. In 1925, the histologist Ruyter was the first to describe granulated cells in the walls of the glomerular arterioles.⁶ The significance of this was realised by Goormaghtigh in 1939⁷ after the concept of renin as a hormone had been rekindled.

The rediscovery of renin as a pressor hormone

In 1934, Goldblatt showed in animal models that clamping of the renal arteries raised blood pressure.⁸ This stimulated a series of important papers over the next six years. Pickering described the partial purification of renin and its ability to increase blood pressure.⁹ Landis also showed that renal extracts had a pressor effect,¹⁰ confirming Tigerstedt's 40 year old results. Braun-Menendez and colleagues¹¹ and Page and colleagues¹² proposed that renin itself was not directly responsible for its pressor

effect but was in fact an enzyme. The names "hypertensin"¹¹ and "angiotonin"¹² were given to the pressor substance formed from the renin substrate by the enzymatic action of renin. Subsequently, it was agreed that the term "angiotensin" would be used to describe this substance. During this period the potential for pathological effects of renin was recognised. Winternitz described necrotising arteriolar lesions in animals which had undergone renal artery ligation and also in nephrectomised animals which had been given kidney extracts.¹³ Finally, the relevance of renal control of blood pressure in man was described by Young who, in 1936, cured a case of malignant hypertension by removing an ischaemic kidney.¹⁴

The elucidation of the renin-angiotensin system

In 1956, Elliott and Peart¹⁵ and Skeggs and colleagues¹⁶ discovered that the product of renin action was a decapeptide which required further enzymatic breakdown to form the active pressor substance, an octapeptide. Based on these results the terms angiotensin I, angiotensin II, and angiotensin converting enzyme (ACE) were coined. In the following year the structure of renin substrate was shown to be a tetradecapeptide¹⁷ which was later referred to as angiotensinogen. Concurrent with the discovery of the structure for angiotensinogen, angiotensin II was synthesised¹⁸ which enabled further definition of its actions. However, it was not until the early 1970s that the mechanism of action of renin, as an acid protease with very narrow substrate specificity, was described.¹⁹

Meanwhile the idea of a relation between the renin-angiotensin system and the adrenal cortex was evolving. In 1953, aldosterone was discovered.²⁰ The following year Gross showed an enhanced pressor response to renin in animals with bilateral nephrectomy and in those with "DOCA-salt" induced hypertension. Another group observed that the amount of granules in the juxtaglomerular apparatus correlated with the width of the zona glomerulosa of the adrenal cortex.²¹ In 1956, Gross showed that the amount of renin in the juxtaglomerular apparatus was inversely proportional to the sodium balance; two years later he went on to suggest that the renin-angiotensin system participated in a negative feedback mechanism with the adrenal cortex to control sodium metabolism.²² Subsequent studies confirmed this hypothesis. Renin and angiotensin II were shown to stimulate aldosterone secretion in sheep²³ and in dogs.²⁴⁻²⁶ Laragh found increased urinary aldosterone excretion in man

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during infusion of angiotensin II.²⁷ Brown and colleagues showed that a low sodium diet in man led to a raised plasma renin concentration²⁸ and vice versa. They also described a plasma renin concentration of 10 times that of normal concentrations in a patient with Addison's disease.²⁹

The increasing ability to accurately measure the various components of the renin-angiotensin-aldosterone system allowed further studies to be conducted to confirm Gross's hypothesis. Assays for plasma aldosterone levels³⁰ and plasma renin activity³¹ were described and the development of radioimmunoassays to measure angiotensin I, angiotensin II, and plasma renin concentrations followed.^{32 33} Using these techniques, studies performed in the human showed that salt depletion resulted in increased plasma levels of angiotensin II³⁴ as well as sensitising the secretion of aldosterone to angiotensin II.³⁵

Through these studies, which spanned a period of 25 years, the concept became established that the renin-angiotensin system was an endocrine pathway linked to aldosterone secretion by the adrenal cortex. This pathway provided a homeostatic control mechanism for sodium balance, intravascular volume, and therefore blood pressure. It also became apparent that angiotensin II influenced blood pressure directly by its vasoconstrictor effect and also by an independent more slowly developing pressor mechanism.^{36 37}

Early evidence of a link between the renin-angiotensin system and cardiac function

In 1956 it was shown that patients who had suffered a myocardial infarction had increased amounts of urinary aldosterone.³⁸ Thirty years later it was confirmed that the renin-angiotensin system is stimulated in man following myocardial infarction, although it was shown that there was a delay in this stimulation with a peak at approximately three days after the infarction.³⁹ In 1972, a study was published which suggested that patients with essential hypertension who had low renin values were at lower risk for subsequent myocardial infarction.⁴⁰ Although the interpretation of these results is still a source of controversy, further results from the same group appear to support the idea that reduced stimulation of the renin-angiotensin system in conjunction with hypertension may protect against ischaemic heart disease.⁴¹

Evidence began to accumulate that angiotensin II had a direct positive inotropic effect on the heart despite often being masked by increased cardiac afterload in experimental conditions. This effect was first noted in 1965⁴² and has subsequently been confirmed.^{43 44} The potential harmful effects of angiotensin II on the heart have also been recorded⁴⁵ and multifocal myocardial necrosis has been demonstrated in rabbits injected with angiotensin II. In these studies necrotic lesions were shown to be most severe in the left ventricle of rabbits as well as in the presence of coexisting hypertension, suggesting an interaction of pressure and workload factors.⁴⁶

In 1975, it was shown that renin release in dogs was modulated by cardiopulmonary receptors.⁴⁷ Further studies revealed that intravenous injections of rat atrial extract induced natriuresis.⁴⁸ Results from these studies led to the isolation of atrial natriuretic factor (ANF) which was found to modulate renin release in a dose dependent fashion. The modulation of renin release by ANF was dependent upon underlying sodium balance and renal function.⁴⁹ In the context of congestive cardiac failure high concentrations of ANF have been found in man.⁵⁰

Two concepts started to emerge concerning the link between the renin-angiotensin system and cardiac function. First, myocardial function was affected by the renin-angiotensin system directly and not simply as an indirect result of blood pressure changes. Second, the heart was able to modulate renin release through ANF and therefore played an integral role in the homeostatic control of intravascular volume and sodium balance.

The contribution of antagonists and inhibitors to the understanding of the renin-angiotensin system

In 1965, it was noted that venom from a Brazilian viper potentiated the effects of bradykinin.⁵¹ An enzyme had been described a few years earlier which inactivated bradykinin⁵² leading to the presumption that substances contained in the snake venom were kininase inhibitors. Meanwhile it was found that peptides from the same venom were able to inhibit ACE.⁵³ From this work emerged the nonapeptide teprotide, which was the first widely used ACE inhibitor. Teprotide was shown to lower blood pressure in rats with induced hypertension⁵⁴ and in sodium depleted dogs.⁵⁵ The race to develop an orally active agent began and eventually SQ14225 emerged, later to be known as captopril. In the early 1970s it became clear that ACE and kininase were the same enzyme,⁵⁶ a finding which may have important implications for the mechanisms of action of ACE inhibitors in the heart.

The discovery of competitive antagonist peptide analogues of angiotensin II was another important landmark. Saralasin was a widely used agent.⁵⁷ The use of this peptide in experimental models uncovered the selective vasoconstrictor properties of angiotensin II; it appeared that a stimulated renin-angiotensin system resulted in vasoconstriction of cardiac, renal, and cerebral vascular beds. This may explain how inhibition of either formation or action of angiotensin II helps to maintain vital organ perfusion pressure even in the face of low systemic blood pressure.⁵⁸ Saralasin was shown to lower blood pressure in sodium depleted dogs,⁵⁹ to lower blood pressure and reverse left ventricular failure in malignant hypertension,⁶⁰ and to lower blood pressure and aldosterone levels in proportion to basal angiotensin II levels.⁶¹ However, its use was restricted for two reasons; first it was not orally active and second it had partial agonist activity at higher concentrations. The search began for

orally active specific antagonists of angiotensin II.⁶² Losartan, a drug fulfilling these criteria, became available for clinical use only recently.⁶³

The final strategy for modification of the renin-angiotensin system lies in the inhibition of renin. While there has been progress,⁶⁴ and some of the early inhibitors provided important information on the active site of renin,⁶⁵ no clinically useful orally active renin inhibitor is available at present.

The use of ACE inhibitors in heart failure and the new interactions between the renin-angiotensin system and the heart

Captopril, by reducing the peripheral effects of angiotensin II, has a vasodilator effect. This was the original basis for its use in the treatment of essential hypertension and in this context it is as effective as either a β blocker or a thiazide diuretic.⁶⁶ Its use was extended to the treatment of congestive cardiac failure because of its vasodilating property; by reducing cardiac preload and afterload, systolic function improved. The beneficial effects of captopril in congestive heart failure were first noted in the late 1970s.^{67,68} However, in subsequent studies it emerged that ACE inhibitors were more than simple peripheral vasodilators. In 1985, a study was published showing that enalapril, another ACE inhibitor, increased the survival rate of patients with congestive heart failure, whereas other types of vasodilators did not.⁶⁹ This finding was confirmed in subsequent studies^{70,71} and was extended to include patients with asymptomatic left ventricular dysfunction.⁷² It was also shown that captopril increased survival in patients who were recovering from myocardial infarction.⁷³ Therefore it became clear that ACE inhibitors exerted unique effects on cardiac function.

ACE INHIBITORS CAUSE REGRESSION OF LEFT VENTRICULAR HYPERTROPHY IN HYPERTENSION
One hundred and sixty years ago, left ventricular hypertrophy (LVH) was noted in conjunction with renal hypertension.¹ Until recent years, LVH was assumed to be a mechanical compensatory mechanism in response to the increased cardiac afterload of hypertension. The importance of increased left ventricular mass as a risk factor for coronary events has been noted.^{74,75} It has been shown that ACE inhibitors cause regression of LVH in spontaneously hypertensive rats.⁷⁶ Subsequent studies in humans have suggested that ACE inhibitors cause a significantly greater degree of regression of LVH than β blockers or calcium antagonists despite similar falls in blood pressure, suggesting that ACE inhibitors may be exerting a direct negative trophic effect on the myocardium.⁷⁷ β Blockers have some action on regression of LVH independent of blood pressure changes⁷⁸ which may reflect the importance of the sympathetic nervous system in this context. It is now generally agreed that angiotensin II has a trophic effect on cardiac muscle.^{79,80} Proposed mechanisms for this effect include stimulation of protein synthesis

and cell growth in myocytes^{81,82} possibly by increased expression of proto-oncogenes and stimulation of protein kinase C activation.⁸³ It follows that ACE inhibition could induce regression of LVH by attenuation or reversal of these mechanisms.

ACE INHIBITORS INCREASE CORONARY BLOOD FLOW

Reference has already been made to the action of angiotensin II as a coronary vasoconstrictor. There is an increasing body of evidence concerning the participation of the renin-angiotensin system in coronary vasomotor control.⁸⁴ For example, administration of a diuretic which enhances the renin-angiotensin system causes reduced coronary blood flow, an effect which is reversed by ACE inhibition.⁸⁵ ACE inhibitors cause coronary vasodilatation in perfused heart preparations,⁸⁶ and intracoronary injection of ACE inhibitors in humans results in increased coronary perfusion and a decreased ejection fraction.⁸⁷ The fact that ACE inhibitors have the ability to increase coronary blood flow despite decreased myocardial oxygen demand⁸⁸ is likely to be crucial to their beneficial effects in ischaemic left ventricular dysfunction. The effect of angiotensin II as a positive inotrope in the failing heart may be compromised by its other effects, namely, of decreasing coronary flow and increasing diastolic dysfunction, resulting in cardiac decompensation.⁸⁹ In this regard ACE inhibitors have been shown to improve diastolic dysfunction in patients with ischaemic heart disease.⁹⁰

ACE INHIBITORS ATTENUATE SYMPATHETIC NERVOUS SYSTEM ACTIVITY IN THE HEART

Angiotensin II has long been known to cause stimulation of the central⁹¹ and peripheral⁹² sympathetic nervous system as well as stimulating release of catecholamines.⁹³ The latter two effects are mediated by facilitating pre-junctional angiotensin II receptors on sympathetic nerves and adrenal medullary cells. Chronic overactivity of the sympathetic nervous system in conditions of left ventricular dysfunction is probably detrimental to long term cardiac function. This theory is supported by the beneficial effects of β blockers in some patients with ischaemic heart disease and in the attenuation of LVH,⁷⁸ some of which is probably mediated by sympathetic nerve activity. The mechanisms by which angiotensin II stimulates the sympathetic nervous system are reviewed elsewhere.⁴⁴ Recently further evidence has been provided that ACE inhibitors may exert some of their beneficial effects on the heart through inhibition of this sympathetic stimulation.⁹⁴

The use of ACE inhibitors in myocardial infarction and the role of the renin-angiotensin system in the regulation of endothelial function

Reference has already been made to the effect of myocardial infarction on stimulation of the renin-angiotensin system.^{38,39} It has been postulated that angiotensin II in this context may

have several unwanted effects; among these are intense vasoconstriction resulting in increased reperfusion injury⁹⁵ and stimulation of sympathetic nerve activity resulting in a higher risk of arrhythmia.⁹⁶ After a moderate to severe myocardial infarction, remodelling of the left ventricle takes place, which results in a more dilated ventricle with reduced functional capacity. ACE inhibitors given following myocardial infarction are known to reduce this process of remodelling; their mechanism is probably a combination of their haemodynamic and metabolic properties.⁹⁷⁻⁹⁸

More recently the kininase inhibiting property of ACE inhibitors has aroused interest within the context of cardioprotection. It has been shown that the administration of bradykinin antagonists abolishes the beneficial effects of ACE inhibitors in the ischaemic rat heart,⁹⁹ and in hypertrophy.¹⁰⁰ It has been postulated that locally elevated levels of bradykinin in the heart may be cardioprotective.⁹⁸ Recent research has documented the vasodilating and antiatherogenic roles of the endothelium derived nitric oxide system. Because bradykinin is a potent stimulus of this system, it is feasible that a major part of the beneficial effect of ACE inhibition may ultimately operate through enhancement of the nitric oxide system. Nitric oxide is known to have anti-trophic properties and therefore may be an important mediator in the development of LVH.¹⁰⁰ It is a potent vasodilator acting on smooth muscle cells and therefore could be responsible for the effect of ACE inhibition on coronary blood flow.¹⁰¹ In addition, there is evidence for an antiatherogenic effect of long term ACE inhibition in a rabbit model¹⁰² and it has been shown that ACE inhibition prevents myointimal proliferation after vascular injury.¹⁰³

It appears, therefore, that as well as having a secondary cardioprotective role, ACE inhibitors also have a role in primary cardioprotection. As stated previously in this review, long term reduced activation of the renin-angiotensin system in some patients with essential hypertension may protect them from subsequent myocardial infarction.⁴⁰⁻⁴¹ In addition, it has recently been reported that individuals with a deletion polymorphism of the gene for ACE, and therefore who tend to have higher serum ACE concentrations, are at increased risk of myocardial infarction.¹⁰⁴⁻¹⁰⁵ Prospective clinical trials designed to assess the effects of ACE inhibition on mortality and left ventricular function in various patient groups have also revealed that the incidence of myocardial infarction is reduced in the treated groups.⁷¹⁻⁷³ Kininase inhibition through the endothelium derived nitric oxide system and its inherent vasodilator and antiatherogenic properties may be another mechanism by which ACE inhibitors play a cardioprotective role.⁸⁹

Evidence for a cardiac renin-angiotensin system

In the early 1970s, evidence was presented which suggested that the heart might have its own intrinsic renin-angiotensin system. This

evidence also supported the theory that the heart was able to respond to change in the circulating humoral system; renin activity was demonstrated in dog heart¹⁰⁶ and conversion of angiotensin I to angiotensin II was noted in isolated perfused heart preparations.¹⁰⁷ Interest in an intrinsic cardiac renin-angiotensin system was further stimulated by the elucidation of the mechanisms of action of ACE inhibitors on the heart. Despite very little change in the systemic indices of the renin-angiotensin system during ACE inhibition, the beneficial effects on the heart remain. This suggests that inhibition of angiotensin II and bradykinin production is occurring predominantly in the heart,¹⁰⁸ and that ACE inhibition may be most effective at a local level. This concept is supported by the fact that ACE inhibitors still have effects when perfused in isolated heart preparations.⁸⁶

Important evidence for a local renin-angiotensin system in the heart is the presence of ACE,¹⁰⁹⁻¹¹¹ renin activity,¹¹² and mRNA for renin and angiotensinogen¹¹³ in cardiac muscle. Other studies have also provided evidence for a local renin-angiotensin system in the heart. In rats, induced myocardial infarction activates the cardiac but not the circulating renin-angiotensin system.¹¹⁴ In end stage cardiac failure, increases in cardiac ACE mRNA levels have been demonstrated.⁸⁹

The idea of an intrinsic cardiac renin-angiotensin system with autocrine and paracrine roles remains controversial but the concept is appealing. It has been postulated that a tissue specific renin-angiotensin system, of which the cardiac system may be one, could contribute to long term vascular control depending on the specific needs of the tissue, while the circulating renin-angiotensin system may be primarily involved in acute responses to intravascular volume and sodium changes.¹⁰⁸ Looking ahead, further elucidation of tissue specific systems has major implications for the possibility of organ specific ACE inhibition.¹¹⁵

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